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Multiply robust estimators of causal effects for survival outcomes

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Abstract

Multiply robust estimators of the longitudinal g-formula have recently been proposed to protect against model misspecification better than the standard augmented inverse probability weighted estimator (Rotnitzky et al., 2017; Luedtke et al., 2018). These multiply robust estimators ensure consistency if one of the models for the treatment process or outcome process is correctly specified at each time point. We study the multiply robust estimators of Rotnitzky et al. (2017) in the context of a survival outcome. Specifically, we compare various estimators of the g-formula for survival outcomes in order to (1) understand how the estimators may be related to one another, (2) understand each estimator's robustness to model misspecification, and (3) construct estimators that can be more efficient than others in certain model misspecification scenarios. We propose a modification of the multiply robust estimators to gain efficiency under misspecification of the outcome model by using calibrated propensity scores over non-calibrated propensity scores at each time point. Theoretical results are confirmed via simulation studies, and a practical comparison of these estimators is conducted through an application to the US Veterans Aging Cohort Study.

KEYWORDS

augmented inverse probability weighting, estimating equations, iterative conditional expectation, local efficiency, multiple robustness, causal inference

1 | INTRODUCTION

In causal inference studies of failure-time outcomes, we are often interested in estimating the probability of survival at a time point that would have been observed had everyone in the study followed a specific treatment strategy of interest. The g-computation formula or g-formula (Robins, 1986) allows us to identify the counterfactual probability of survival under the assumptions of consistency, positivity, and exchangeability given the measured confounders, even in the presence of treatment-confounder feedback.

Two algebraically equivalent representations of the g-formula include a series of iterative conditional expectations (ICE) over time (Robins, 1986, 1997) and an inverse probability weighted (IPW) expectation. ICE requires one to iteratively standardize over the past outcomes, treatment and confounders, and IPW estimation requires one to upweight the individuals who followed the treatment strategy of interest to account for individuals who did not. Due to the curse of dimensionality, practical implementations of these estimators often require one to parametrically estimate a subset of components of the observed data likelihood and then substitute the estimated components into their corresponding estimating equations. As a result, the IPW estimator requires one to postulate a sequence of models for the probability of treatment assignment at each time point, conditional on past outcomes, treatments and confounders, and the ICE estimator requires one to postulate a sequence of models for the conditional mean of the counterfactual outcome given past outcomes, treatments, and confounders. The consistency of the IPW estimator requires the sequence of treatment models to be correctly specified, and the ICE estimator requires the sequence of outcome regression models to be correctly specified.

To a certain degree, model misspecification is almost always expected when we use parametric models in our analyses. This motivated the need for finding estimators that are robust to model misspecification compared with the singly robust ICE and IPW estimators. Doubly robust (DR) estimators can be generated by combining ICE and inverse probability weighting (Bang & Robins, 2005; Petersen et al., 2014; Robins, 2000; Robins et al., 1994; Scharfstein et al., 1999; Tchetgen Tchetgen, 2009). These estimators are consistent as long as one, but not necessarily both, of the sequences of models is correctly specified. For time-to-event outcomes, doubly robust estimation has been used, for example, to estimate the effect of hepatitis C viral clearance on end-stage liver disease in an HIV co-infected cohort (Schnitzer et al., 2014), the effects of glucose-lowering strategies on albuminuria development or progression in patients with diabetes (Neugebauer et al., 2014; Sofrygin et al., 2017), and the effect of nutritional interventions on clinical outcomes among critically ill children (Kreif et al., 2017). All of these applications use an estimator similar to that of Bang and Robins (2005) which van der Laan and Gruber (2011) refer to as the targeted maximum likelihood estimator. More recently, Molina et al. (2017) and Rotnitzky et al. (2017) showed that the DR estimator from Bang and Robins (2005) actually confers *more* protection to model misspecification than originally thought. For J total number of treatment time points, they showed that Bang and Robins' estimator is consistent as long as the first j models for the treatment processes and the last $J-j$ outcome regression models are correctly specified ($j = 0, \ldots, J$) and are therefore $J+1$ multiply robust.

Tchetgen Tchetgen (2009) first described a 2^J multiply robust augmented inverse probability weighted (AIPW) estimator for the mean outcome at the end of a longitudinal study under the monotone missing at random assumption. The estimator is 2^J multiply robust in the sense that it is consistent as long as one of the treatment or outcome regression models is correctly specified at each time point. However, this estimator may fall outside the parameter space.

Rotnitzky et al. (2017) provided a new class of estimators that are 2^J multiply robust and are sample-bounded (i.e., they fall within the parameter space with probability 1). Similarly, Luedtke et al. (2018) extended the targeted maximum-likelihood estimator to an infinite-dimensional targeted maximum-likelihood estimator that also allows for 2^J multiply robustness. However, neither Rotnitzky et al. (2017) nor Luedtke et al. (2018) outline and compare multiply robust estimators for survival outcomes rigorously. The contributions of our paper to the doubly and multiply robust estimation literature include (1) an overview of estimators to make causal inference for survival outcomes and how they are related to the AIPW estimator. These estimators include existing ones as well as our new proposals, which include an extension of 2^J multiply robust of Rotnitzky et al. (2017) to survival outcomes; (2) an illustration of this extension in simulation studies and data application, which to the best of our knowledge has not been done in the past; and (3) and a proposal to improve the efficiency of multiply robust estimators when the models for the treatment process is correctly specified but the outcome regression models are misspecified.

Our paper will be organized as follows. In the Section 2, we define the observed data structure, the causal estimand of interest, and the assumptions to identify the causal estimand. In Section 3, we describe the ICE estimator and the IPW estimator for the g-formula. In Sections 4 and 5, we describe an AIPW estimator and present two other $J+1$ multiply robust estimators for survival outcomes. In Section 6, we modify the 2^J multiply robust estimator from Rotnitzky et al. (2017) for failure-time outcomes. In Section 7 we propose a modification to improve efficiency in the multiply robust estimators, and in Sections 8 and 9, compare their performance through simulation studies and an application to data from the US Veterans Aging Cohort Study. In Section 10, we compare and discuss some practical implications of these estimators.

2 | OBSERVED DATA STRUCTURE, COUNTERFACTUAL CONTRASTS, AND IDENTIFYING ASSUMPTIONS

We first introduce some notation for longitudinal studies with time-varying treatments and confounders. Let $j = 0, 1, 2, \dots, J$ represent the month of follow-up where J is the end of follow-up of interest. Let A_j denote the observed time-varying binary treatment indicator, L_j denote a vector of observed time-varying confounders, and Y_j denote an indicator of survival during time interval j (i.e., $Y_j = 1$ if subject is alive during interval j and 0 otherwise). We observe n independent and identically distributed sample of $(L_0, A_0, Y_1, \dots L_{J-1}, A_{J-1}, Y_J)$. If $Y_j = 0$, then $L_j = A_j = \dots = L_{J-1} = A_{J-1} = \emptyset$ and $Y_{j+1} = \dots Y_J = 0$. For a random variable X, let $\overline{X}_j = (X_0, \dots, X_j)$ denote its history through time j. By definition, $Y_0 = 1$, $\overline{L}_{-1} = \emptyset$ and $\bar{A}_{-1} = 0$. Throughout this paper, we let $\text{expit}(u) = \{1 + \exp(-u)\}^{-1}$, $\text{logit}(u) = \log\{u/(1-u)\}$ and $\mathbb{P}_n(X) = n^{-1}\sum_{i=1}^{n} X_i$.

A treatment strategy is a rule that assigns treatment at each time j as an independent draw from an intervention distribution $f^{\text{int}}(a_j | Y_j = 1, \bar{l}_j, \bar{a}_{j-1})$ that may, at most, depend on $(\bar{a}_{j-1}, \bar{l}_j)$, which is a realization of $(\bar{A}_{j-1}, \overline{L}_j)$ (Hernán & Robins, 2020; Robins, 1986). Treatment strategies are deterministic if at each time point j, $f^{\text{int}}(a_j | Y_j = 1, \bar{l}_j, \bar{a}_{j-1})$ either equals 0 or 1 for all $(\bar{l}_j, \bar{a}_{j-1})$. Otherwise, the treatment strategy is random. In this paper, we will focus on deterministic treatment strategies. Extensions to random treatment strategies will be reported elsewhere. We denote $g = \{g_j(\bar{a}^g_{j-1}, \bar{l}_j); j = 0, \dots, J-1\}$ as the deterministic treatment strategy defined by $f^{\text{int}}(a_j | Y_j = 1, \bar{l}_j, \bar{a}^g_{j-1}) = 1$ if $a_j = a^g_j$ and 0 otherwise, where $a^g_j = g_j(\bar{a}^g_{j-1}, \bar{l}_j)$ is the treatment value assigned at time j under g (for $j = 0, \dots, J-1$).

A treatment strategy is static if the rule for assigning treatment at each time point does not depend on past covariates. For example, a static treatment strategy is 'initiate antiretroviral therapy at time 0 and continue to treat during the study,' which corresponds to $a_j^g = 1$ for all j and for any $(\bar{a}_{j-1}, -l_j)$. Otherwise, a treatment strategy is dynamic if it depends on the history of time-varying covariates. An example of a dynamic treatment strategy is `initiate antiretroviral therapy (ART) when CD4 cell count drops below x cells per μL.

Let Y_j^g denote the counterfactual outcome had an individual followed a treatment strategy g at time j (for $j = 1, \ldots, J$). We are interested in the intervention specific probability of survival at time J. For identifiability, we make the following assumptions sequentially at each time point j for treatment strategy g. These assumptions include:

(1) Exchangeability: $(Y_{j+1}^g, \ldots, Y_J^g) \perp\!\!\!\perp A_j | \bar{L}_j = \bar{l}_j, \bar{A}_{j-1} = \bar{a}_{j-1}^g, Y_j = 1$
(2) Positivity: $f_{\bar{L}_j, \bar{A}_{j-1}, Y_j}(\bar{l}_j, \bar{a}_{j-1}^g, 1) > 0 \rightarrow f_{A_j | \bar{L}_j, \bar{A}_{j-1}, Y_j}(a_j^g | \bar{l}_j, \bar{a}_{j-1}^g, 1) > 0$
(3) Consistency: If $\bar{A}_j = \bar{A}_j^g$ then $\overline{Y}_{j+1} = \overline{Y}_{j+1}^g$ and $\overline{L}_{j+1} = \overline{L}_{j+1}^g$

Provided that these assumptions hold, the counterfactual probability of survival defined as the parameter $\mu \equiv \mathrm{E}(Y_J^g)$ under $g$can be estimated from the observed data and written as the g-formula (Robins, 1986), which can also be expressed as a series of ICE:

$$\mathrm{E}\left(\mathrm{E}\left[\ldots \mathrm{E}\left\{\mathrm{E}(Y_J | \overline{Y}_{J-1}, \overline{L}_{J-1}, \bar{A}_{J-1} = \bar{A}_{J-1}^g) | \overline{Y}_{J-2}, \overline{L}_{J-2}, \bar{A}_{J-2} = \bar{A}_{J-2}^g\right\} \ldots | L_0, A_0 = A_0^g\right]\right). \quad (1)$$

To fix ideas, we assume that there is no censoring due to incomplete follow-up. Extensions of the estimators described herein that allow for censoring in the observed data are described in Web Appendix J in the Supplementary Materials. In the next section, we briefly review the IPW and the ICE estimators. They correspond to two different representations of the g-formula for the probability of survival under g. Another estimator of this g-formula is the parametric g-formula estimator (Young et al., 2011, 2014), the details of which are outside the scope of this paper.

3 | SINGLY ROBUST ESTIMATORS

3.1 | IPW estimator

The IPW estimator upweights the outcomes of those who followed treatment strategy g to account for those who did not follow the strategy. Let $h_j = h_j(\bar{L}_j, \bar{A}_j, Y_j = 1) = f(A_j | \bar{A}_{j-1}, \bar{L}_j, Y_j = 1)$ and $\pi_j = \pi_j(\bar{L}_j, \bar{A}_j, Y_j = 1) = \prod_{k=0}^{j} h_k$. Furthermore, let $\hat{h}_j$ and $\hat{\pi}_j$ denote the corresponding estimates for h_j, π_j, respectively. An unbounded Horvitz–Thompson IPW estimator $\hat{\mu}_{\mathrm{IPW,HT}}$ for the probability of survival at time J under treatment strategy g can be obtained from the following:

$$\hat{\mu}_{\mathrm{IPW,HT}} = \mathbb{P}_n \left\{ \frac{I(\bar{A}_{J-1} = \bar{A}_{J-1}^g)}{\hat{\pi}_{J-1}} Y_J \right\}. \quad (2)$$

The estimator $\hat{\mu}_{\text{IPW,HT}}$ in (2), however, is not guaranteed to lie within [0, 1] (Robins et al., 2007). To see this, suppose that at time J there are 1000 at-risk individuals, and there is a subject alive at $J$with $I(\bar{A}_{J-1} = \bar{A}^g_{J-1}) = 1$ whose $\hat{\pi}_{J-1}$ is less than 1/10,000. In this case $\hat{\mu}_{\text{IPW,HT}} > 10$, which is logically impossible for a binary outcome. To circumvent this problem, we study the following IPW estimator, which is sample-bounded in the sense that the estimated value of $\text{E}(Y^g_J)$ will always be within the [0, 1] range. A bounded IPW estimator $\hat{\mu}_{\text{IPW,BD}}$ can be obtained as a product of J conditional probabilities of survival or $\hat{\mu}_{\text{IPW,BD}} = \prod_{j=0}^{J-1} \hat{\Upsilon}_{\text{IPW},j}$. Here, $\hat{\Upsilon}_{\text{IPW},j}$ is the estimated conditional probability of survival at time j given survival at time $j-1$ under treatment strategy g and can be obtained by solving for $\Upsilon_{\text{IPW},j}$ in the following estimating equations:

$$\mathbb{P}_n \left\{ Y_j \frac{I(\bar{A}_j = \bar{A}^g_j)}{\hat{\pi}_j} (Y_{j+1} - \Upsilon_{\text{IPW},j}) \right\} = 0. \tag{3}$$

The estimator $\hat{\mu}_{\text{IPW,BD}}$ uses conditional probabilities of survival from previous time points. Moreover, $\hat{\Upsilon}_{\text{IPW},j}$ will always be bounded between 0 and 1 because it is a convex combination of the observed Y_{j+1}-values, and thus $\hat{\mu}_{\text{IPW,BD}}$ will always be bounded between [0, 1]. For these reasons, $\hat{\mu}_{\text{IPW,BD}}$ generally be much more efficient and stable than $\hat{\mu}_{\text{IPW,HT}}$ (Neugebauer et al., 2016). Nonparametric estimation of the propensity score (or probability of treatment assignment) may not be feasible when L_j is high-dimensional, but we can impose, for example, working models $h_j(\alpha_j) = f(A_j|\bar{A}_{j-1}, \overline{L}_j, Y_j = 1; \alpha_j)$ for h_j. Henceforth, for ease of exposition we assume that the initial estimate $h_j(\hat{\alpha}_j)$ of h_j is obtained by computing the maximum likelihood estimate (MLE) $\hat{\alpha}_j$ of α_j from the observed data, and we shall le t $\pi_j(\hat{\alpha}) = \prod_{k=0}^{j} h_k(\hat{\alpha}_k)$.

3.2 | Iterative conditional expectation estimator

The ICE estimator requires one to iteratively standardize over past outcomes, treatment and confounders to estimate expression (1). We describe an ICE estimator of the probability of survival at time J under treatment strategy g. Let $T_J = Y_J$. Iteratively from $j = J-1, \ldots, 0$, let $T_j \equiv T_j(\overline{L}_j, \overline{Y}_j, \bar{A}_j = \bar{A}^g_j) = \text{E}(T_{j+1}|\overline{L}_j, \bar{A}_j = \bar{A}^g_j, \overline{Y}_j)$. In particular, it can be shown that $T_j = \text{E}(T_{j+1}|\overline{L}_j, \bar{A}_j = \bar{A}^g_j, Y_j = 1)$ if $Y_j = 1$ and $T_j = 0$ if $Y_j = 0$. We can impose working outcome regression models for T_j to obtain predictions $\hat{T}_j$ when $Y_j = 1$. Note that for $j < J$, $\hat{T}_j$ is a predicted value of T_j taking value in [0, 1]. For $j < J-1$, $\hat{T}_j$ can be estimated by fitting a generalized linear model on $\hat{T}_{j+1}$ and specifying a quasi-binomial family with a logit link function (Papke & Wooldridge, 2008). This type of regression is known as fractional logistic regression. The ICE estimator algorithm is as follows:

1. Set $\hat{T}_J = Y_J$ and set $q = 1$.
2. Let $j = J - q$: For those whose $Y_j = 1$ and who followed the strategy $\bar{A}_j = \bar{A}^g_j$, fit a regression model $\eta(\overline{L}_j; \theta_j) = \text{expit}\{\theta_j^T \phi(\overline{L}_j)\}$ for the conditional expectation $\text{E}(\hat{T}_{j+1}|\overline{L}_j, \bar{A}_j = \bar{A}^g_j, Y_j = 1)$, where $\phi(\overline{L}_j)$ is a known function of $\overline{L}_j$.
3. Set $\hat{T}_j = \eta_j(\overline{L}_j; \hat{\theta}_j)$ for those whose $(Y_j, \bar{A}_{j-1}) = (1, \bar{A}^g_{j-1})$. $\hat{T}_j = 0$ if $Y_j = 0$. If $q < J$, then $q = q + 1$ and return to step 2.
4. Calculate the ICE estimator $\hat{\mu}_{ICE} = \mathbb{P}_n(\hat{T}_0)$.

4 | AIPW ESTIMATOR

In this section, we describe Robins and colleague's AIPW estimator (Bang & Robins, 2005; Robins, 2000; Robins et al., 1994; Rotnitzky et al., 2017) for failure-time outcomes to estimate the probability of survival at time J under treatment strategy g. This estimator is a DR estimator in the sense that it provides consistent estimates of the mean of the counterfactual outcome as long as either (1) all of the models for the treatment process are correctly specified or (2) all of the outcome regression models for T_j are correctly specified. We define a *standard* AIPW estimator that assumes, for each j, a logistic regression model for h_j indexed by α_j which is estimated by its MLE $\hat{\alpha}_j$, and uses the estimators $\hat{T}_j$ computed in the preceding algorithm (i.e., via ICE). We distinguish the *general*AIPW estimator from the standard AIPW estimator in that the estimators $\hat{h}_j$, $\hat{\pi}_j$ and $\hat{T}_j$ for h_j, π_j and T_j are not yet specified in the general AIPW estimator. We do so because how one estimates h_j, π_j, and T_j can markedly change the properties of the standard AIPW estimator, as we demonstrate later. The general AIPW estimator $\hat{\mu}_{\text{AIPW}}$ for $\text{E}(Y_J^g)$ is defined as:

$$\hat{\mu}_{\text{AIPW}} = \mathbb{P}_n \left\{ Y_{J-1} \frac{I(\bar{A}_{J-1} = \bar{A}^g_{J-1})}{\hat{\pi}_{J-1}} (Y_J - \hat{T}_{J-1}) + \sum_{j=0}^{J-2} Y_j \frac{I(\bar{A}_j = \bar{A}^g_j)}{\hat{\pi}_j} (\hat{T}_{j+1} - \hat{T}_j) + \hat{T}_0 \right\}, \tag{4}$$

which can also be rewritten as

$$\hat{\mu}_{\text{AIPW}} = \mathbb{P}_n \left[\frac{I(\bar{A}_{J-1} = \bar{A}^g_{J-1})}{\hat{\pi}_{J-1}} Y_J - \sum_{j=0}^{J-1} \hat{T}_j Y_j \frac{I(\bar{A}_{j-1} = \bar{A}^g_{j-1})}{\hat{\pi}_{j-1}} \left\{ \frac{I(A_j = A^g_j)}{\hat{h}_j} - 1 \right\} \right]. \tag{5}$$

In what follows, we define $\hat{\Sigma} = \mathbb{P}_n \left[\sum_{j=0}^{J-1} \hat{T}_j Y_j I(\bar{A}_{j-1} = \bar{A}^g_{j-1}) \hat{\pi}^{-1}_{j-1} \left\{ I(A_j = A^g_j) \hat{h}^{-1}_j - 1 \right\} \right]$. The ICE and the two IPW estimators from Sections 3.1 and 3.2 can all be obtained from the standard AIPW estimator. Specifically, the ICE estimator from Section 3.2 can be obtained if $1/\pi_j(\hat{\alpha})$ is set to zero for all j in (4); the Horvitz–Thompson IPW estimators from Section 3.1 can be obtained if $\hat{\Sigma} = 0$ in (5) (e.g., by setting $\hat{T}_j$ to zero for all j); and the bounded IPW estimator from Section 3.1 can be obtained if $\hat{\Sigma} = 0$ *and* if $\hat{T}_j$ is set to 1 for all j in (5) (see Web Appendix D for a proof).

Suppose that $\mathcal{H}_j$ correspond to a class of working models for h_j and that $\mathcal{G}_j$ correspond to a class of working models for T_j. Then it can be shown following Scharfstein et al. (1999), Robins and Rotnitzky (2001), and Tsiatis (2006) that the standard AIPW estimator is consistent under $(\cap_{j=0}^{J-1} \mathcal{H}_j) \cup (\cap_{j=0}^{J-1} \mathcal{G}_j)$. Here, in a slight abuse of notation, $(\cap_{j=0}^{J-1} \mathcal{H}_j) \cup (\cap_{j=0}^{J-1} \mathcal{G}_j)$ denotes a model for the observed data law such that $\mathcal{H}_j$ holds for all j or $\mathcal{G}_j$ holds for all j. A formal proof of this is provided in Web Appendix A.

The right-hand side of (4) with $\hat{\pi}_j$ and $\hat{T}_j$ replaced by π_j and T_j minus the true μ is equal to the unique efficient influence function for μ under a nonparametric model that imposes no restrictions on the observed data law (see Web Appendix B). Furthermore, the standard AIPW estimator is locally efficient in the sense that, when all working models are correctly specified, it achieves the semi-parametric efficiency bound for estimating μ. However, analogous to the reasoning for the Horvitz–Thompson estimator described in Section 3.1, difficulties can arise when $\pi_j(\hat{\alpha})$ is close to 0 for some individuals, which can result in unbounded estimates for the standard AIPW estimator. In the next section, we describe estimators that are also based on the efficient influence function but are sample-bounded and locally efficient. The first is a weighted ICE

estimator, and the second is a bounded Horvitz–Thompson estimator. Both estimators guarantee sample-boundedness.

5 | ALTERNATIVE ESTIMATORS BASED ON THE EFFICIENT INFLUENCE FUNCTION

5.1 | Weighted ICE estimator

The weighted ICE estimator is a variation of the DR estimator introduced by Bang and Robins (2005) (see also Robins, 2000; Robins et al., 2007; Rotnitzky et al., 2017). The procedure for survival outcomes is as follows:

1. Compute the MLE $\hat{\alpha}_j$ of α_j from the observed data for $j = 0, \dots, J-1$.
2. Set $\hat{T}_J = Y_J$ and set $q = 1$.
3. Let $j = J - q$: For those whose $Y_j = 1$ and who followed the strategy $\bar{A}_j = \bar{A}_j^g$, fit a regression model $\eta(\overline{L}_j; \kappa_j) = \text{expit}\{\kappa_j^T \phi(\overline{L}_j)\}$ for $\mathrm{E}(\hat{T}_{j+1} | \overline{L}_j, \bar{A}_j = \bar{A}_j^g, Y_j = 1)$, where each observation is weighted by $\pi_j(\hat{\alpha})^{-1}$ and $\phi(\overline{L}_j)$ is a known function of $\overline{L}_j$. More specifically, solve for κ_j in the following estimating equations:

$$\mathbb{P}_n \left[Y_j \frac{I(\bar{A}_j = \bar{A}_j^g)}{\pi_j(\hat{\alpha})} \phi_j(\overline{L}_j) \left\{ \hat{T}_{j+1} - \eta_j(\overline{L}_j; \kappa_j) \right\} \right] = 0. \tag{6}$$

4. Set $\hat{T}_j = \eta_j(\overline{L}_j; \hat{\kappa}_j)$ for those whose $(Y_j, \bar{A}_{j-1}) = (1, \bar{A}_{j-1}^g)$. $\hat{T}_j = 0$ if $Y_j = 0$. If $q < J$, then $q = q + 1$ and return to step 3.
5. Calculate the weighted ICE estimator $\hat{\mu}_{\text{WICE}} = \mathbb{P}_n(\hat{T}_0)$.

There are three key observations: (1) it is trivial to see that if the propensity score model contains only the intercept, then $\hat{\mu}_{\text{WICE}} = \hat{\mu}_{\text{ICE}}$; (2) as long as '1' is a component in $\phi_j(\overline{L}_j)$, this ensures that $\mathbb{P}_n\{Y_j I(\bar{A}_j = \bar{A}_j^g)\pi_j^{-1}(\hat{\alpha})(\hat{T}_{j+1} - \hat{T}_j)\} = 0$ for all $j = 0, \dots, J-1$ (It then follows from Equation (4) that $\hat{\mu}_{\text{AIPW}} = \hat{\mu}_{\text{WICE}}$ provided that $\hat{\pi}_j = \pi_j(\hat{\alpha})$ and $\hat{T}_j$ is obtained from $\eta_j(\overline{L}_j; \hat{\kappa}_j)$ for all $j = 0, \dots, J-1$); 3) it can be shown that if $\phi_j(\overline{L}_j) = 1$ (i.e., $\eta_j(\overline{L}_j; \hat{\kappa}_j) = \text{expit}(\kappa_{j0})$) for all $j = 0, \dots, J-1$ then $\hat{\mu}_{\text{IPW,BD}} = \hat{\mu}_{\text{WICE}}$ (see Web Appendix C). This is intuitive, because if $\phi_j(\overline{L}_j) = 1$ then the weighted ICE estimator exploits no further information from the data beyond the propensity scores.

Robins et al. (2007) noted that the weighted ICE estimator will likely outperform the DR estimator of Bang and Robins (2005) when $\pi_j(\hat{\alpha})^{-1}$ is highly variable because $\pi_j(\hat{\alpha})^{-1}$ in Bang and Robins (2005) is used as a covariate in the models for T_j, which can lead to extrapolation problems in trying to obtain fitted values for the outcome. Another closely related estimator of the weighted ICE estimator is the targeted maximum likelihood estimator (van der Laan & Gruber, 2011). The difference between the targeted maximum likelihood estimator and the weighted ICE or Bang and Robins (2005) estimators is whether T_j is estimated greedily or not for all j (see Richardson & Rotnitzky, 2014; Rotnitzky et al., 2017 for more details). A comparison between the weighted ICE and the targeted maximum likelihood estimators was done by Tran et al. (2019) for survival outcomes, who found that both methods performed comparably while also outperforming the

standard AIPW and Bang and Robins' covariate-based DR estimator in terms of bias and mean squared error.

5.2 | Bounded Horvitz–Thompson estimator

In this section we propose an extension of the bounded Horvitz–Thompson estimator of Robins et al. (2007) to the longitudinal setting for both static and dynamic treatment strategies on survival outcomes. The bounded Horvitz–Thompson estimator aims to improve upon the initial estimate of $h_j(\hat{\alpha}_j)$ (with $\hat{\alpha}_j$ the MLE of α_j) by incorporating information from ICE to obtain a new estimator that has the double robustness property. The procedure is as follows:

1. Compute the MLE $\hat{\alpha}_j$ of α_j from the observed data for $j = 0, \ldots, J-1$, and obtain $\hat{T}_j$ iteratively using ICE from $j = J-1, \ldots, 0$.
2. Iteratively from $j = 0, \ldots, J-1$, solve for γ_j in the following set of estimating equations by setting $\text{logit}\{h_j(\hat{\alpha}_j)\}$ as an offset:

$$\mathbb{P}_n \left[Y_j \frac{I(\bar{A}_{j-1} = \bar{A}^g_{j-1})}{\pi^{\Delta}_{j-1}(\hat{\alpha}, \hat{\gamma}, \hat{\theta})} \left\{ \frac{I(A_j = A^g_j)}{h^{\Delta}_j(\hat{\alpha}_j, \gamma_j, \hat{\theta}_j)} - 1 \right\} s_j(\overline{L}_j; \hat{\theta}_j) \right] = 0, \tag{7}$$

   where $s_j(\overline{L}_j; \hat{\theta}_j) = (1, \hat{T}_j)^T$, $h^{\Delta}_k(\hat{\alpha}_k, \gamma_k, \hat{\theta}_k) = \text{expit}\{\text{logit}(h_k(\hat{\alpha}_k)) + \gamma_k^T s_k(\overline{L}_k; \hat{\theta}_k)\}$, and $\pi^{\Delta}_j(\hat{\alpha}, \hat{\gamma}, \hat{\theta}) = \prod_{k=0}^{j} h^{\Delta}_k(\hat{\alpha}_k, \hat{\gamma}_k, \hat{\theta}_k)$.
3. Calculate:

$$\hat{\mu}_{\text{BHT}} = \mathbb{P}_n \left\{ \frac{I(\bar{A}_{J-1} = \bar{A}^g_{J-1})}{\pi^{\Delta}_{J-1}(\hat{\alpha}, \hat{\gamma}, \hat{\theta})} Y_J \right\}.$$

We emphasize that the term $s_j(\overline{L}_j; \hat{\theta}_j)$ is equal to $(1, \hat{T}_j)^T$ for all $j = 0, \ldots, J-1$. The constant '1' ensures that the estimate of $\text{E}(Y^g_J)$ is bounded between $[0, 1]$ (see Web Appendix F). The inclusion of $\hat{T}_j$ in $s_j(\overline{L}_j; \hat{\theta}_j)$ ensures that $\hat{\Sigma} = 0$ in Equation (5). Therefore, it can be shown from Equation (4) that $\hat{\mu}_{\text{AIPW}} = \hat{\mu}_{\text{BHT}}$ provided that $\hat{\pi}_j = \pi^{\Delta}_j(\hat{\alpha}, \hat{\gamma}, \hat{\theta})$ and $\hat{T}_j$ is obtained from ICE for all $j = 0, \ldots, J-1$ (see Web Appendix F).

Note that the sum of the weighted outcomes in those who followed the treatment strategy g, $\mathbb{P}_n\{Y_j I(\bar{A}_j = \bar{A}^g_j)/\pi^{\Delta}_j(\hat{\alpha}, \hat{\gamma}, \hat{\theta})\}$, is no greater than the sample size n at each time point. This idea is used for calibration weighting in the survey sampling literature (Deville & Särndal, 1992). Like the stabilized weights discussed in Robins et al. (2000), it ensures that the estimated propensity scores do not vary too much between individuals, thereby improving the stability of the IPW estimator for the counterfactual probability of survival (Cao et al., 2009; Vansteelandt et al., 2012). For this reason, Vansteelandt et al. (2012) noted that this form of estimation of the propensity scores is a "stabilized estimation" procedure. Henceforth, we will call the propensity scores estimates $h_j(\hat{\alpha}_j)$ (obtained from MLE) 'non-calibrated propensity scores,' and the propensity score estimates $h^{\Delta}_j(\hat{\alpha}_j, \hat{\gamma}_j, \hat{\theta}_j)$ 'calibrated propensity scores.'

Let $L(\gamma_j)$ be a function defined as follows:

$$L(\gamma_j) = \mathbb{P}_n \left\{ Y_j \frac{I(\bar{A}_{j-1} = \bar{A}^g_{j-1})}{\pi^{\Delta}_{j-1}(\hat{\alpha}, \hat{\gamma}, \hat{\theta})} \left[-I(A_j = A^g_j) e^{\{-\text{logit}\{h_j(\hat{\alpha}_j)\} - \gamma_j^T s_j(\overline{L}_j; \hat{\theta}_j)\}} - \{1 - I(A_j = A^g_j)\} \gamma_j^T s_j(\overline{L}_j; \hat{\theta}_j) \right] \right\}.$$

Solving for $\hat{\gamma}_j$ that maximizes $L(\gamma_j)$ is equivalent to solving Equation (7) because $\partial L(\gamma_j)/\partial\gamma_j$ equals to the left-hand side of (7). The estimator $\hat{\gamma}_j$ that maximizes $L(\gamma_j)$ will be unique as long as $L(\gamma_j)$ is strictly concave and bounded from above, which will be true as long as the set $\{\gamma_j \neq 0 : \gamma_j^T s_j(\overline{L}_{ij};\hat{\theta}_j) \geq 0, \textit{ for } i = 1,\ldots,n \textit{ with } I(\bar{A}_{ij} = \bar{A}_{ij}^g) = 1, \textit{ and } \mathbb{P}_n[Y_j I(\bar{A}_{j-1} = \bar{A}_{j-1}^g)\{1 - I(A_j = A_j^g)\}\pi_{j-1}^{\Delta}(\hat{\alpha},\hat{\gamma},\hat{\theta})^{-1}\gamma_j^T s_j(\overline{L}_j;\hat{\theta}_j)] \leq 0\}$ is empty (see Tan, 2010 and Vermeulen & Vansteelandt, 2015 for an analogous proof). This condition amounts to some form of nonseparation based on the predictor $\gamma_j^T s_j(\overline{L}_j;\hat{\theta}_j)$ between the treated and untreated groups at time j (Tan, 2020). Unlike the weighted ICE estimator, the calibrated propensity scores cannot be solved using standard off-the-shelf statistical regression software. Instead, we can solve for the calibrated propensity scores using the R optimization/root-solving packages nleqslv (Hasselman, 2018).

Note that the bounded Horvitz–Thompson estimator $\hat{\mu}_{\text{BHT}}$ is equivalent to the bounded IPW estimator $\hat{\mu}_{\text{IPW,BD}}$ in Section 3.1 if we estimate π_j by the calibrated propensity scores in Equation (3). This follows from the fact that $\hat{\mu}_{\text{IPW,BD}} = \hat{\mu}_{\text{AIPW}}$ provided that when $\hat{T}_j = 1$ (for all j), $\hat{\Sigma}$ equals 0 in Equation (5)—a condition that is fulfilled under the calibrated weights. A proof can be found in Web Appendix D. This also explains the stability and boundedness of the bounded Horvitz–Thompson estimators: under the calibrated weights, the Horvitz–Thompson and the bounded IPW estimators are equivalent.

Figure 1 shows the relationships between the various estimators that we have discussed thus far via their relationships to the general AIPW estimator. These allow us to understand why some estimators are double robust while others are not.

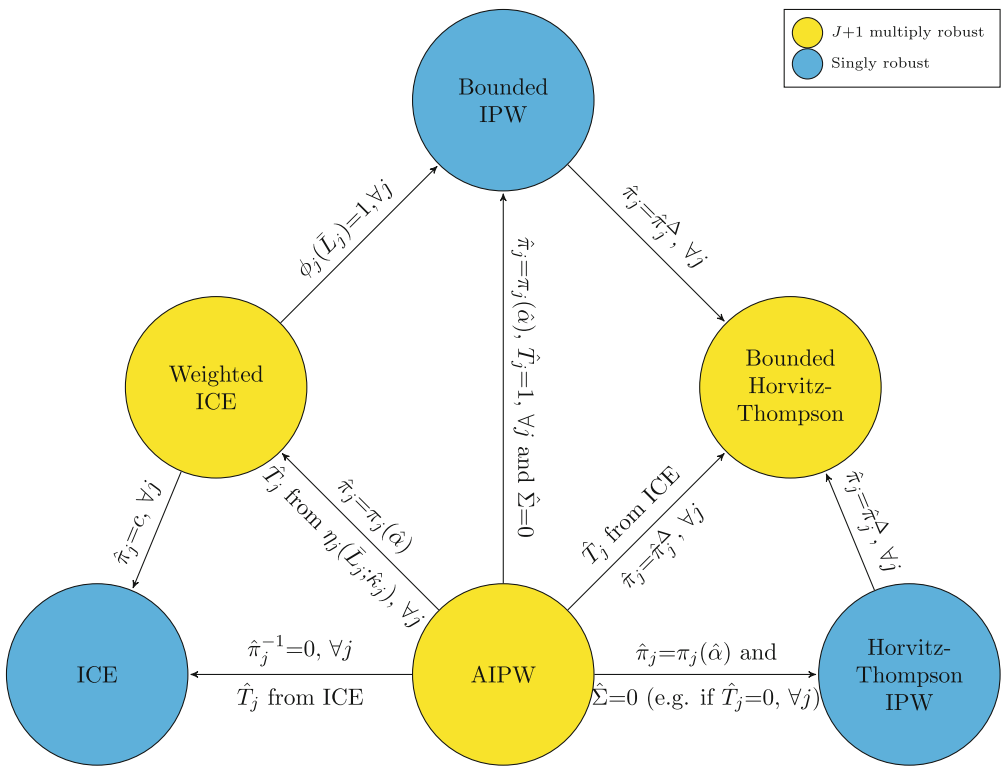

FIGURE 1 Relationship between various singly and multiply robust estimators; →: can be made to equal

5.3 | The standard AIPW, weighted ICE and bounded Horvitz–Thompson estimators are $J+1$ multiply robust

Molina et al. (2017) and Rotnitzky et al. (2017) recently showed that the DR estimator from Bang and Robins (2005) is actually $J+1$ multiply robust in the sense that as long as the first j models for the treatment processes and the last $J-j$ outcome regression models are correctly specified ($j=0,\dots,J$) then it will be consistent and asymptotically normal. In fact, in Web Appendices E and F we show that the standard AIPW estimator described in Section 4 is also $J+1$ multiply robust, which implies so are the weighted ICE and the bounded Horvitz–Thompson estimators. Mathematically, it can be shown that the general AIPW estimator can potentially be 2^J multiply robust, but not if $\hat{T}_j$ is estimated from ICE or weighted ICE as we presented above. This follows from the fact that where $\hat{T}_j$ is estimated from ICE or weighted ICE, outcome regression model misspecification at one iteration is propagated to subsequent iterations and thus such an estimator will be biased even if the outcome regression models in subsequent iterations are all correctly specified. In order for the general AIPW estimator to be 2^J multiply robust, the misspecification from an outcome regression model at time $j+1$ cannot affect the consistent estimation of the conditional mean outcome at time j under a correctly specified outcome regression model at time j. One way to ensure this is to restrict $1 \subset \phi_j(\bar{L}_j) \subset \phi_{j+1}(\bar{L}_{j+1}), \forall j$ in the weighted ICE estimator (Rotnitzky et al., 2017). The same is not true for the bounded Horvitz–Thompson estimator with the exception of continuous outcomes. Henceforth, this modified estimator will be referred to as the *restricted* weighted ICE estimator. It follows then that the restricted weighted ICE estimator ($\hat{\mu}_{2J,\text{rWICE}}$) is consistent and asymptotically normal under $\cap_{j=0}^{J-1}(\mathcal{H}_j \cup \mathcal{G}_j)$. Here, in a slight abuse of notation, $\cap_{j=0}^{J-1}(\mathcal{H}_j \cup \mathcal{G}_j)$ denotes a model for the observed data law such that for each time point $j \in \{0,\dots,J-1\}$, at least one of $\mathcal{H}_j$ or $\mathcal{G}_j$ holds. This estimator then confers more protection to model misspecification compared with the weighted ICE estimator and the bounded Horvitz–Thompson estimator, which are consistent under $\cup_{j=0}^{J}\{(\cap_{k=0}^{j-1}\mathcal{H}_k) \cap (\cap_{k=j}^{J-1}\mathcal{G}_k)\}$. Here, in a slight abuse of notation, $\cup_{j=0}^{J}\{(\cap_{k=0}^{j-1}\mathcal{H}_k) \cap (\cap_{k=j}^{J-1}\mathcal{G}_k)\}$ denotes a model for the observed data law such that for some $j \in \{0,\dots,J\}$, $\mathcal{H}_k$ holds for $0 \le k \le j-1$ and $\mathcal{G}_k$ holds for $j \le k \le J-1$. The condition that $1 \subset \phi_j(\bar{L}_j) \subset \phi_{j+1}(\bar{L}_{j+1}), \forall j$ is quite restrictive when J is large and/or when there are many confounders. Instead, in the next section we describe a 2^J multiply robust estimator that relaxes this requirement.

6 | A 2^J MULTIPLY ROBUST ESTIMATOR OF THE CAUSAL ESTIMAND

In this section, we modify the 2^J robust estimator given in Rotnitzky et al. (2017) that relaxes the restrictions on the $\phi(\bar{L}_j)$ coefficients as stated above to accommodate survival outcomes. In our estimator, we let $\hat{T}^{(0)}_{J,\text{MR}} = \dots = \hat{T}^{(J-1)}_{J,\text{MR}} = Y_J$ and we assume that $1 \subset \phi(L_0)$. The procedure is as follows:

1. Compute the MLE $\hat{\alpha}_j$ of α_j from the observed data for all $j=0,\dots,J-1$.
2. Iteratively, from $j=J-1$ to 1:
   (a) Solve for θ_j in the following estimating equations using a regression model:

$$\mathbb{P}_n\left(Y_j I(\bar{A}_j = \bar{A}_j^g)\phi(\bar{L}_j)\left[\hat{T}^{(j)}_{j+1,\text{MR}} - \text{expit}\{\theta_j^T\phi(\bar{L}_j)\}\right]\right) = 0$$

(b) Iteratively from $k = j-1$ to 1 ($k \geq 1$), solve for $\zeta_{k,j}$ in the following estimating equations using a weighted regression model with the offset $\hat{\theta}_j^T \phi(\bar{L}_j) + \sum_{m=k+1}^{j-1} \hat{\xi}_{m,j}^T \phi(\bar{L}_m)$:

$$\mathbb{P}_n \left(Y_j \frac{I(\bar{A}_j = \bar{A}_j^g)\phi(\bar{L}_k)}{\prod_{m=k+1}^{j} h_m(\hat{\alpha}_m)} \left[\hat{T}_{j+1,MR}^{(k)} - \text{expit} \left\{ \hat{\theta}_j^T \phi(\bar{L}_j) + \sum_{m=k+1}^{j-1} \hat{\xi}_{m,j}^T \phi(\bar{L}_m) + \zeta_{k,j}^T \phi(\bar{L}_k) \right\} \right] \right) = 0.$$

(c) For $k = 0$, solve for $\zeta_{0,j}$ in the following estimating equations using a weighted regression model with the offset $\hat{\theta}_j^T \phi(\bar{L}_j) + \sum_{m=1}^{j-1} \hat{\xi}_{m,j}^T \phi(\bar{L}_m)$:

$$\mathbb{P}_n \left(Y_j \frac{I(\bar{A}_j = \bar{A}_j^g)\phi(L_0)}{\pi_j(\hat{\alpha})} \left[\hat{T}_{j+1,MR}^{(0)} - \text{expit} \left\{ \hat{\theta}_j^T \phi(\bar{L}_j) + \sum_{m=1}^{j-1} \hat{\xi}_{m,j}^T \phi(\bar{L}_m) + \zeta_{0,j}^T \phi(L_0) \right\} \right] \right) = 0.$$

(d) For those who followed the treatment strategy through time $j-1$ and survived through time j, predict

$$\hat{T}_{j,\text{MR}}^{(k)} = \text{expit} \left\{ \hat{\theta}_j^T \phi(\bar{L}_j) + \sum_{m=k}^{j-1} \hat{\xi}_{m,j}^T \phi(\bar{L}_m) \right\},$$

for $k = 0, \ldots, j-1$. Set $\hat{T}_{j,\text{MR}}^{(k)}$ to zero for those who did not survive through time j.

3. Solve for θ_0 in the following estimating equations using a weighted regression model:

$$\mathbb{P}_n \left(\frac{I(A_0 = A_0^g)}{h_0(\hat{\alpha}_0)} \phi(L_0) \left[\hat{T}_{1,\text{MR}}^{(0)} - \text{expit}\{\theta_0^T \phi(L_0)\} \right] \right) = 0.$$

4. Set $\hat{T}_{0,\text{MR}}^{(0)} = \text{expit}\{\hat{\theta}_0^T \phi(L_0)\}$ for every subject and calculate $\hat{\mu}_{2J,\text{RRB}} = \mathbb{P}_n(\hat{T}_{0,\text{MR}}^{(0)})$.

An example of this estimator for $J = 2$ is given in Web Appendix G. Note that from Equation (4) it can be shown that $\hat{\mu}_{\text{AIPW}} = \hat{\mu}_{2J,\text{RRB}}$ provided that $\hat{\pi}_j = \pi_j(\hat{\alpha})$ and $\hat{T}_j$ is obtained from $\hat{T}_{j,\text{MR}}^{(0)}$ for all $j = 0, \ldots, J-1$, respectively.

7 | IMPROVEMENTS ON THE MULTIPLY ROBUST ESTIMATORS

Along the lines of Tan (2006, 2010), Cao et al. (2009), Rotnitzky et al. (2012), and Han (2016), we aim to find estimators that are guaranteed to be more efficient than the IPW and standard AIPW estimators when the propensity score models are correctly specified but the outcome regression models are not necessarily correctly specified. This may be the case, for example, in a sequentially randomized trial where the propensity scores are known in advance by design (Benkeser et al., 2020; Wang et al., 2012). It is well known that in this scenario the IPW and standard AIPW estimators that use the estimated propensity score are more efficient than those that use the true propensity score (Rotnitzky & Robins, 1995). To accomplish this, we will describe an *efficient* calibration structure for the propensity scores in the bounded Horvitz–Thomspon estimator.

Instead of solving for γ_j in the estimating Equations (7) in the bounded Horvitz–Thompson estimator, we solve for

$$\mathbb{P}_n\left[Y_j\frac{I(\bar{A}_{j-1}=\bar{A}^g_{j-1})}{\pi^{\text{eff}}_{j-1}(\hat{\alpha},\hat{\gamma},\hat{\theta})}\left\{\frac{I(A_j=A^g_j)}{h^{\text{eff}}_j(\hat{\alpha}_j,\gamma_j,\hat{\theta}_j)}-1\right\}s_j(\bar{L}_j;\hat{\theta}_j)\right]=0, \tag{8}$$

where

$$h^{\text{eff}}_j(\hat{\alpha}_j,\gamma_j,\hat{\theta}_j)=\text{expit}\left[\text{logit}\left\{h_j(\hat{\alpha}_j)\right\}+\frac{\gamma_j^T}{\pi_j(\hat{\alpha})}s_j(\bar{L}_j;\hat{\theta}_j)\right],$$

$\pi^{\text{eff}}_j(\hat{\alpha},\hat{\gamma},\hat{\theta})=\prod_{k=0}^{j}h^{\text{eff}}_k(\hat{\alpha}_k,\hat{\gamma}_k,\hat{\theta}_k)$ and $s_j(\bar{L}_j;\hat{\theta}_j)=(1,\hat{T}_j)^T$. Then, as before, we solve for $\hat{\mu}_{\text{BHT,eff}}$ by taking the average of Y_J weighted by the calibrated propensity scores in those who followed the treatment strategy until time J. Han (2016) took a similar approach to deal with missing data using a bounded Hajek estimator, but did not consider survival outcomes or a causal framework. Moreover, they did not consider the logistic form of calibration for $h^{\text{eff}}_j(\hat{\alpha}_j,\hat{\gamma}_j,\hat{\theta}_j)$, which have been used in the past for point-treatment processes (Robins et al., 2007; Tan, 2020; Vermeulen & Vansteelandt, 2015). Instead, they consider two other calibration structures for the propensity scores—multiplicative and additive. Unlike the logistic structure, these calibration structures do not ensure that the estimated propensity scores fall within the parameter space of 0 and 1, making them harder to interpret and also allowing for extrapolation beyond this range. Interestingly $h^{\text{eff}}_j(\hat{\alpha}_j,\hat{\gamma}_j,\hat{\theta}_j)$ is similar to the propensity score model proposed by Rotnitzky and Robins (1995) for their IPW estimator. However, unlike Rotnitzky and Robins (1995) we update the propensity scores by solving for γ_j in Equation (8) instead of the MLE of $(\alpha_j,\gamma_j)^T$ to ensure multiple robustness as well as sample boundedness of our estimator.

Let $(\mu^*,\gamma^*,\theta^*,\alpha^*)$ denote the probability limits of $(\mu,\gamma,\theta,\alpha)$. Let $T^*_j=\eta_j(\bar{L}_j;\theta^*_j)$ when $Y_j=1$ and let $T^*_j=0$ when $Y_j=0$. When the model for the treatment process is correctly specified, then $\alpha^*=\alpha$, $\gamma^*=\gamma=0$ and $\mu^*=\mu$. Let

$$\Psi(\mu,\gamma,\theta^*,\alpha)=Y_{J-1}\frac{I(\bar{A}_{J-1}=\bar{A}^g_{J-1})}{\pi_{J-1}}(Y_J-T^*_{J-1})+\sum_{j=0}^{J-2}Y_j\frac{I(\bar{A}_j=\bar{A}^g_j)}{\pi_j}(T^*_{j+1}-T^*_j)+T^*_0-\mu.$$

Moreover, let

$$M_j=Y_j\frac{I(\bar{A}_{j-1}=\bar{A}^g_{j-1})}{\pi_{j-1}}\left\{\frac{I(A_j=A^g_j)}{h_j}-1\right\}s^*_j,$$

where $s^*_j=(1,T^*_j)^T$, and let $\Omega_j=\{\text{span}(M_j)\}$ denote the linear subspace in the Hilbert space $\mathcal{H}$ spanned by M_j. Let $\Omega=\{\text{span}(\omega):\ \omega=[M_0^T,\ldots,M_{J-1}^T]^T\}=\Omega_0\oplus\Omega_1\oplus\ldots\oplus\Omega_{J-1}$, where the direct sum $\oplus$ indicates orthogonality of Ω_j. Let λ denote the scores functions corresponding to the propensity scores model parameters α obtained from MLE and let $\Lambda=\{\text{span}(\lambda)\}$ denote the linear subspace in $\mathcal{H}$ spanned by λ. In the Web Appendix H, we show that the asymptotic variance of $n^{1/2}(\hat{\mu}_{\text{BHT,eff}}-\mu)$ is equal to the variance of $\Psi(\mu,\gamma,\theta^*,\alpha)-\Pi[\Psi(\mu,\gamma,\theta^*,\alpha)|\Gamma]$, where $\Gamma=\{\text{span}(\omega^T,\lambda^T)^T\}$. We also show that when the models for the propensity scores are correct,

even if the outcome regression models are all misspecified, $\hat{\mu}_{\text{BHT,eff}}$ will be at least as efficient as $\hat{\mu}_{\text{IPW,HT}}$, $\hat{\mu}_{\text{IPW,BD}}$ as well as the standard AIPW estimator.

We can also improve upon the efficiency of the weighted ICE estimator by plugging in $h_j^{\text{eff}}(\hat{\alpha}_j, \hat{\gamma}_j, \hat{\theta}_j)$ and $\pi_j^{\text{eff}}(\hat{\alpha}, \hat{\gamma}, \hat{\theta})$ in place of $h_k(\hat{\alpha}_k, \hat{\gamma}_k)$ and $\pi_j(\hat{\alpha}, \hat{\gamma})$, respectively. In Web Appendix H, we show that when the models for the propensity scores are correct, even if the outcome regression models are all misspecified, $\hat{\mu}_{\text{WICE,eff}}$ will be at least as efficient as the $\hat{\mu}_{\text{WICE}}$ that uses MLE $\hat{\alpha}$ to estimate the propensity scores and $\eta_j(\bar{L}_j, \hat{\kappa}_j)$ to estimate the counterfactual outcome given past data. Similarly, we can plug in $h_j^{\text{eff}}(\hat{\alpha}_j, \hat{\gamma}_j, \hat{\theta}_j)$ and $\pi_j^{\text{eff}}(\hat{\alpha}, \hat{\gamma}, \hat{\theta})$ in place of $h_k(\hat{\alpha}_k, \hat{\gamma}_k)$ and $\pi_j(\hat{\alpha}, \hat{\gamma})$, respectively, in the 2^J multiply robust estimators. This ensures improvement in efficiency when the models for the propensity scores are correct, even if the outcome regression models are all misspecified. Moreover, the calibrated propensity score estimation procedure can avoid weights that are too variable across individuals, therefore estimators that use calibrated weights may perform similarly (or better) than estimators that do not, under other misspecification scenarios.

8 | SIMULATION STUDY

8.1 | Simulation set-up

We conducted a simulation study to compare the different estimators discussed in this paper. Each study was based on 1000 simulated data sets of sample size $n = (500, 1000)$ and our aim was to estimate the probability of survival at time 4 under treatment strategy g. We simulated the following variables: $(L_{10}, L_{20}, A_0, Y_1, L_{11}, L_{21}, A_1, Y_2, \dots, Y_4)$ where L_{1j} and L_{2j} are time-dependent confounders. In particular, $L_{10} \sim \text{Ber}(0.5)$ and $L_{20} \sim \text{Ber}(0.5)$. The outcome at each time j ($j \geq 1$) is simulated from $Y_j \sim \text{Ber}\{\text{expit}(-1 + 2A_{j-1} + 2L_{1,j-1} - 2L_{2,j-1} + 2L_{1,j-1}L_{2,j-1})\}$ if $Y_{j-1} = 1$ and is set to 0 if $Y_{j-1} = 0$. The first confounder at time j ($j \geq 1$) is simulated from $L_{1j} \sim \text{Ber}\{\text{expit}(A_{j-1} + L_{1,j-1} - L_{2,j-1})\}$ if $Y_j = 1$. The second confounder at time j ($j \geq 1$) is simulated from $L_{2j} \sim \text{Ber}\{\text{expit}(-2 - 2A_{j-1} - L_{1j})\}$ if $Y_j = 1$ and $L_{2,j-1} = 0$, and is set to 1 if $Y_j = 1$ and $L_{2,j-1} = 1$. Treatment at time j ($j \geq 0$) is simulated from $A_j \sim \text{Ber}\{\text{expit}(1 - 2L_{1j} + L_{2j} + L_{1j}L_{2j})\}$ if $Y_j = 1$ and $A_{j-1} = 0$, and is set to 1 if $Y_j = 1$ and $A_{j-1} = 1$. As before, we assume that treatment has not initiated before baseline (i.e., $\bar{A}_{-1} = 0$). In addition, $(L_{1j}, L_{2j}, A_j) = (\emptyset, \emptyset, \emptyset)$ if $Y_j = 0$.

We consider the ICE estimator ($\hat{\mu}_{\text{ICE}}$) described in Section 3, the unbounded Horvitz-Thompson estimator ($\hat{\mu}_{\text{IPW,HT}}$) and the bounded IPW estimator ($\hat{\mu}_{\text{IPW,BD}}$) described in Section 3.1, the standard AIPW estimator ($\hat{\mu}_{\text{st.AIPW}}$) described in Section 4, the weighted ICE estimator ($\hat{\mu}_{\text{WICE}}$) described in Section 5.1, the bounded Horvitz–Thompson estimator ($\hat{\mu}_{\text{BHT}}$) described in Section 5.2, the restricted weighted ICE estimator ($\hat{\mu}_{2J,\text{rWICE}}$) described in Section 5.3, and the weighted RRB estimator ($\hat{\mu}_{2J,\text{RRB}}$) described in Section 6. To show the gain in efficiency from the estimators described in Section 7 in situations when the propensity score models are correctly specified but the outcome regression models are misspecified, we also show results from multiply robust estimators that use the efficiently calibrated propensity scores ($\hat{\mu}_{\text{BHT,eff}}$, $\hat{\mu}_{\text{WICE,eff}}$, $\hat{\mu}_{2J,\text{rWICE,eff}}$ and $\hat{\mu}_{2J,\text{RRB,eff}}$).

For each estimator, we calculated the Monte Carlo bias (Bias), the Monte Carlo standard error (SE), the root-mean-square error (RMSE), and the median absolute errors (MAE). We used numerical optimization to solve for the calibrated weights.

We consider a treatment strategy where treatment initiation is delayed until the first time L_{1j} becomes 0. For example, if L_{1j} is an indicator that a subject's CD4 cell count is greater than 500 μL, then treatment would be initiated the first time that a subject's CD4 cell count drops to 500 μL or below. In addition, let Q_j be an indicator that CD4 has dropped to 500 μL or below by time j, that is, $Q_j = \prod_{k=0}^{j} \mathrm{I}(L_{1k} = 0)$.

Due to the data generating mechanism, approximately 18% of the individuals in a simulated cohort follow this strategy. The correct treatment model for inverse probability weighting is the one used in the data generation process. The true outcome regression model at time j equals $\mathrm{expit}\{\theta_j[1, L_{1j}, L_{2j}, L_{1j}L_{2j}, Q_j, L_{2j}Q_j]^T\}$ $(j = 1, 2, 3)$ for $\theta_j = [\theta_{j0}, \ldots, \theta_{j5}]$, and the true outcome regression model at time 0 equals $\mathrm{expit}\{\theta_0[1, L_{10}, L_{20}, L_{10}L_{20}]^T\}$ for $\theta_0 = [\theta_{00}, \ldots, \theta_{03}]$. At a time point j, the misspecified treatment model is $\mathrm{expit}\{\alpha_j[L_{1j}, L_{2j}]^T\}$ for $\alpha_j = [\alpha_{j1}, \alpha_{j2}]$, and the misspecified outcome regression model is $\mathrm{expit}\{\theta_j[1, L_{1j}, L_{2j}]^T\}$ for $\theta_j = [\theta_{j0}, \theta_{j1}, \theta_{j2}]$.

We consider six different scenarios: (1) $(\cap_{j=0}^{3}\mathcal{H}_j) \cap (\cap_{j=0}^{3}\mathcal{G}_j)$ where all the models are correct, (2) $(\cap_{j=0}^{3}\mathcal{G}_j)$ where only the outcome regression models are correct, (3) $(\cap_{j=0}^{3}\mathcal{H}_j)$ where only the treatment models are correct, (4) $\mathcal{G}_0 \cap \mathcal{H}_1 \cap \mathcal{G}_2 \cap \mathcal{H}_3$ where the outcome regression models are correct only at times 0 and 2 and the treatment models are correct only at times 1 and 3, (5) $\mathcal{G}_0 \cap (\cap_{j=1}^{3}\mathcal{H}_j)$ where the outcome regression model is correct only at time 0 and the treatment models are correct only at times 1, 2 and 3, (6) all models are incorrect.

In Web Appendix I, we illustrate the $J + 1$ multiply robustness of the multiply-robust estimators by looking at (7)$\mathcal{H}_0 \cap (\cap_{j=1}^{3}\mathcal{G}_j)$ where the treatment model is correct in the first time point and the outcome models are correct in the last three time points and (8) $(\cap_{j=0}^{1}\mathcal{H}_j) \cap (\cap_{j=2}^{3}\mathcal{G}_j)$ where the treatment models are correct in the first two time points and the outcome models are correct in the last two time points.

8.2 | Simulation results

Simulation results for the dynamic treatment strategy are given in Tables 1 and 2. They show that when all of the working models are correctly specified, all of the estimators are nearly unbiased. According to theory, under scenarios (3) and (4), both of the 2^J multiply robust estimators should be consistent but the singly robust and $J + 1$ multiply robust estimators will not be. The performance of the estimators observed for $n = 500$ and $n = 1000$ agrees with the asymptotic results: $\hat{\mu}_{2J,\mathrm{rWICE}}$ and $\hat{\mu}_{2J,\mathrm{RRB}}$ are nearly unbiased but the other methods are more biased. In general, the 2^J multiply robust estimators have smaller bias than other methods, which indicates that multiply robust estimation provides more protection against model misspecification. Even in the unfavorable scenario where all models are misspecified, the bias from the 2^J multiply robust estimators is smaller than that of other estimators. Although not predicted by theory, estimators that use the efficiently calibrated weights generally had smaller bias and MSE than their noncalibrated counterparts in scenarios where the estimators should theoretically be biased. Table 1 in Web Appendix I shows that in scenarios (7) and (8), the singly robust methods are biased but the $J + 1$ and the 2^J multiply robust methods are nearly unbiased.

When all of the working models are correctly specified, all of the $J + 1$ and 2^J multiply robust estimators are more efficient than the IPW estimators $\hat{\mu}_{\mathrm{IPW,HT}}$ and $\hat{\mu}_{\mathrm{IPW,BD}}$, which agrees with asymptotic theory. Interestingly, with the exception of $\hat{\mu}_{\mathrm{st.AIPW}}$, the $J + 1$ and 2^J multiply robust estimators are similarly efficient. The performance of the improved estimators (i.e., estimators that use the efficiently calibrated weights) also agree with asymptotic theory. Specifically, for both $n = 500$ and $n = 1000$ the results show that when the models for the propensity scores are

TABLE 1 Simulation study for dynamic treatment strategy ($n = 500$). True counterfactual probability of survival at time 4 is 0.266. Bias, standard error (SE), root-mean-square error (RMSE) and median absolute error (MAE) are multiplied by 100

	$(\cap_{j=0}^{3}\mathcal{H}_j) \cap (\cap_{j=0}^{3}\mathcal{G}_j)$				$(\cap_{j=0}^{3}\mathcal{G}_j)$			
Estimator	**BIAS**	**SE**	**RMSE**	**MAE**	**BIAS**	**SE**	**RMSE**	**MAE**
$\hat{\mu}_{\text{ICE}}$	−0.16	3.08	3.09	2.12	−0.16	3.08	3.09	2.12
$\hat{\mu}_{\text{IPW,HT}}$	−0.38	5.98	6.00	2.53	8.07	6.25	10.21	7.11
$\hat{\mu}_{\text{IPW,BD}}$	0.33	4.40	4.41	2.75	3.31	4.32	5.44	3.83
$\hat{\mu}_{\text{st.AIPW}}$	0.00	3.91	3.91	2.39	−0.01	3.86	3.86	2.37
$\hat{\mu}_{\text{WICE}}$	−0.01	3.55	3.55	2.20	−0.01	3.53	3.53	2.24
$\hat{\mu}_{\text{WICE,eff}}$	−0.02	3.60	3.60	2.26	−0.02	3.59	3.59	2.31
$\hat{\mu}_{\text{BHT}}$	−0.01	3.64	3.64	2.30	−0.01	3.63	3.63	2.32
$\hat{\mu}_{\text{BHT,eff}}$	−0.01	3.66	3.66	2.30	−0.01	3.65	3.65	2.33
$\hat{\mu}_{2J,\text{rWICE}}$	0.02	3.77	3.77	2.40	0.02	3.78	3.78	2.39
$\hat{\mu}_{2J,\text{rWICE,eff}}$	0.02	3.77	3.77	2.40	0.00	3.82	3.82	2.42
$\hat{\mu}_{2J,\text{RRB}}$	−0.12	3.74	3.74	2.34	−0.13	3.75	3.75	2.36
$\hat{\mu}_{2J,\text{RRB,eff}}$	−0.14	3.75	3.75	2.34	−0.14	3.76	3.76	2.36
	$(\cap_{j=0}^{3}\mathcal{H}_j)$				$\mathcal{G}_0 \cap \mathcal{H}_1 \cap \mathcal{G}_2 \cap \mathcal{H}_3$			
$\hat{\mu}_{\text{ICE}}$	2.07	2.67	3.38	2.25	3.10	2.88	4.23	3.10
$\hat{\mu}_{\text{IPW,HT}}$	−0.38	5.98	6.00	2.53	6.56	6.37	9.14	5.70
$\hat{\mu}_{\text{IPW,BD}}$	0.33	4.40	4.41	2.75	3.16	4.33	5.36	3.60
$\hat{\mu}_{\text{st.AIPW}}$	0.13	5.19	5.20	2.73	0.93	3.43	3.55	2.26
$\hat{\mu}_{\text{WICE}}$	0.41	3.72	3.74	2.39	1.26	3.54	3.75	2.16
$\hat{\mu}_{\text{WICE,eff}}$	0.08	3.57	3.57	2.21	0.69	3.52	3.59	2.18
$\hat{\mu}_{\text{BHT}}$	0.22	3.56	3.57	2.30	0.92	3.46	3.58	2.15
$\hat{\mu}_{\text{BHT,eff}}$	0.17	3.58	3.59	2.28	0.74	3.51	3.58	2.22
$\hat{\mu}_{2J,\text{rWICE}}$	−0.07	3.52	3.52	2.23	0.12	3.71	3.71	2.45
$\hat{\mu}_{2J,\text{rWICE,eff}}$	−0.19	3.47	3.47	2.23	0.05	3.73	3.73	2.41
$\hat{\mu}_{2J,\text{RRB}}$	0.12	3.63	3.64	2.32	0.20	3.74	3.74	2.34
$\hat{\mu}_{2J,\text{RRB,eff}}$	0.00	3.57	3.57	2.23	0.07	3.75	3.75	2.33
	$\mathcal{G}_0 \cap (\cap_{j=1}^{3}\mathcal{H}_j)$				**All incorrect**			
$\hat{\mu}_{\text{ICE}}$	3.57	2.87	4.58	3.49	2.07	2.67	3.38	2.25
$\hat{\mu}_{\text{IPW,HT}}$	5.88	6.25	8.58	4.92	8.07	6.25	10.21	7.11
$\hat{\mu}_{\text{IPW,BD}}$	3.19	4.35	5.39	3.67	3.31	4.32	5.44	3.83
$\hat{\mu}_{\text{st.AIPW}}$	1.07	3.67	3.82	2.35	1.70	5.05	5.33	3.23
$\hat{\mu}_{\text{WICE}}$	1.41	3.66	3.92	2.45	1.92	3.79	4.25	2.63

(Continues)

TABLE 1 (Continued)

	$(\cap_{j=0}^{3}\mathcal{H}_j) \cap (\cap_{j=0}^{3}\mathcal{G}_j)$				$(\cap_{j=0}^{3}\mathcal{G}_j)$			
Estimator	**BIAS**	**SE**	**RMSE**	**MAE**	**BIAS**	**SE**	**RMSE**	**MAE**
$\hat{\mu}_{\text{WICE,eff}}$	0.69	3.50	3.57	2.22	1.43	3.50	3.78	2.27
$\hat{\mu}_{\text{BHT}}$	1.01	3.46	3.60	2.17	1.73	3.41	3.82	2.23
$\hat{\mu}_{\text{BHT,eff}}$	0.82	3.51	3.60	2.20	1.60	3.40	3.76	2.24
$\hat{\mu}_{2J,\text{rWICE}}$	0.09	3.72	3.72	2.33	0.88	3.75	3.85	2.32
$\hat{\mu}_{2J,\text{rWICE,eff}}$	−0.01	3.69	3.69	2.30	0.52	3.54	3.58	2.19
$\hat{\mu}_{2J,\text{RRB}}$	0.25	3.77	3.78	2.41	1.17	3.84	4.01	2.46
$\hat{\mu}_{2J,\text{RRB,eff}}$	0.14	3.74	3.74	2.34	0.82	3.60	3.69	2.32

correctly specified but the outcome regression models are misspecified, $\hat{\mu}_{\text{BHT,eff}}$, $\hat{\mu}_{\text{WICE,eff}}$, $\hat{\mu}_{2J,\text{rWICE,eff}}$ and $\hat{\mu}_{2J,\text{RRB,eff}}$ are at least as efficient than $\hat{\mu}_{\text{st.AIPW}}$, μ_{WICE}, $\hat{\mu}_{2J,\text{rWICE}}$ and $\hat{\mu}_{2J,\text{RRB}}$, respectively. In fact, our results show that all of the multiply robust estimators are more efficient than $\hat{\mu}_{\text{st.AIPW}}$, $\hat{\mu}_{\text{IPW,HT}}$ and $\hat{\mu}_{\text{IPW,BD}}$. Simulation results also show that in general, estimators with calibrated weights slightly improved the finite-sample bias over estimators with noncalibrated weights and both produced similarly efficient estimates in other model misspecification scenarios. Interestingly, $\hat{\mu}_{\text{BHT}}$ is just as efficient as $\hat{\mu}_{\text{BHT,eff}}$ in all scenarios. In Web Appendix I, we also compare our proposed logistic calibration structure with those of Han (2016). The results are similar, but at smaller sample sizes the simulation results show the logistic calibration structure has slightly smaller mean squared error.

In Web Appendix I, we consider a second treatment strategy where treatment is initiated at time 1. That is, $(a_0^g, a_1^g, a_2^g, a_3^g) = (0, 1, 1, 1)$ for all individuals. Results from this static treatment strategy are given in Tables 3 and 4 of Web Appendix I. In Web Appendix J, we show results from a simulation study where individuals may be censored during follow-up. Conclusions from the results are consistent with those from the dynamic treatment simulation study.

9 | EXAMPLE

We applied the multiply robust estimators to the US Veterans Aging Cohort Study of individuals aged ≥50 years at baseline ($n = 2672$) to estimate the 12-months ($J = 12$) mortality risk under two strategies of ART treatment initiation: (1) immediate initiation and (2) initiation of ART as soon as an individual's CD4 count drops below 500 cells/mm^3. Previous studies have shown that older patients who develop HIV have a diminished immunological response to treatment and therefore may be at a higher risk of developing AIDS or death (Grabar et al., 2004; Sabin et al., 2008). For this reason, it is important to compare the effect of various treatment initiation strategies for this group of individuals.

The observed probability of survival at month 12 is 5.65% and approximately 8.91% of individuals were censored during follow-up. The median CD4 count at diagnosis of HIV infection was 284 μL (IQR 128–471) and approximately 21.7% of the individuals have a baseline CD4 greater than 500 μL. Even with such low CD4 counts, only 19.3% of the individuals started ART at baseline. We compared results from the singly robust estimators as well as multiply robust estimators with efficiently calibrated propensity scores. As described in the previous sections,

TABLE 2 Simulation study for dynamic treatment strategy ($n = 1000$). True counterfactual probability of survival at time 4 is 0.266. Bias, standard error (SE), root-mean-square error (RMSE) and median absolute error (MAE) are multiplied by 100

	$(\cap_{j=0}^{3}\mathcal{H}_j) \cap (\cap_{j=0}^{3}\mathcal{G}_j)$				$(\cap_{j=0}^{3}\mathcal{G}_j)$			
Estimator	**BIAS**	**SE**	**RMSE**	**MAE**	**BIAS**	**SE**	**RMSE**	**MAE**
$\hat{\mu}_{\text{ICE}}$	−0.15	2.35	2.35	1.58	−0.15	2.35	2.35	1.58
$\hat{\mu}_{\text{IPW,HT}}$	−0.19	4.99	4.99	2.07	8.35	5.24	9.86	7.49
$\hat{\mu}_{\text{IPW,BD}}$	0.13	3.44	3.44	2.17	3.17	3.27	4.56	3.49
$\hat{\mu}_{\text{st.AIPW}}$	−0.02	2.98	2.98	1.88	−0.03	3.01	3.01	1.87
$\hat{\mu}_{\text{WICE}}$	−0.04	2.69	2.69	1.80	−0.04	2.68	2.68	1.79
$\hat{\mu}_{\text{WICE,eff}}$	−0.07	2.74	2.74	1.83	−0.07	2.73	2.73	1.82
$\hat{\mu}_{\text{BHT}}$	−0.08	2.75	2.75	1.83	−0.08	2.75	2.76	1.84
$\hat{\mu}_{\text{BHT,eff}}$	−0.10	2.78	2.78	1.83	−0.10	2.77	2.77	1.82
$\hat{\mu}_{2J,\text{rWICE}}$	−0.07	2.90	2.90	1.93	−0.07	2.90	2.90	1.94
$\hat{\mu}_{2J,\text{rWICE,eff}}$	−0.09	2.89	2.90	1.96	−0.08	2.90	2.90	1.96
$\hat{\mu}_{2J,\text{RRB}}$	−0.27	2.85	2.87	1.92	−0.27	2.87	2.88	1.93
$\hat{\mu}_{2J,\text{RRB,eff}}$	−0.29	2.87	2.89	1.96	−0.30	2.87	2.89	1.97
	$(\cap_{j=0}^{3}\mathcal{H}_j)$				$\mathcal{G}_0 \cap \mathcal{H}_1 \cap \mathcal{G}_2 \cap \mathcal{H}_3$			
$\hat{\mu}_{\text{ICE}}$	2.04	1.92	2.80	2.07	3.07	2.05	3.69	3.06
$\hat{\mu}_{\text{IPW,HT}}$	−0.19	4.99	4.99	2.07	6.77	5.16	8.51	5.88
$\hat{\mu}_{\text{IPW,BD}}$	0.13	3.44	3.44	2.17	3.00	3.38	4.52	3.35
$\hat{\mu}_{\text{st.AIPW}}$	0.03	3.94	3.94	2.19	0.92	2.48	2.65	1.74
$\hat{\mu}_{\text{WICE}}$	0.27	2.83	2.84	1.96	1.17	2.69	2.94	1.92
$\hat{\mu}_{\text{WICE,eff}}$	−0.03	2.67	2.67	1.82	0.65	2.62	2.70	1.68
$\hat{\mu}_{\text{BHT}}$	0.10	2.66	2.67	1.80	0.86	2.57	2.71	1.77
$\hat{\mu}_{\text{BHT,eff}}$	0.05	2.67	2.67	1.78	0.69	2.60	2.69	1.70
$\hat{\mu}_{2J,\text{rWICE}}$	−0.05	2.67	2.67	1.80	−0.05	2.71	2.71	1.74
$\hat{\mu}_{2J,\text{rWICE,eff}}$	−0.19	2.61	2.62	1.71	−0.10	2.72	2.72	1.76
$\hat{\mu}_{2J,\text{RRB}}$	0.10	2.77	2.77	1.85	0.05	2.76	2.76	1.84
$\hat{\mu}_{2J,\text{RRB,eff}}$	−0.05	2.71	2.71	1.80	−0.07	2.78	2.78	1.82
	$\mathcal{G}_0 \cap (\cap_{j=1}^{3}\mathcal{H}_j)$				**All incorrect**			
$\hat{\mu}_{\text{ICE}}$	3.54	2.05	4.09	3.53	2.04	1.92	2.80	2.07
$\hat{\mu}_{\text{IPW,HT}}$	6.11	5.15	7.99	5.19	8.35	5.24	9.86	7.49
$\hat{\mu}_{\text{IPW,BD}}$	3.01	3.41	4.55	3.41	3.17	3.27	4.56	3.49
$\hat{\mu}_{\text{st.AIPW}}$	1.05	2.72	2.92	1.91	1.63	3.99	4.31	2.57
$\hat{\mu}_{\text{WICE}}$	1.28	2.78	3.06	2.04	1.81	2.90	3.42	2.25
$\hat{\mu}_{\text{WICE,eff}}$	0.58	2.63	2.70	1.68	1.39	2.58	2.93	1.79
$\hat{\mu}_{\text{BHT}}$	0.88	2.59	2.73	1.75	1.67	2.51	3.02	1.96

(Continues)

TABLE 2 (Continued)

	$(\cap_{j=0}^{3}\mathcal{H}_j)\cap(\cap_{j=0}^{3}\mathcal{G}_j)$				$(\cap_{j=0}^{3}\mathcal{G}_j)$			
Estimator	**BIAS**	**SE**	**RMSE**	**MAE**	**BIAS**	**SE**	**RMSE**	**MAE**
$\hat{\mu}_{\text{BHT,eff}}$	0.68	2.61	2.70	1.70	1.56	2.47	2.92	1.82
$\hat{\mu}_{2J,\text{rWICE}}$	0.04	2.76	2.76	1.83	0.95	2.87	3.02	1.86
$\hat{\mu}_{2J,\text{rWICE,eff}}$	−0.12	2.73	2.73	1.79	0.60	2.62	2.69	1.68
$\hat{\mu}_{2J,\text{RRB}}$	0.15	2.81	2.81	1.89	1.19	2.94	3.17	2.04
$\hat{\mu}_{2J,\text{RRB,eff}}$	0.00	2.79	2.79	1.85	0.86	2.67	2.81	1.75

TABLE 3 12-month probability of survival from multiply robust estimators using the US Veterans Aging Cohort Study. Relative rate of survival compares immediate to CD4-based strategies. All values are multiplied by 100

	Immediate		**CD4-based**		**Relative rate**	
Initiation	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
$\hat{\mu}_{\text{ICE}}$	96.4	(94.6, 97.7)	95.8	(94.2, 97.1)	1.006	(0.997, 1.015)
$\hat{\mu}_{\text{IPW,BD}}$	96.4	(94.7, 97.8)	95.6	(93.7, 97.1)	1.009	(1.005, 1.014)
$\hat{\mu}_{\text{WICE,eff}}$	96.3	(94.5, 97.6)	95.7	(93.7, 97.1)	1.006	(1.003, 1.013)
$\hat{\mu}_{\text{BHT,eff}}$	96.3	(94.5, 97.7)	95.7	(93.8, 97.0)	1.006	(1.002, 1.013)
$\hat{\mu}_{2J,\text{RRB,eff}}$	96.8	(94.1, 98.9)	96.1	(93.3, 98.0)	1.007	(0.977, 1.042)

the Horvitz–Thompson and standard AIPW estimators do not guarantee sample-boundedness, and the restricted weighted ICE estimator may be infeasible when J is large. For these reasons, results from these estimators are omitted from the analysis. In the data analysis, all models included as covariates the most recent value of treatment, AIDS diagnosis, time since last CD4 count measurement, time since last HIV-RNA viral load measurement, log CD4 count and log HIV-RNA, and the following baseline variables: log CD4 count, HIV-RNA levels ($<$ 10,000, 10,000–100,000, $>$ 100,000 copies/ml), sex, transmission group, calendar year and age. To reduce model misspecification, we used models with flexible functional forms (restricted cubic splines).

Figure 2 shows the estimated survival curves under the immediate and CD4-based strategies, respectively, and Table 3 shows the estimated 12-month chance of survival under each strategy as well as the relative rates of survival comparing the immediate versus CD4-based strategies. Point estimates of the probability of survival were similar in all of the estimators for both intervention strategies, and the relative rates generally suggest that the chance of 12-month survival under the immediate treatment initiation strategy is at least as high as (and maybe slightly higher than) the CD4-based treatment initiation strategy. For instance, using $\hat{\mu}_{\text{WICE,eff}}$ the 12-month chance of survival was 96.3% (95% CI = (94.5, 97.6)) under the immediate treatment initiation strategy and 95.7% (95% CI = (93.7, 97.1)) under the CD4-based treatment initiation strategy. In addition, the relative rate of survival comparing the immediate versus CD4-based strategies was 1.006 (95% CI = (1.003, 1.013)). Results from the nonefficiently calibrated propensity scores were very similar and can be found in Web Appendix K.

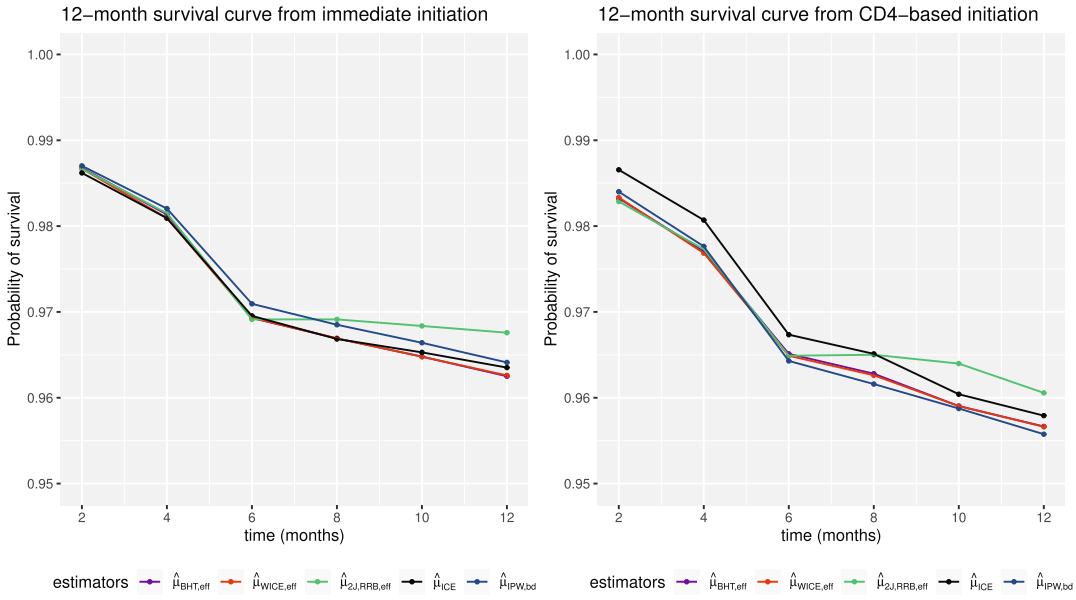

FIGURE 2 12-month survival curve from multiply robust estimators using the US Veterans Aging Cohort Study

10 | DISCUSSION

In this paper we discussed various methods to estimate causal estimands for failure-time outcomes. Specifically, we discussed singly robust estimators (IPW and ICE), $J+1$ multiply robust estimators (standard AIPW, weighted ICE and bounded Horvitz-Thompson) and 2^J multiply robust estimators (restricted weighted ICE and the modified estimator from Rotnitzky et al., 2017). We have also made connections between these estimators by explicitly stating how they all relate to the general AIPW estimator. To compare the various multiply robust estimators in practice, we analyzed data from the US Veterans Aging Cohort Study. The results did not differ much between the multiply robust estimators, although the 2^J multiply robust estimator was more difficult to implement compared with the $J+1$ multiply robust estimators. Our results were consistent with those previously published findings (Lodi et al., 2015, 2017; Wen et al., 2021), and our estimates indicate that immediate initiation of ART is at least as effective as CD4-based initiation of ART in terms of prolonging survival.

We proposed using efficiently calibrated propensity scores in the multiply robust estimators over noncalibrated propensity scores, and showed through simulation studies that the efficiently calibrated propensity scores can improve precision when the propensity scores models are correctly specified but the outcome regression models are misspecified. This can occur in sequentially randomized trials where propensity scores are known in advance by design, and randomization probabilities can depend on past treatment, health statuses, and covariates. Our simulation studies also show that even in cases where treatment models are only partly correctly specified or fully misspecified, estimators that use the calibrated propensity scores perform just as well in terms of bias and precision as using noncalibrated propensity scores. Thus, even if the propensity scores are not known, effort should be put into approximating them well. If the propensity score models are (approximately) correct, then the calibrated propensity scores are

guaranteed to be at least as efficient as estimators that do not use these scores. However, if the models at certain time points are misspecified, the multiply robust estimators can protect against these misspecifications.

Practical considerations for each of the estimators are given in Table 4. Although multiply robust estimators are generally more complex to implement than singly robust estimators, the benefits of their asymptotic properties—robustness to model misspecification and desirable properties in efficiency—exceeds this complexity. However, we note that even though 2^J multiply robust estimators are theoretically appealing because they offer the most protection against model misspecification, $J + 1$ multiply robust estimators may be used more often in practice because they are easier to implement using standard off-the-shelf regression software. In the Supplementary Materials we provide R code to implement the 2^J multiply robust estimators from the simulation setup in Section 8 to make them more accessible.

We have assumed a discretized ordering of (L_j, A_j, Y_{j+1}) throughout, which in the presence of time-varying confounders and treatment-confounder feedback, is essential for identification of the causal estimand in survival analysis. Indeed, in real-world applications, measurements on, for example, treatment and covariates, are taken in discrete intervals rather than continuously (Hernán & Robins, 2020). Even under a point treatment process with the observed data structure being $O = (L, A, X, \Delta)$ where $X = \min(T, C)$ (T = time of event; C = time of censoring) and $\Delta = I(X = T)$, identification of the causal estimand $E\{P(T > t|A = 1, L)\}$ can be ascertained by mapping O to a discretized observed data structure (Cai & van der Laan, 2019). The presence of censoring requires one to define an implicit static treatment strategy that abolishes censoring throughout, which creates a 'treatment-confounder' feedback where 'treatment' abolishes censoring at time $j + 1$ and 'confounder' is Y_j (for $j = 0, \ldots, J - 1$), and so the estimand is identified under the usual causal assumptions. We need to discretize time finely enough to capture the temporal sequence of confounders and treatments. In practice, the interval length depends on the frequency with which treatment and confounders can change (Young et al., 2019). For instance, in HIV treatment initiation studies, time is usually discretized monthly because treatment rarely changes more often than once per month (HIV-CAUSAL Collaboration, 2011; Lodi et al., 2015, 2017; Wen et al., 2021). Sensitivity analyses can also be conducted to test the robustness of the chosen discretization.

One area of future research is on dealing with sparse or rare outcomes. Previous researchers have found that using logistic regression for these binary (extremely) sparse events can lead to large bias, problems with estimator convergence, and unreliable inference (Balzer et al., 2016; King & Zeng, 2001; Peduzzi et al., 1996; Schnitzer et al., 2016). Balzer et al. (2016) proposed using outcome transformations by incorporating a priori information on the upper and lower bounds of the conditional mean outcome into the estimation procedure for point treatment processes. Through simulation studies, they showed that the targeted maximum likelihood estimator that utilizes this information performed just as well, if not better than IPW, standard AIPW and the standard targeted maximum likelihood estimators. Extensions to a longitudinal setting with time-varying treatment and confounders can be informative.

Lastly, machine learning algorithms can be used to estimate h_j and T_j in the multiply robust estimators instead of using parametric models, and sample splitting can further be used to avoid the Donsker class conditions (Rotnitzky et al., 2017; Van der Vaart, 2000). However, implementation of the estimators with machine learning algorithms are beyond the scope of this paper and will be reported elsewhere.

TABLE 4 Practical advantages and disadvantages of the estimators and their relations to the standard AIPW estimator. *Estimators are arranged from easiest to the most difficult to implement*

Estimator	Advantages	Disadvantages	Relation to $\hat{\mu}_{\text{AIPW}}$
$\hat{\mu}_{\text{IPW,HT}}$	◇ Easiest to implement	◇ Not sample bounded	If $\hat{\pi}_j = \pi_j(\hat{\alpha})$ and and $\hat{\Sigma} = 0$ (e.g. if $\hat{T}_j = 0, \forall j$) in Equation (5) then $\hat{\mu}_{\text{IPW,HT}} = \hat{\mu}_{\text{AIPW}}$
		◇ Can be inefficient; subject to small-sample bias	
		◇ Singly robust	
$\hat{\mu}_{\text{IPW,BD}}$	◇ Sample-bounded	◇ Can be inefficient; subject to small-sample bias	If $\hat{\pi}_j = \pi_j(\hat{\alpha})$, $\hat{T}_j = 1\ \forall j$ *and* if $\hat{\Sigma} = 0$ in Equation (5) then $\hat{\mu}_{\text{IPW,BD}} = \hat{\mu}_{\text{AIPW}}$
		◇ Singly robust	
$\hat{\mu}_{\text{ICE}}$	◇ Most efficient estimator if models are correctly specified	◇ Iterative nature of the outcome regression models makes them hard to correctly specify especially at earlier time points	If $1/\hat{\pi}_j = 0$ and $\hat{T}_j$ is obtained from ICE $\forall j$ in Equation (4) then $\hat{\mu}_{\text{ICE}} = \hat{\mu}_{\text{AIPW}}$
	◇ Sample-bounded	◇ Singly robust	
$\hat{\mu}_{\text{st.AIPW}}$	◇ Locally efficient when all models are correctly specified	◇ Not sample-bounded (if as described in Section 4)	$\hat{\mu}_{\text{st.AIPW}}$ is a special case of $\hat{\mu}_{\text{AIPW}}$ where $\hat{\pi}_j = \pi_j(\hat{\alpha})$ and $\hat{T}_j$ is predicted from ICE $\forall j$
	◇ $J+1$ multiply robust	◇ Not 2^J multiply robust	
$\hat{\mu}_{\text{WICE}}$	◇ Locally efficient when all models are correctly specified	◇ Not 2^J multiply robust	If $\hat{T}_j$ is predicted using $\eta_j(\overline{L}_j; \hat{\kappa}_j)$ and $\hat{\pi}_j = \pi_j(\hat{\alpha})\ \forall j$ in Equation (4) then $\hat{\mu}_{\text{WICE}} = \hat{\mu}_{\text{AIPW}}$
	◇ $J+1$ multiply robust		
	◇ Sample-bounded		

(Continues)

TABLE 4 (Continued)

Estimator	Advantages	Disadvantages	Relation to $\hat{\mu}_{\text{AIPW}}$
$\hat{\mu}_{\text{BHT}}$	◇ Locally efficient when all models are correctly specified ◇ $J+1$ multiply robust ◇ Sample-bounded	◇ Not 2^J multiply robust	If $\hat{\pi}_j = \pi_j^{\Delta}(\hat{\alpha}, \hat{\gamma}, \hat{\theta})$ and $\hat{T}_j$ is predicted from ICE $\forall j$ in Equation (4) then $\hat{\mu}_{\text{BHT}} = \hat{\mu}_{\text{AIPW}}$ $(= \hat{\mu}_{\text{IPW,BD}})$
$\hat{\mu}_{2J,\text{rWICE}}$	◇ Locally efficient when all models are correctly specified ◇ 2^J multiply robust ◇ Sample-bounded	◇ May be infeasible for a large J and/or if there are many confounders	If $\hat{T}_j$ is predicted using $\eta_j(\overline{L}_j; \hat{\kappa}_j)$ and $\hat{\pi}_j = \pi_j(\hat{\alpha})$ $\forall j$ in Equation (4) then $\hat{\mu}_{2J,\text{rWICE}} = \hat{\mu}_{\text{AIPW}}$
$\hat{\mu}_{2J,\text{RRB}}$	◇ Locally efficient when all models are correctly specified ◇ 2^J multiply robust ◇ Sample-bounded	◇ Most difficult to implement (especially difficult for a large number of follow-ups)	If $\hat{T}_j$ is predicted using $\hat{T}_{j,MR}^{(0)}$ and $\hat{\pi}_j = \pi_j(\hat{\alpha})$ $\forall j$ in Equation (4) then $\hat{\mu}_{2J,\text{RRB}} = \hat{\mu}_{\text{AIPW}}$

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CONFLICT OF INTEREST

None declared.

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