Improved precision in the analysis of randomized trials with survival outcomes, without assuming proportional hazards

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Abstract We present a new estimator of the restricted mean survival time in randomized trials where there is right censoring that may depend on treatment and baseline variables. The proposed estimator leverages prognostic baseline variables to obtain equal or better asymptotic precision compared to traditional estimators. Under regularity conditions and random censoring within strata of treatment and baseline variables, the proposed estimator has the following features: (i) it is interpretable under violations of the proportional hazards assumption; (ii) it is consistent and at least as precise as the Kaplan–Meier and inverse probability weighted estimators, under identifiability conditions; (iii) it remains consistent under violations of independent censoring (unlike the Kaplan–Meier estimator) when either the censoring or survival distributions, conditional on covariates, are estimated consistently; and (iv) it achieves the nonparametric efficiency bound when both of these distributions are consistently estimated. We illustrate the performance of our method using simulations based on resampling data from a completed, phase 3 randomized clinical trial of a new surgical treatment for stroke; the proposed estimator achieves a 12% gain in relative efficiency compared to the Kaplan–Meier estimator. The proposed estimator has potential advantages over existing approaches for randomized trials with time-to-event outcomes, since existing methods either rely on model assumptions that are untenable in many applications, or

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10985-018-9428-5) contains supplementary material, which is available to authorized users.

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lack some of the efficiency and consistency properties (i)–(iv). We focus on estimation of the restricted mean survival time, but our methods may be adapted to estimate any treatment effect measure defined as a smooth contrast between the survival curves for each study arm. We provide R code to implement the estimator.

**Keywords** Covariate adjustment · Efficiency · Targeted minimum loss based estimation · Random censoring

1 Introduction

A standard approach to analyze clinical trials with survival outcomes is to estimate the survival curve in each study arm using the Kaplan–Meier estimator. This approach assumes that the censoring time is independent of the event time for each study arm. This assumption would typically be false, e.g., if high baseline disease severity is prognostic for both earlier drop-out and earlier time to death. To accommodate this type of situation, we focus throughout on the weaker assumption of random censoring, defined as censoring being independent of the event time within strata of the study arm and baseline variables. This assumption allows informative censoring, i.e., censoring correlated with the event time in a manner fully explained by study arm and baseline variables.

The Kaplan–Meier estimator is an unadjusted estimator, that is, it ignores baseline variables. Unadjusted estimators have the following potential drawbacks: (a) they can yield inconsistent estimators of the survival function under informative censoring as discussed above, and (b) even under independent censoring (defined as censoring independent of event time and baseline variables, for each arm), they are inefficient if baseline variables are prognostic of the outcome. Appropriate adjustment for baseline variables provides an opportunity to avoid these drawbacks by (a) providing consistent estimators of the treatment effect under random censoring and consistent estimation of either the censoring or survival distribution, and (b) increasing efficiency (i.e., asymptotic precision) of the estimators, thereby decreasing the required sample size and saving resources.

A commonly used method to analyze randomized trials with survival outcomes is the proportional hazards model (Cox 1972). A drawback of this approach is that the treatment effect estimate becomes uninterpretable and may be misleading under violations of proportional hazards and other parametric assumption (Schemper 1992; Tian et al. 2014). These violations can lead to false conclusions in an otherwise well designed and executed randomized trial.

Several alternatives are available to define the effect of assignment to treatment versus control on a survival outcome. We focus on estimation of the marginal (i.e., unconditional) treatment effect defined as the difference between the restricted mean survival time (RMST) in the two study arms. The RMST is the expected survival time restricted to (i.e., truncated at) a time $\tau$. This parameter has a model-free, clinically meaningful interpretation (Chen and Tsiatis 2001; Royston and Parmar 2011; Zhao et al. 2012; Tian et al. 2014). For example, if $\tau = 180$ days, then a 14 day improvement
in RMST due to treatment means 2 more weeks alive on average during the first 6 months; this may be more directly interpretable than a hazard ratio.

Although we focus on the RMST, our methods may be adapted to estimation of any smooth contrast between the marginal survival curves for each study arm. For example, the difference between the median survival times may be of interest, e.g., for heavy-tailed survival times. An alternative goal, not considered here, is to estimate a conditional effect of treatment, i.e., a contrast between distributions conditioned on the values of certain baseline variables. Though our ultimate goal is to estimate unconditional treatment effects, we harness information in baseline variables both to handle informative censoring (which could lead to bias if ignored) and to adjust for chance imbalances between study arms (which leads to to improvements in precision).

Our methods assume the outcome is observed on a discrete time scale. If the outcome is measured on a continuous time scale, our proposal may still be used by finely discretizing time. In our motivating example, we observe time at the day level, and consider a period of $\tau = 180$ days.

We propose a new doubly robust estimator of the RMST with the following properties:

(i) it is interpretable under violations of the proportional hazards assumption;
(ii) it is consistent and at least as precise as the Kaplan–Meier and inverse probability weighted estimators, under identifiability conditions;
(iii) it remains consistent under violations of independent censoring (unlike the Kaplan–Meier estimator) when either the censoring or survival distributions, conditional on covariates, are estimated consistently; and
(iv) it achieves the nonparametric efficiency bound when both of these distributions are consistently estimated.

Our estimator is derived using the general targeted minimum loss based estimation (TMLE) framework of van der Laan and Rubin (2006). Our estimator combines key ideas from Moore and van der Laan (2009a), Rotnitzky et al. (2012) and Gruber and van der Laan (2012), as we describe in Sect. 5. To the best of our knowledge, our proposed estimator is the first to achieve properties (i)–(iv) simultaneously for our problem.

Existing estimators for our problem can be broken into the following three families: methods based on modeling the survival function conditional on treatment and baseline variables (referred to as outcome regression models), methods based on modeling the censoring probability conditional on treatment and baseline variables, and methods called doubly robust estimators that combine these models. We describe these in Sect. 2 where we show existing methods lack one or more of the features (i)–(iv) above.

In Sect. 2, we review commonly used methods for our problem and highlight their strengths and limitations. In Sects. 3 and 4, we define our estimation problem and present estimators from related work, respectively. In Sect. 5, we present our new estimator. In Sect. 6.1, our motivating application is presented: the analysis of a completed Phase III randomized trial of a new treatment for stroke. Simulation studies are presented in Sect. 6, based on our motivating application. These simulation studies demonstrate that our estimator can lead to substantial improvements in efficiency. We conclude with a brief discussion and directions of future research.
2 Related work

Various methods have been proposed that satisfy some but not all of the properties (i)–(iv) from the introduction. Zhang (2014) propose a method to estimate the survival function at a single time point, by using a linear working model for the outcome. A working model is defined as a statistical model used to construct an estimator, but that is not necessarily assumed to be correctly specified. Unlike our proposal, the method of Zhang (2014) requires censoring to be independent of the event time within each study arm to achieve (i)–(iv). In addition, unlike our estimator, their method requires outcome regression models to be linear (and not, e.g., logistic). Parast et al. (2014) propose an estimator that adjusts for covariates through a kernel regression of the outcome on a one-dimensional dimension reduction defined as the linear predictor of a proportional hazards model. They further incorporate intermediate event to improve efficiency. Their estimator achieves properties (i)–(ii), but not (iii)–(iv).

Lu and Tsiatis (2011, Section 3) give a general approach for constructing estimators using longitudinal data. Their approach, if it were applied to estimate the RMST, would have properties (i)–(ii), but not (iii)–(iv). Unlike here, they require the censoring distribution to be known. An advantage of their estimator over our proposal is the incorporation of post-baseline covariates to adjust for time dependent confounding (i.e., when censoring and the event time have time-varying common causes). Though we do not address this problem, the techniques in this paper may be generalized to accommodate such scenarios. Stitelman et al. (2012) and Brooks et al. (2013) also handle time dependent confounding for survival outcomes; their estimators have properties (i), (iii), (iv) but not (ii).

Methods based on estimating the censoring distribution (Cole and Hernán 2004; Xie and Liu 2005; Rotnitzky and Robins 2005) are consistent under correct specification of the censoring model. However, these estimators are typically not as efficient as the covariate adjusted estimators described later, and thus do not fully leverage the often expensive data collected in a clinical trial.

Under consistent estimation of the censoring and outcome distributions at rate faster than $n^{1/4}$, doubly robust estimators are asymptotically efficient in the non-parametric model that only assumes treatment is assigned independent of baseline variables (Robins and Rotnitzky 1992; Hubbard et al. 2000; van der Laan and Robins 2003; Moore and van der Laan 2009a; Stitelman et al. 2012). Under outcome regression model misspecification but correct censoring model specification, doubly robust estimators remain consistent but they can be inefficient with variance larger than the variance of inverse probability weighted estimators. Under independent censoring, they can also have variance larger than unadjusted alternatives such as the Kaplan–Meier estimator. (A large sample illustration, for a related problem, is in the Web Appendix of Díaz et al. 2015). This is problematic since there is no guarantee that the effort placed in constructing adjusted estimators will lead to improved precision in estimation of the treatment effect.

The efficiency theory that we develop has roots in the work of Pfanzagl and Wefelmeyer (1985), Robins and Rotnitzky (1992), Robins et al. (1994), Bickel et al. (1997), Hahn (1998), Scharfstein et al. (1999), Bang and Robins (2005), among others who laid the foundation for locally efficient estimation of causal effects. Their methods
have been extended to incorporate enhanced efficiency properties, e.g., by Tan (2006, 2010), van der Laan and Rubin (2006), Zhang et al. (2008), Tsiatis et al. (2008), Cao et al. (2009), Rotnitzky et al. (2012) and Gruber and van der Laan (2012).

We use the general framework of van der Laan and Rubin (2006) and Gruber and van der Laan (2012) to construct a targeted minimum loss based estimator of the RMST that satisfies the properties described in the introduction. Targeted minimum loss based estimation (TMLE) of the effect of treatment on binary, continuous, and time to event outcomes in randomized trials was discussed in Moore and van der Laan (2009b) and Stitelman et al. (2012). Based on the work of Gruber and van der Laan (2012), Díaz et al. (2015) proposed a TMLE for ordinal outcomes with enhanced efficiency properties analogous to those of the estimator we propose in this manuscript.

The general estimation approach of Moore and van der Laan (2009a) has properties (i), (iii), (iv), but not (ii). Our main innovation is to enhance this approach so that it also achieves (ii). The enhancement is not trivial to achieve, and relies on the general strategy from Rotnitzky et al. (2012) and Gruber and van der Laan (2012), whose work builds on enhanced efficiency methods described above.

3 Data structure, RMST parameter, and identification

3.1 Observed data structure for each participant

Assume $K$ equally spaced time points $t = \{1, \ldots, K\}$, e.g., representing days, at which participants are monitored. Let $T$ denote a discrete, time-to-event outcome taking values in $\{1, \ldots, K\} \cup \{\infty\}$, where $T = \infty$ represents no event occurring during times $1, \ldots, K$. Let $C \in \{0, \ldots, K\}$ denote the censoring time defined as the time at which the participant is last observed in the study; if a participant remains on study through time point $K$, we let $C = K$, which represents administrative censoring. Let $A \in \{0, 1\}$ denote study arm assignment, and let $W$ denote a vector of baseline variables. The observed data vector for each participant is

$$O = (W, A, \Delta, \tilde{T}),$$

where $\tilde{T} = \min(C, T)$, and $\Delta = \mathbb{1}\{T \leq C\}$ is the indicator that the participant’s event time is observed (uncensored). Here $\mathbb{1}(X)$ is the indicator variable taking value 1 if $X$ is true and 0 otherwise.

We assume the observed data vector for each participant $i$, denoted $O_i = (W_i, A_i, \Delta_i, \tilde{T}_i)$, is an independent, identically distributed draw from the unknown joint distribution $P_0$ on $(W, A, \Delta, \tilde{T})$. We assume $P_0 \in \mathcal{M}$, where $\mathcal{M}$ is the nonparametric model defined as all continuous densities on $O$ with respect to a dominating measure $\nu$ such that $A$ is independent of $W$, which holds by randomization. Our asymptotic results are in the limit as sample size $n$ goes to infinity, with the number of time points $K$ being fixed.

We can equivalently encode a single participant’s data vector $O$ using the following longitudinal data structure:

$$O = (W, A, R_0, L_1, R_1, L_2, \ldots, R_{K-1}, L_K),$$

where $R_t = \mathbb{1}\{\tilde{T} = t, \Delta = 0\}$ and $L_t = \mathbb{1}\{\tilde{T} = t, \Delta = 1\}$, for $t \in \{0, \ldots, K\}$. The sequence $R_0, L_1, R_1, L_2, \ldots, R_{K-1}, L_K$ in the above display consists of all 0’s until
the first time that either the event is observed or censoring occurs, i.e., time $t = \tilde{T}$. In the former case $L_t = 1$; otherwise $R_t = 1$. For a random variable $X$, we denote its history through time $t$ as $X_t = (X_0, \ldots, X_t)$. For a given scalar $x$, the expression $X_t = x$ denotes element-wise equality. The corresponding vector (1) for participant $i$ is denoted by $(W_i, A_i, R_{0,i}, L_{1,i}, R_{1,i}, L_{2,i}, \ldots, R_{K-1,i}, L_{K,i})$.

Define the following indicator variables for each $t \geq 1$:

$$I_t = \mathbb{1} \left\{ \tilde{R}_{t-1} = 0, \tilde{L}_{t-1} = 0 \right\}, \quad J_t = \mathbb{1} \left\{ \tilde{R}_{t-1} = 0, \tilde{L}_{t} = 0 \right\}.$$  

The variable $I_t$ is the indicator based on the data through time $t - 1$ that a participant is at risk of the event being observed at time $t$; in other words, $I_t = 1$ means that all the variables $R_0, L_1, R_1, L_2, \ldots, L_{t-1}, R_{t-1}$ in the data vector (1) equal 0, which makes it possible that $L_t = 1$. Analogously, $J_t$ is the indicator based on the outcome data through time $t$ and censoring data before time $t$ that a participant is at risk of censoring at time $t$. By convention we let $J_0 = 1$.

Define the hazard function for survival at time $m \in \{1, \ldots, K\}$:

$$h(m, a, w) = P_0 (L_m = 1 | I_m = 1, A = a, W = w),$$

among the population at risk at time $m$ within strata of study arm and baseline variables. Similarly, for the censoring variable $C$, define the censoring hazard at time $m \in \{0, \ldots, K\}$:

$$g_R(m, a, w) = P_0 (R_m = 1 | J_m = 1, A = a, W = w).$$

We use the notation $g_A(a, w) = P_0(A = a | W = w)$ and $g = (g_A, g_R)$. Let $p_W$ denote the marginal distribution of the baseline variables $W$. We add the subscript 0 to $p_W$, $g$, $h$ to denote the corresponding quantities under $P_0$. The joint distribution $P_0$ on the observed data vector $O = (W, A, \Delta, \tilde{T})$ is completely characterized by the components $p_{W,0}, g_0, h_0$, i.e., $P_0 = (p_{W,0}, g_0, h_0)$.

### 3.2 RMST parameter definition in terms of potential outcomes

Define the potential outcomes $T_a : a \in \{0, 1\}$ as the event times that would have been observed had study arm assignment $A = a$ and censoring time $C = K$ been externally set with probability one. For a restriction time $\tau \in \{1, \ldots, K\}$ of interest, the target estimand is the difference between the restricted mean survival time setting study arm to $a = 1$ versus $a = 0$:

$$\theta^c = E \{\min(T_1, \tau) - \min(T_0, \tau)\}.$$  

The superscript $c$ denotes a causal parameter, that is, a parameter of the distribution of the potential outcomes $T_{1}$ and $T_{0}$. We prove in the Web Appendix that $E \{\min(T_a, \tau)\} = \sum_{t=0}^{\tau-1} S^c(t, a)$, where $S^c(t, a) = P(T_a > t)$ is the survival probability corresponding to the potential outcome under assignment to arm $A = a$. As a result, $\theta^c$ may be expressed as

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\[ \theta^c = \sum_{t=1}^{\tau-1} \left\{ S^c(t, 1) - S^c(t, 0) \right\}, \]  

since \( S^c(0, a) = 1 \) for \( a \in \{0, 1\}. \)

### 3.3 Identification of RMST parameter \( \theta^c \) in terms of observed data generating distribution \( P_0 \)

We show how the RMST parameter \( \theta^c \), which is defined above in terms of potential outcomes, can be equivalently expressed as a function \( \theta \) of the observed data distribution \( P_0(W, A, \Delta, \hat{T}) \), under the assumptions (a)–(d) below. This is useful since the potential outcomes are not always observed, in contrast to the observed data vector \((W, A, \Delta, \hat{T})\) for each participant (whose distribution we can make direct statistical inferences about); we refer to \( \theta \) as a statistical parameter, which is shorthand for saying it is a mapping from the observed data distribution \( P \in \mathcal{M} \) to \( \mathbb{R} \).

Define the following assumptions:

(a) \( T = \mathbb{1}(A = 0)T_0 + \mathbb{1}(A = 1)T_1 \) (consistency);
(b) \( A \) is independent of \((T_a, W)\), for each \( a \in \{0, 1\} \) (randomization);
(c) \( C \) is independent of \( T_a \) conditional on \((A, W)\), for each \( a \in \{0, 1\} \) (random censoring);
(d) \( g_{A,0}(a, w) > 0 \) and \( g_{R,0}(t, a, w) < 1 \) whenever the \( P_0\)-density of \( W \) is positive at \( W = w \), for each \( a \in \{0, 1\} \) and \( t \in \{0, \ldots, \tau - 1\} \) (positivity assumption).

We make assumptions (a)–(d) throughout the manuscript. Assumption (a) connects the potential outcomes to the observed outcome. Assumption (b) holds by design in a randomized trial. Assumption (c), which is similar to that in Rubin (1987), means that censoring is random within strata of treatment and baseline variables (which we abbreviate as “random censoring”). Assumption (d) states that each treatment arm has a positive probability, and that every time point has a hazard of censoring smaller than one, within each baseline variable stratum \( W = w \) with positive density under \( P_0 \).

Denote the survival function for \( T \) at time \( t \in \{1, \ldots, \tau - 1\} \) conditioned on study arm \( a \) and baseline variables \( w \) by

\[ S(t, a, w) = P(T > t | A = a, W = w). \]  

Similarly, define the following function of the censoring distribution:

\[ G(t, a, w) = P(C \geq t | A = a, W = w). \]  

Under assumptions (a)–(d), we have \( T \perp\!\!\!\perp C | A, W \) and therefore \( S(t, a, w) \) and \( G(t, a, w) \) have the following product formula representations:

\[ S(t, a, w) = \prod_{m=1}^{t} \{1 - h(m, a, w)\}; \quad G(t, a, w) = \prod_{m=0}^{t-1} \{1 - g_R(m, a, w)\}. \]
The potential outcome survival function \( S^c(t, a) \) can be equivalently represented in terms of the observed data distribution as

\[
S(t, a) = E_{pW} \prod_{m=1}^{t} \{1 - h(m, a, W)\},
\]

for \( t \in \{1, \ldots, K\} \), \( a \in \{0, 1\} \); equality of \( S^c(t, a) \) and the above display follows from (5) and

\[
S^c(t, a) = P(T_a > t) = E_{pW} P(T_a > t | W) = E_{pW} P(T > t | A = a, W) = E_{pW} S(t, a, W),
\]

where the third equality above follows from (a) and (b).

It follows from (2) that the causal parameter \( \theta^c \) is equal to the following statistical parameter:

\[
\theta = \sum_{t=1}^{T-1} \left[ E_{pW} \left\{ \prod_{m=1}^{t} \{1 - h(m, 1, W)\} \right\} - E_{pW} \left\{ \prod_{m=1}^{t} \{1 - h(m, 0, W)\} \right\} \right].
\]

Our goal is to estimate \( \theta \) based on \( n \) independent, identically distributed observations \( O_i = (W_i, A_i, \Delta_i, \bar{T}_i) \) drawn from \( P_0 \). We construct an estimator with properties (i)–(iv) in the introduction.

Since the parameter of interest \( \theta \) is defined as a function of \( (pW, h) \) through (7), a natural estimation strategy would be to plug estimates of \( pW \) and \( h \) in these formulas. Estimators constructed in this way are called substitution or plug-in estimators, and have the advantage that they remain within bounds of the parameter space; this is desirable in estimation of probabilities and other bounded parameters such as the RMST. Our proposed estimator is a substitution estimator.

Define independent censoring to be \( C \perp \perp (T_a, W) | A \), for each \( a \in \{0, 1\} \). This is a stronger (more restrictive) assumption than random censoring. We refer to a censoring mechanism \( G(t, a, w) \) as non-informative if it does not depend on \( w \), and as informative if it depends on \( w \). Under independent censoring, \( G(t, a, w) \) is non-informative.

4 Several estimators of RMST (\( \theta \)) from related work

4.1 Unadjusted estimators of \( \theta \): Kaplan–Meier and inverse probability weighted

Throughout this subsection only, we additionally assume independent censoring. This implies \( S(t, a) = \prod_{m=1}^{t} \{1 - h(m, a)\} \) for \( h(m, a) = P(L_m = 1 | I_m = 1, A = a) \), as proved in the Supplementary Material. Therefore, we have the following simpler representation of \( \theta \):
\[
\hat{\theta} = \sum_{t=1}^{\tau-1} \left[ \prod_{m=1}^{t} \{1 - h(m, 1)\} - \prod_{m=1}^{t} \{1 - h(m, 0)\} \right].
\] (8)

The Kaplan–Meier estimator for \(S(t, a)\) is defined as
\[
\hat{S}_{km}(t, a) = \prod_{m=1}^{t} \left\{ 1 - \frac{\sum_{i=1}^{n} \{I_{m,i} = 1, I_{m,i} = 1, A_i = a\}}{\sum_{i=1}^{n} \{I_{m,i} = 1, A_i = a\}} \right\},
\] (9)

where we set the above fraction to be 0 if the denominator is 0. The right side of (9) was obtained by substituting the empirical counterpart of each \(h(m, a)\) in the formula for \(S(t, a)\) above. The corresponding Kaplan–Meier estimator of \(\theta\) is defined analogously, as
\[
\hat{\theta}_{km} = \sum_{t=1}^{\tau-1} \left\{ \hat{S}_{km}(t, 1) - \hat{S}_{km}(t, 0) \right\}.
\]

Since \(\hat{\theta}_{km}\) is a smooth function of at most \(4(\tau - 1)\) empirical means, the delta method (Theorem 3.1 van der Vaart 1998) implies
\[
\sqrt{n}(\hat{\theta}_{km} - \theta) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} D_{km}(O_i) + o_P(1),
\]

where, for an observation \(O\),
\[
D_{km}(O) = -\sum_{t=1}^{\tau-1} \sum_{m=1}^{t} \left[ \frac{(2A - 1)I_m}{g_A(A)G(m, A)} \frac{S(t, A)}{S(m, A)} \{L_m - h(m, A)\} \right].
\] (10)

is the influence function of \(\hat{\theta}_{km}\). The above influence function \(D_{km}\) may be derived from Lemma 1 below, noting that the Kaplan–Meier estimator is the maximum likelihood estimator in the nonparametric model where only \((A, \Delta, \tilde{T})\) (and not \(W\)) are measured, and therefore it is asymptotically linear with influence function equal to the efficient influence function in the model for \((A, \Delta, \tilde{T})\). As a consequence, \(\sqrt{n}(\hat{\theta}_{km} - \theta)\) converges to a mean zero normal distribution with asymptotic variance \(\text{Var}(D_{km}(O))\).

This estimator is consistent and efficient for the case where only \((A, \Delta, \tilde{T})\) is observed. However, the unadjusted estimator is generally inefficient for the case where \((W, A, \Delta, \tilde{T})\) is observed. Intuitively, this is because the unadjusted estimator fails to leverage the prognostic information in baseline variables \(W\). Furthermore, under the less restrictive random censoring assumption, the unadjusted estimator will generally not be consistent, while adjusted estimators remain consistent if the censoring distribution is consistently estimated.

We next define the unadjusted, inverse probability weighted (IPW) estimator. Let \(\hat{G}_{km}(t, a)\) denote the Kaplan–Meier estimator of the censoring distribution \(G(t, a) = \prod_{m=0}^{t-1} \{1 - g_R(m, a)\}\), defined as
\[ \hat{G}_{km}(t, a) = \prod_{m=0}^{t-1} \left[ 1 - \frac{1}{\sum_{i=1}^{n} \mathbb{1}\{R_{m,i} = 1, J_{m,i} = 1, A_i = a\}} \right]. \]

The unadjusted IPW estimator of \( S(t, a) \) is defined as
\[ \hat{S}_{ipw}(t, a) = \frac{1}{n} \sum_{i=1}^{n} \frac{\mathbb{1}\{A_i = a, \tilde{R}_{t-1,i} = 0, \tilde{L}_{t,i} = 0\}}{\hat{g}_A(a) \hat{G}_{km}(t, a)}, \]
where \( \hat{g}_A(a) \) denotes the sample mean of \( \mathbb{1}\{A = a\} \). Zhao et al. (2016) show that
\[ \sqrt{n} \left( \hat{S}_{ipw}(t, a) - \hat{S}_{km}(t, a) \right) = o_P(1), \]
i.e., the asymptotic distributions of these two estimators are equal up to \( o_P(1/\sqrt{n}) \), and the estimator of \( \theta \) given by \( \hat{\theta}_{ipw} = \sum_{i=1}^{n} \left[ \hat{S}_{ipw}(t, 1) - \hat{S}_{ipw}(t, 0) \right] \) also satisfies
\[ \sqrt{n}(\hat{\theta}_{ipw} - \theta) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} D_{km}(O_i) + o_P(1). \]

An important consequence is that both \( \sqrt{n}(\hat{\theta}_{km} - \theta) \) and \( \sqrt{n}(\hat{\theta}_{ipw} - \theta) \) converge in distribution to \( N(0, \sigma_{km}^2) \), where \( \sigma_{km}^2 = \text{Var}(D_{km}(O)) \).

### 4.2 Covariate adjustment: inverse probability weighted estimators

A direct approach to estimating the RMST is to first construct an estimator \( \hat{h}(t, a, w) \) of \( h(t, a, w) \) and then standardize by plugging this into (7) with \( E_{Pw} \) replaced by the empirical distribution of \( W \). For example, \( \hat{h}(t, a, w) \) could be based on a Cox model fit combined with an estimator of the baseline hazard. If \( \hat{h}(t, a, w) \) is a consistent estimator of \( h(t, a, w) \), then under regularity conditions the corresponding substitution estimator based on (7) is consistent for \( \theta \). However, under model misspecification, this substitution estimator will generally be inconsistent. Model misspecification remains an issue even if slightly more flexible models (e.g., stratified by treatment arm) are fitted. This is particularly problematic for randomized trials with independent censoring, in which an unadjusted, consistent estimator can be obtained through the Kaplan–Meier survival function.

As an alternative, an adjusted, inverse probability weighted (IPW) estimator of \( S(t, a) \) [where here and below we use the definition of \( S(t, a) \) in (6)] is given by
\[ \hat{S}_{adj,ipw}(t, a) = \frac{1}{n} \sum_{i=1}^{n} \frac{\mathbb{1}\{A_i = a, \tilde{R}_{t-1,i} = 0, \tilde{L}_{t,i} = 0\}}{\hat{g}_A(a, W_i) \hat{G}(t, a, W_i)}, \]
where \( \hat{g}_A(a, w) \) and \( \hat{G}(t, a, w) \) are estimators of \( g_A(a, w) \) and \( G(t, a, w) \), respectively. The adjusted IPW estimator of the \( \tau \)-restricted mean survival time, given by
\( \hat{\theta}_{\text{adj,ipw}} = \sum_{t=1}^{T} \{ \hat{S}_{\text{adj,ipw}}(t, 1) - \hat{S}_{\text{adj,ipw}}(t, 0) \} \), is consistent for \( \theta \) if the estimators \((\hat{g}_A, \hat{g}_R)\) are consistent at a fast enough rate.

We focus on the case where \( \hat{g}_R(t, a, w) \) and \( \hat{g}(a, w) \) are estimators having saturated terms for time, treatment, and their interaction. We define such estimators as estimators that satisfy

\[
\sum_{i=1}^{n} J_{m,i} \left\{ R_{m,i} - \hat{g}_R(m, A_i, W_i) \right\} = \sum_{i=1}^{n} A_i J_{m,i} \left\{ R_{m,i} - \hat{g}_R(m, A_i, W_i) \right\}
\]

\[
= \sum_{i=1}^{n} \{ A_i - \hat{g}_A(1, W_i) \} = 0,
\]

for \( m = 0, \ldots, K - 1 \). An example of estimators with saturated terms for time, treatment and their interaction is given by maximum likelihood estimators for logistic regression models of \( g_R(t, a, w) \) and \( g_A(a, w) \), respectively, that include at least an intercept, main terms for \( A \) and each time \( t \in \{1, \ldots, K\} \), and interaction terms for \( A \) by each time \( t \in \{1, \ldots, K\} \); arbitrary and data-adaptive additional terms involving \( t, a, w \) can be included in these models.

When using \( \hat{G}(t, a, w) \) and \( \hat{g}(a, w) \) estimated with such saturated terms, under independent censoring, \( \hat{S}_{\text{adj,ipw}}(t, a) \) is consistent for \( S(t, a) \). If these models contain no terms involving \( w \), then \( \hat{S}_{\text{adj,ipw}}(t, a) \) and \( \hat{S}_{\text{ipw}}(t, a) \) (both using the corresponding estimators \( \hat{G} \) and \( \hat{g} \)) are identical. Williamson et al. (2014) use this observation to show that, under independent censoring, the asymptotic variance of \( \hat{S}_{\text{adj,ipw}}(t, a) \) is smaller or equal than the asymptotic variance of \( \hat{S}_{\text{ipw}}(t, a) \); this, together with the delta method, implies

\[
\sqrt{n} \left( \hat{\theta}_{\text{adj,ipw}} - \theta \right) \rightarrow N \left( 0, \sigma_{\text{adj,ipw}}^2 \right),
\]

where \( \sigma_{\text{adj,ipw}}^2 \leq \sigma_{\text{km}}^2 \). (Throughout, \( \rightarrow \) indicates convergence in distribution as \( n \) goes to infinity.) A weakness of \( \hat{\theta}_{\text{adj,ipw}} \) is that under informative censoring, it will generally be inconsistent if the model for \( G \) is misspecified. This motivates considering double robust estimators described in Sect. 4.3.

Adjusted estimators (such as the adjusted IPW above) often involve fitting a parametric model for \( g_A \), even though \( g_A \) is known by design in a randomized trial. Intuitively, the purpose of this model fit is to capture chance imbalances of the baseline variables \( W \) between study arms for a given data set; these imbalances can then be adjusted to improve efficiency. The general theory underlying efficiency improvements through estimation of known nuisance parameters such as \( g_A \) is presented, e.g., by Robins et al. (1994) and van der Laan and Robins (2003).

### 4.3 Augmented inverse probability weighted (double robust) estimator

We start by presenting the efficient influence function for estimation of \( \theta \) in model \( \mathcal{M} \). The following lemma may be proved by applying the delta method to the definition

\[
\sum_{i=1}^{n} \{ A_i - \hat{g}_A(1, W_i) \} = 0.
\]
of $\theta$ in (7) and using the efficient influence function of $S(t, a)$ as presented in Moore and van der Laan (2009a):

**Lemma 1** The efficient influence function for estimating $\theta$ in the model $\mathcal{M}$ is

$$D(O) = \sum_{m=1}^{\tau-1} [I_m Z(m, A, W) \{L_m - h(m, A, W)\} + S(m, 1, W) - S(m, 0, W)] - \theta,$$

where $Z(m, A, W) = Z_1(m, A, W) - Z_0(m, A, W)$, and

$$Z_a(m, A, W) = -\sum_{t=m}^{\tau-1} \frac{\mathbb{I}\{A = a\}}{g_A(a, W) G(m, a, W) S(m, a, W)} S(t, a, W).$$

For conciseness, we suppress the dependence of $D$ on $g$ and $h$. The function $D$ has two important properties for estimation of $\theta$. First, it is a doubly robust estimating function, i.e., for given estimators $\hat{h}$ and $\hat{g}$ of $h$ and $g = (g_A, g_R)$, respectively, the estimator formed by solving for $\theta$ in the following estimating equation is consistent if at least one of $h$ or $g$ is estimated consistently (while the other converges to a limit that may be incorrect):

$$0 = \sum_{i=1}^{n} \left\{ \sum_{m=1}^{\tau-1} \left[ \sum_{t=m}^{\tau-1} \frac{-2A_i - 1}{\hat{S}_A(A_i, W_i) \hat{G}(m, A_i, W_i)} \frac{\hat{S}(t, A_i, W_i)}{\hat{S}(m, A_i, W_i)} \{L_m - \hat{h}(m, A_i, W_i)\} \right] + \hat{S}(m, 1, W_i) - \hat{S}(m, 0, W_i) \right\} - \theta,$$

where $\hat{S}(m, a, w) = \prod_{m'=1}^{m} [1 - \hat{h}(m', a, w)]$ and $\hat{G}(m, a, w) = \prod_{m'=0}^{m-1} [1 - \hat{g}_R(m', a, w)]$. This estimator is often referred to as the augmented IPW estimator, and we denote it by $\hat{\theta}_{aipw}$. The double robustness property is desirable since it guarantees that improper adjustment for covariates through a misspecified working model for $h$ still leads to a consistent estimator of $\theta$ in randomized trials with random censoring if $g_R$ is consistently estimated.

Second, the efficient influence function (11) characterizes the information bound for estimation of $\theta$ in the model $\mathcal{M}$ (Bickel et al. 1997). Specifically, under consistent estimation of $h$ and $g$ at a sufficiently fast rate, $\hat{\theta}_{aipw}$ has variance smaller or equal to that of any regular, asymptotically linear estimator of $\theta$ in $\mathcal{M}$ (a property called local efficiency); in this case, if independent censoring holds, then $\hat{\theta}_{aipw}$ has equal or smaller asymptotic variance compared to $\hat{\theta}_{km}$. Unfortunately, under misspecification of the model for $h$, the estimator of $h$ will generally be inconsistent, which could lead to $\hat{\theta}_{aipw}$ having worse asymptotic efficiency than $\hat{\theta}_{km}$ under independent censoring. In other words, the added robustness of $\hat{\theta}_{aipw}$ may come at the price of lower efficiency compared to $\hat{\theta}_{km}$. This motivates the question of whether this added robustness can be achieved at no cost. I.e., can we construct a doubly robust estimator with the added
guarantee of equal or better asymptotic precision as $\hat{\theta}_{km}$ if independent censoring holds? We construct such an estimator below.

5 Proposed estimator

We develop a doubly robust estimator, denoted $\hat{\theta}_{\text{adj,eff}}$ that has properties (i)–(iv) of the introduction. We will sometimes use the following modified representation of the data set:

\[
\{(m, W_i, A_i, J_{m,i}, R_{m,i}, I_{m+1,i}, L_{m+1,i}) : m = 0, \ldots, K - 1; i = 1, \ldots, n\}. \tag{14}
\]

This data set is referred to as the long form, and the original data set \{(W_i, A_i, \Delta_i, \tilde{T}_i) : i = 1, \ldots, n\}, \tag{15}

is referred to as the short form. An observation in the long form data set is a vector of the form \((m, W_i, A_i, J_{m,i}, R_{m,i}, I_{m+1,i}, L_{m+1,i})\). We define the following auxiliary variables:

\[
M(W) = \sum_{t=1}^{\tau-1} \left[ S(t, 1, W) \frac{S(t, 0, W)}{g_A(1, W)} + S(t, 0, W) \right], \tag{16}
\]

\[
H(m, A, W) = -\sum_{t=m+1}^{\tau-1} \frac{(2A - 1)}{g_A(A, W)} \frac{1}{S(m, A, W)} G(m + 1, A, W). \tag{17}
\]

These auxiliary covariates are constructed from a decomposition of the efficient influence function targeting improved efficiency of the estimators as described after Theorem 2 below.

Our proposed estimator $\hat{\theta}_{\text{adj,eff}}$ is defined as the output of the following algorithm (which follows the TMLE template):

Step 1. Initial estimators Obtain initial estimators $\hat{g}_A$, $\hat{g}_R$, and $\hat{h}$ of $g_A$, $g_R$, and $h$, respectively. Let $\hat{p}_W$ denote the empirical distribution of $W$.

Step 2. Iteratively update estimates of $h$ and $g$ Initialize $l = 0$, and let $\hat{h}^l = \hat{h}$, $\hat{g}_A^l = \hat{g}_A$, $\hat{g}_R^l = \hat{g}_R$.

(a) Update $\hat{h}^l$. Let $\hat{S}^l$, $\hat{G}^l$ denote $S$, $G$ after substituting $\hat{h}^l$, $\hat{g}_R^l$, $\hat{p}_W$ for $h$, $g_R$, $p_W$ in (5) and (7). Augment each observation in the long form data set (14) by two covariates $\hat{Z}_{a}^l(m, A_i, W_i) : a \in \{0, 1\}$, where each $\hat{Z}_{a}^l(m, A_i, W_i)$ is constructed by substituting the estimates $\hat{S}^l$, $\hat{G}^l$, $\hat{g}_A^l$ evaluated at $(m, A_i, W_i)$ in (12). Estimate the parameter vector $\epsilon = (\epsilon_1, \epsilon_0)$ in the logistic hazard submodel $h^l_\epsilon$ for $h$:

\[
\logit h^l_\epsilon (m, a, w) = \logit \hat{h}^l(m, a, w) + \epsilon_1 \hat{Z}_{1}^l(m, a, w) + \epsilon_0 \hat{Z}_{0}^l(m, a, w), \tag{18}
\]
by computing the following maximum likelihood estimator:

\[ \hat{\epsilon} = \arg \max_{\epsilon} \sum_{i=1}^{n} \sum_{m=1}^{\tau-1} L_{m,i} \log \left\{ h_{\epsilon}'(m, A_i, W_i)^{L_m,i} \left( 1 - h_{\epsilon}(m, A_i, W_i) \right)^{1-L_m,i} \right\}. \quad (19) \]

The maximizer \( \hat{\epsilon} \) can be computed using standard statistical software by a logistic regression of \( L_{m,i} \) on the variables \( Z_{l}(m, A_i, W_i), \hat{Z}_{l}(m, A_i, W_i) \) among observations with \( L_{m,i} = 1 \) and \( m < \tau \) in the long form data set (14), and using \( \logit \hat{h}_{l}(m, A_i, W_i) \) as an offset. Define \( \hat{h}_{l+1} = h_{\epsilon}^{l} \).

(b) Update \( \hat{g}_{R}^{l} \). Let \( \hat{H}_{l}^{l}(m, A, W) \) denote \( H(m, A, W) \) with \( \hat{S}_{l}, \hat{G}_{l}, \hat{g}_{A}^{l} \) substituted for \( S, G, g_{A} \), respectively, in (17). Augment each observation in the long form data set (14) by \( \hat{H}_{l}^{l}(m, A_i, W_i) \). In the long form data set, estimate the parameter \( \gamma \) in the following logistic regression submodel for \( g_{R}(m, a, w) \):

\[ \logit g_{R,\gamma}^{l}(m, a, w) = \logit \hat{g}_{R}^{l}(m, a, w) + \gamma \hat{H}_{l}^{l}(m, a, w), \quad (20) \]

by logistic regression of \( R_{m,i} \) on the single covariate \( \hat{H}_{l}^{l}(m, A_i, W_i) \) and with offset \( \logit \hat{g}_{R}^{l}(m, A, W) \) among observations with \( m < \tau - 1 \) and \( J_{m,i} = 1 \). Denote the corresponding maximum likelihood estimate of \( \gamma \) by \( \hat{\gamma} \).

(c) Update \( \hat{g}_{A}^{l} \). Let \( \hat{M}_{l}(W) \) denote \( M(W) \) with \( \hat{g}_{A}^{l}, \hat{S}_{l} \) substituted for the corresponding components in (16). Augment each observation in the short form data set by \( \hat{M}_{l}(W_i) \). In the short form data set, estimate the parameter \( \nu \) in the following logistic regression submodel for \( g_{A}(1|w) \):

\[ \logit g_{A,\nu}^{l}(1|w) = \logit \hat{g}_{A}^{l}(1|w) + \nu \hat{M}_{l}(w), \quad (21) \]

by logistic regression of \( A_{i} \) on the covariate \( \hat{M}_{l}(W_i) \) and with offset \( \logit \hat{g}_{A}^{l}(1|W_i) \) among all participants \( i = 1, \ldots, n \). Denote the corresponding maximum likelihood estimate of \( \nu \) by \( \hat{\nu} \).

Define \( \hat{h}_{l+1} = h_{\epsilon}^{l}, \hat{g}_{R}^{l+1} = g_{R,\hat{\gamma}}, \) and \( \hat{g}_{A}^{l+1} = g_{A,\hat{\nu}} \).

Step 3. Update \( l = l + 1 \) and iterate the previous step until convergence. We stop at the first iteration for which the sample mean of the squared differences of predictions based on \( \hat{h}_{l}, \hat{g}_{R}, \hat{g}_{A}^{l} \) between step \( l \) and step \( l + 1 \) is smaller or equal to \( 10^{-4}/n \).

Denote \( \hat{h}^{*}, \hat{g}_{A}^{*}, \) and \( \hat{g}_{R}^{*} \) the estimators obtained in the last iteration of the above algorithm, and define the enhanced efficiency TMLE estimator of \( \theta \) as

\[ \hat{\theta}_{\text{adj, eff}} = \sum_{l=1}^{\tau-1} \left[ \frac{1}{n} \sum_{i=1}^{n} \prod_{m=1}^{l} \left\{ 1 - \hat{h}^{*}(m, 1, W_i) \right\} - \frac{1}{n} \sum_{i=1}^{n} \prod_{m=1}^{l} \left\{ 1 - \hat{h}^{*}(m, 0, W_i) \right\} \right]. \quad (22) \]

The above display is the substitution estimator of \( \theta \) based on (7) where the sample means over baseline variables \( W_i, i = 1, \ldots, n \) correspond to expectation with respect to the empirical distribution of \( W \).
Having defined the estimation algorithm, we now present our main results giving conditions under which \( \hat{\theta}_{\text{adj,eff}} \) is guaranteed to be at least as efficient as \( \hat{\theta}_{\text{adj,ipw}} \) and \( \hat{\theta}_{\text{km}} \).

**Theorem 1** (Equal or greater asymptotic efficiency compared to adjusted IPW estimator) Assume (a)–(d), \( \hat{g}^*_A \) and \( \hat{g}^*_R \) are \( n^{1/2} \)-consistent in \( L^2(P_0) \) norm, and \( \hat{h}^* \) converges to some limit \( h_1 \) in \( L^2(P_0) \) norm as \( n \to \infty \). Then we have the following convergence in distribution results:

\[
\sqrt{n} \left( \hat{\theta}_{\text{adj,eff}} - \theta \right) \to N \left( 0, \sigma_{\text{adj,eff}}^2 \right), \quad \sqrt{n} \left( \hat{\theta}_{\text{adj,ipw}} - \theta \right) \to N \left( 0, \sigma_{\text{adj,ipw}}^2 \right),
\]

where \( \sigma_{\text{adj,eff}}^2 \leq \sigma_{\text{adj,ipw}}^2 \). In addition, if \( h_1 \) equals the true \( h_0 \), then \( \hat{\theta}_{\text{adj,eff}} \) achieves the semiparametric efficiency bound in \( \mathcal{M} \).

The consistency rates required in our previous theorem are more restrictive than necessary to obtain the convergence in distribution \( \sqrt{n} (\hat{\theta}_{\text{adj,eff}} - \theta) \to N(0, \sigma_{\text{adj,eff}}^2) \). In the Web Appendix we present a more general result, Theorem 3, which shows that this convergence holds under standard, less restrictive, doubly robust convergence assumptions on \((\hat{g}^*, \hat{h}^*)\).

We next consider ways to construct the initial estimators of \( h \) and \( g \) for step 1 above. The outcome hazard function \( h \) may be estimated by running a prediction algorithm for the probability of \( L_m = 1 \) as a function of \( A, W, \) and \( m \) among observations with \( I_m = 1 \) in the long form data set (14). The censoring hazard \( g_R \) may be estimated by running an analogous prediction algorithm of the probability that \( R_m = 1 \) as a function of \( A, W, \) and \( m \) among observations with \( J_m = 1 \). In general, the functional relation between \( R_m \) and \( (A, W) \) is unknown to the researcher. Flexible statistical learning methods such as regression trees, support vector machines, neural networks, multivariate adaptive regression splines, boosting, and others may be used in these cases. Model stacking (Wolpert 1992) or super learning (van der Laan et al. 2007) may be used to build ensembles of these estimators. The interested reader is referred to Theorem 3 in the Web Appendix for technical conditions required from these estimators in order to maintain asymptotic normality and enhanced efficiency. The treatment mechanism \( g_A \) may be estimated by fitting a parametric model for the probability of \( A = 1 \) as a function of \( W \) in the short form data set. In a randomized trial, \( g_A \) is set by design. However, efficiency of the TMLE can be improved by estimating \( g_A \) using, e.g., the proportion of individuals in the treatment group, or a logistic regression model that contains baseline variables and an intercept term.

The following is our main result:

**Theorem 2** (Equal or greater asymptotic efficiency compared to Kaplan–Meier estimator, under independent censoring) Assume (a)–(d), independent censoring, and that \( \hat{h}^* \) converges as in the first sentence of Theorem 1. Assume also that \( \hat{g}^*_A, \hat{g}^*_R \) are estimated using models with saturated terms for time, treatment, and their interaction. Then

\[
\sqrt{n} \left( \hat{\theta}_{\text{adj,eff}} - \theta \right) \to N \left( 0, \sigma_{\text{adj,eff}}^2 \right), \quad \sqrt{n} \left( \hat{\theta}_{\text{ipw}} - \theta \right) \to N \left( 0, \sigma_{km}^2 \right),
\]
\[ \sqrt{n} \left( \hat{\theta}_{\text{adj,ipw}} - \theta \right) \to N \left( 0, \sigma_{\text{adj,ipw}}^2 \right), \quad \sqrt{n} \left( \hat{\theta}_{\text{km}} - \theta \right) \to N \left( 0, \sigma_{\text{km}}^2 \right), \]

where \( \sigma_{\text{adj,eff}}^2 \leq \sigma_{\text{adj,ipw}}^2 \leq \sigma_{\text{km}}^2 \).

These results guarantee that the proposed TMLE has asymptotic variance that never exceeds that of the Kaplan–Meier estimator, under independent censoring (when the latter is consistent). To the best of our knowledge, this is the first estimator to achieve the properties in the previous theorems for our problem.

The algorithm above [i.e., steps 1–3 and the formula (22)] that generates the TMLE \( \hat{\theta}_{\text{adj,eff}} \) combines key ideas from Moore and van der Laan (2009a), Rotnitzky et al. (2012) and Gruber and van der Laan (2012). Moore and van der Laan (2009a) present a TMLE algorithm for estimating the survival difference \( S(t, 1) - S(t, 0) \) in the model \( \mathcal{M} \), which involves a step similar to 2a above; this estimator has properties (i), (iii), and (iv) but not (ii). The crux of our approach to achieve property (ii) (without sacrificing the other properties) is to augment the censoring and treatment models through steps 2b and 2c. These augmented models use the covariates (16)–(17) that were specifically constructed to achieve property (ii).

The idea of augmenting censoring and treatment models to achieve enhanced efficiency properties can be traced back at least to Robins et al. (1994). More recently, Rotnitzky et al. (2012) built on this idea to construct an estimator that has equal or better asymptotic precision than a certain parametric family of estimators including the adjusted IPW estimator, and then Gruber and van der Laan (2012) showed how to do the same in the TMLE framework.

It is not trivial to determine precisely how to augment the censoring and treatment models in order to guarantee (ii) holds. We explain the intuition for how we achieved this, which uses general ideas from the above related work. Assume the conditions in Theorem 1. First, consider the simpler case where the censoring and treatment distributions \( g_R, g_A \) are known. Define the simplified TMLE to be as in steps 1–3 above, except omitting steps 2b and 2c and using the known \( g_R, g_A \) in step 2a. The simplified TMLE’s influence function equals the influence function of the adjusted IPW estimator minus the following expression (derived in the Web Appendix):

\[ M(W) [A - g_A(1, W)] + \sum_{m=0}^{\tau-2} J_m H(m, A, W) [R_m - g_R(m, A, W)], \tag{23} \]

for \( M \) and \( H \) the auxiliary variables in (16) and (17), respectively.

Second, consider the case where the censoring and treatment distributions \( g_R, g_A \) are unknown and estimates \( \hat{g}_R, \hat{g}_A \) are used by the TMLE that involves all of steps 1–3, called the enhanced efficiency TMLE (i.e., \( \hat{\theta}_{\text{adj,eff}} \)). The influence function for \( \hat{\theta}_{\text{adj,eff}} \) equals that of the simplified TMLE minus the latter’s projection on the tangent space \( T_{\theta_*} \) spanned by the scores of the models used to estimate \( g_R, g_A \). [See van der Vaart (1998, Section 25.3) for background on tangent spaces and projections as used here.] Subtracting off such a projection is helpful since it can only decrease or leave unchanged the influence function’s variance, which equals the asymptotic variance of the estimator. By augmenting the model for \( g_R \) by \( H \) as in (20) in step
2b, the corresponding score is the second term in (23); by augmenting the model for \( g_A \) by \( M \) as in (21) in step 2c, the corresponding score is the first term in (23). This implies (23) is in the tangent space \( T_{g^*} \), and therefore the influence function for \( \hat{\theta}_{\text{adj,eff}} \) is orthogonal to (23). Combining the above argument with the last line in the previous paragraph, it follows that the influence function for \( \hat{\theta}_{\text{adj,eff}} \) equals the adjusted IPW influence function minus the latter’s projection on \( T_{g^*} \). Therefore, \( \hat{\theta}_{\text{adj,eff}} \) has asymptotic variance at most that of the adjusted IPW estimator, which gives the main conclusion of Theorem 1. Theorem 2 then follows from the asymptotic equivalence of the adjusted IPW and Kaplan–Meier estimators under the added assumptions of independent censoring and the model for \( g_R \) being saturated as described above. A more detailed argument that fleshes out and justifies the above outline is in the Web Appendix.

In addition to the efficiency properties stated in the above results, our estimator inherits the doubly robust property of the Moore and van der Laan (2009a) TMLE (i.e., the TMLE above but without steps 2b and 2c). Under random censoring, this means that our proposal has two opportunities to achieve consistency in estimating the causal effect, in contrast to the proportional hazard model which relies exclusively on the assumption that the outcome regression is correctly specified.

Under the assumptions of Theorem 1, for a consistent estimate \( \hat{\sigma}_{\text{adj,eff}} \), a Wald-type confidence interval \( \hat{\theta}_{\text{adj,eff}} \pm z_{\alpha/2} \hat{\sigma}_{\text{adj,eff}} / \sqrt{n} \) is guaranteed to have \( 1 - \alpha \) asymptotic coverage probability. If the initial estimators \( \hat{h} \) and \( \hat{g}_R \) in step 1 are \( M \)-estimators (e.g., if they are estimated through maximum likelihood in parametric working models), the nonparametric bootstrap (Efron 1979) may be used to obtain a consistent estimate \( \hat{\sigma}_{\text{adj,eff}} \) (see Corollary 3.1 and 3.2 in Wellner and Zhan 1996). The performance of the nonparametric bootstrap is unknown when \( \hat{h} \) or \( \hat{g}_R \) are data-adaptive estimators (e.g., if \( \hat{h} \) involves variable selection). The development of a consistent variance estimator in this case remains an open question.

6 Motivating application and simulation study

6.1 CLEAR III trial

The CLEAR III trial (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III) is a completed Phase III multicenter randomized controlled trial (Hanley et al. 2017). 500 individuals with intraventricular hemorrhage (IVH) were randomized with equal allocation to receive either alteplase (treatment) or saline (control) for IVH removal. The primary outcome was defined as a score of 3 or less on the modified Rankin Scale (mRS) of functional disability at 180 days (where smaller values correspond to better function). The proportions with mRS at most 3 at 180 days were 48 versus 45% in the treatment versus control arms, respectively. A key secondary outcome was all-cause mortality at 180 days: 18 and 29% of patients experienced death by 180 days in the treatment versus control arms, respectively. Though covariate adaptive randomization was used to assign study arms, we ignore this in illustrating our method.
We reanalyzed data from the CLEAR III trial by defining the outcome as time to death in days from randomization, and the treatment effect as the difference in the RMST (at $\tau = 180$ days) comparing treatment versus control arms. Figure 1 displays the estimated Kaplan–Meier survival curve for each study arm. Using the Kaplan–Meier estimator, the unadjusted estimate of the difference in the RMST is 14.9 days (with standard error 5.4). The CLEAR III investigators identified several baseline variables believed to be prognostic for mortality; these include age, the Glasgow Coma Score (GCS), the National Institute of Health Stroke Scale (NIHSS) score, intracerebral hemorrhage (ICH) location (thalamus vs. other) and ICH volume. After adjusting for these baseline variables using our proposed method described in Sect. 5, the estimated difference in the RMST is 14.6 days (with standard error, SE, 5.0). Our adjusted estimator yields an estimated variance that is roughly 16% smaller than the (unadjusted) RMST difference based on the Kaplan–Meier estimator. In the context of the CLEAR III trial, such a precision gain would allow a reduction by approximately 70 (out of original 500) patients in the required sample size to achieve a desired power, if a Wald-test were used based on the adjusted versus the unadjusted estimator. In the CLEAR III trial, the adjusted IPW and AIPW estimators yielded similar results to our proposed method (adjusted IPW: RMST 13.8, SE 5.0; AIPW: RMST 14.7, SE 5.0) (Table 1).

6.2 Data generating distributions

We refer to each of the twelve data generating distributions used in our simulation study as a simulation scenario. For each simulation scenario, the true parameter value, i.e., the restricted mean survival time $\theta$, is known (i.e., the data generating mechanism is constructed by us such that $\theta$ has a certain value). Specifically, we consider two values
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Table 1 Estimated RMST (standard error) with 95% bias-corrected and accelerated (BCa) bootstrap confidence intervals based on the CLEAR III trial

| Estimator | RMST (SE) | 95% BCa confidence interval |
|-----------|-----------|-----------------------------|
| KM        | 14.9 (5.4) | (4.9, 25.5)                 |
| IPW       | 14.9 (5.4) | (4.9, 25.5)                 |
| Adj. IPW  | 13.8 (5.0) | (3.7, 24.0)                 |
| AIPW      | 14.7 (5.0) | (4.7, 24.6)                 |
| TMLE      | 14.6 (5.0) | (4.7, 24.5)                 |

of the restricted mean survival time: $\theta = 0$ (no treatment effect) and $\theta = 14.9$ (positive treatment effect). More generally, features of the data generating distributions that are set by us include the following: the true RMST, the randomization probabilities, the prognostic value of the baseline covariates as a fraction of the prognostic value in the CLEAR III dataset, and the model for the censoring hazard conditional on baseline covariates and treatment status.

Each data generating distribution is constructed based on the empirical, joint distribution of $(W, Y)$ from the CLEAR III data. Different scenarios are generated by modifying this distribution depending on our choice for the treatment effect and for coarsening of the correlation between $W$ and $Y$, as described below; we also set the censoring distribution. The advantage of using the empirical, joint distribution of $(W, Y)$ from a real data set, rather than specifying a simple parametric model for this distribution, is that the former is more closely tied to a real clinical setting. It also avoids overly optimistic performance evaluation which could result if data generating distributions were set to be parametric models and the same models were used in the estimation procedure; this would fail to capture any performance degradation due to model misspecification, which is relevant in real applications.

Our data generating distributions are based on resampling data from the CLEAR III trial (described in Sect. 6.1) in order to mimic key features of the trial. The baseline variables for each participant are $W = (W_1, W_2, W_3, W_4, W_5) =$ (age, GCS, NIHSS score, ICH location, ICH volume), each scaled to have mean 0 and standard deviation 1. The outcome is time until death in days, denoted by $T$. Define the treatment effect $\theta$ to be the difference in the RMST at restriction time $\tau = 180$ days. We compare the performance of the following estimators defined above: Kaplan–Meier, unadjusted IPW, adjusted IPW, augmented IPW (AIPW), and proposed TMLE. The adjusted IPW is referred to simply as IPW. We ran simulations at two sample sizes: $n = 500$ and $n = 2000$.

We consider twelve data generating distributions, where we vary the correlation between $T$ and $W$ (using three scenarios labeled A, B, C defined below), the treatment effect $\theta$, and the censoring mechanism. Some of these are set to mimic features of the CLEAR III data, as described below. For each data generating distribution and sample size, we generated 10,000 simulated data sets, and report on the empirical distribution of each estimator.

The key feature that determines the magnitude of precision gains for the adjusted estimators is how correlated the baseline variables are with the outcome. To give a rough sense of the observed correlations in the CLEAR III trial data set, we
fit a logistic regression model for the hazard of death that includes time, treatment, time by treatment interactions, and main effects for each baseline variable in $W = (W_1, W_2, W_3, W_4, W_5)$. We report $\exp(\hat{\beta}_j)$: $j = 1, 2, 3, 4, 5$, where $\hat{\beta}_j$ is the estimated coefficient for $W_j$ in the model fit. These were $1.5, 0.9, 1.7, 1.0, 1.1$, respectively. We do not assume the above model is correct; we only used it to roughly measure correlations in the CLEAR III data set. In our simulations, the data generating distributions for scenario A mimic the above correlations; in scenarios B and C, the correlations are reduced as described below.

In each simulated trial, the data vector $(W, A, T, C)$ for each participant is generated as an independent, identically distributed draw from a joint distribution $P$ that satisfies assumptions (a)–(d). This distribution will depend on the scenario A–C, censoring mechanism, and treatment effect $\theta$. For scenario A, each simulated participant’s data vector is generated by first resampling a participant with replacement from the CLEAR III data among the 491 patients who did not drop out, and recording only his/her pair $(W, T)$. The resulting distribution preserves the empirical correlation between $W$ and $T$ from the CLEAR III trial. Such resampling may lead to more realistically complex distributions than drawing from a regression model fit for $T$ given $W$. In each scenario B and C, we generate an initial $(W, T)$ as just described, and with probability 0.5 and 1, respectively, we replace $W$ by an independent draw (with replacement) from the marginal distribution of $W$ in the CLEAR III trial. The impact is that the correlation between $T$ and $W$ decreases as one proceeds from scenario A to scenario C, with scenario C having $T$ and $W$ independent (i.e., baseline variables not prognostic for the outcome).

Next, we assign $A$ independent of $(W, T)$ by a Bernoulli draw with probability 0.5 of being 1 or 0. This ensures that the randomization assumption (b) holds, and induces a distribution with $\theta = 0$ (no treatment effect). We also consider distributions with a positive treatment effect ($\theta = 14.9$); this value was selected since it is the unadjusted Kaplan–Meier estimate of $\theta$ from the CLEAR III data. To obtain such distributions, we generate $(W, A, T)$ as above except now if $A = 1$ we add to $T$ an independently generated draw from a $\chi^2$ distribution with mean $\mu = 56$, where $\mu$ was calibrated to achieve $\theta = 14.9$.

For each scenario and treatment effect $\theta \in \{0, 14.9\}$, given $(W, A, T)$ we generate $C$ based on either a non-informative or informative censoring model. Specifically, the censoring time $C$ is generated based on drawing from the corresponding distribution $g_R(t, a, w)$ given below, for each $t \in \{0, \ldots, T - 1\}$ in turn:

- **Non-Informative** $g_R$: logit $P[R_t = 1 | J_t = 1, A, W] = -5.5 + 0.007t$;
- **Informative** $g_R$: logit $P[R_t = 1 | J_t = 1, A, W] = -6.5 + 0.007t + 0.6W_3A + 0.3(W_1 + W_5)$.

The percentage of censored patients due to drop-out depends on the censoring model, treatment effect and scenario. The non-informative and informative censoring distributions yield on average 62–68 and 32–38% censored patients due to drop-out, respectively (with values varying within these intervals depending on $\theta$ and the scenario A–C). Though these are higher drop-out rates than typically expected in a randomized trial, we evaluate performance under this substantial censoring to illustrate that the estimators can have good performance even in this challenging case.
tions (a)–(d) from Sect. 3.3 hold for all of our data generating distributions, while independent censoring holds only under the non-informative censoring mechanism.

In our simulations, we do not include a scenario in which the conditional censoring and survival distributions are inconsistent. Our aim is to illustrate the theoretical properties of our estimators in comparison with existing methods. If the censoring and survival distributions are both inconsistent, the magnitude of the bias depends on the amount and type of misspecification, and therefore simulation results under a particular misspecification model are uninformative.

6.3 Estimators $\hat{h}$, $\hat{g}_A$, $\hat{g}_R$ used by the adjusted estimators

Each of $\hat{h}$, $\hat{g}_A$, $\hat{g}_R$ is based on a logistic regression working model fit. The logistic regression model for $g_A$ includes an intercept and a main term for each component of $W$. Since treatment is assigned with $P(A = 1 | W) = 0.5$ for all simulated studies, the model for $g_A$ is correctly specified. To account for censoring due to patient drop-out, the model for $g_R$ for the IPW includes saturated terms for time, treatment, and their interaction. The model for $g_R$ for the adjusted estimators includes main terms for time (linear), treatment and their interaction, in addition to main terms for $W_1$ and $W_5$ and a treatment by $W_3$ interaction. Therefore, the model for $g_R$ satisfies the condition in Theorem 2 and is correctly specified when the data is generated under either non-informative or informative censoring. We use the long form data set to fit the model for $g_R$, and set $\hat{g}_R(m, a, w) = 0$ for $m$ when the corresponding risk set is empty. The model for $h$ consists of an intercept, main terms for time (as a real value rather than categorical) and treatment, and treatment-time interaction, as well as main terms for each component of $W$. For scenarios A and B, the data generating distribution is based on resampling pairs $W, T$ from the CLEAR III trial; therefore, the parametric model for $h$ is likely to be misspecified, which could easily occur in practice. However, in scenario C where $T$ is independent of $W$, the model for $h$ is correctly specified.

6.4 Simulation results

Tables 2 and 3 summarize the main results of our simulations, at sample sizes $n = 500$ and $n = 2000$, respectively. Under non-informative censoring, where all the estimators are consistent, all have relatively small bias. Under informative censoring and scenarios A and B (where the baseline covariates are prognostic for the outcome), the Kaplan–Meier and unadjusted IPW estimators are more biased compared to their adjusted counterparts. The informative censoring distribution depends on baseline variables ($W_1, W_3, W_5$), which under scenarios A and B are also correlated with the outcome, therefore causing confounding and non-negligible bias even at the large sample size ($n = 2000$); the bias is relatively small for scenario C, since censoring and the outcome do not share any common causes.

We measure relative efficiency as the ratio of mean squared error (RMSE) comparing the Kaplan–Meier estimator to each of the other estimators. First consider scenario A, where the correlation between $W$ and $T$ mimics that from the CLEAR
### Table 2 Simulation results for studies of size \( n = 500 \)

| Scenario | Estimator | Zero treatment effect (\( \theta = 0 \)) | Positive treatment effect (\( \theta = 14.9 \)) |
|----------|-----------|----------------------------------|---------------------------------|
|          |           | Bias | Var    | MSE | RMSE | CP  | Bias | Var    | MSE | RMSE | CP  |
|          |           |      |        |     |      |     |      |        |     |      |     |
| Non-informative censoring, i.e., censoring independent of baseline variables |
| A        | KM        | 0.031 | 35.23  | 35.23 | 1.000 | 0.947 | 0.013 | 26.54  | 26.54 | 1.000 | 0.948 |
|          | IPW       | 0.032 | 35.59  | 35.59 | 0.990 | 0.947 | 0.044 | 26.86  | 26.86 | 0.988 | 0.947 |
|          | Adj. IPW  | 0.001 | 31.76  | 31.76 | 1.109 | 0.947 | 0.004 | 24.29  | 24.29 | 1.093 | 0.954 |
|          | AIPW      | -0.020 | 31.22  | 31.21 | 1.128 | 0.952 | -0.027 | 23.95  | 23.95 | 1.108 | 0.946 |
|          | TMLE      | -0.019 | 30.96  | 30.96 | 1.138 | 0.950 | -0.074 | 23.74  | 23.74 | 1.118 | 0.948 |
| B        | KM        | 0.062 | 36.09  | 36.09 | 1.000 | 0.945 | -0.059 | 27.40  | 27.40 | 1.000 | 0.952 |
|          | IPW       | 0.063 | 36.46  | 36.46 | 0.990 | 0.942 | -0.029 | 27.72  | 27.72 | 0.988 | 0.950 |
|          | Adj. IPW  | 0.069 | 35.89  | 35.89 | 1.005 | 0.946 | -0.046 | 27.26  | 27.26 | 1.005 | 0.950 |
|          | AIPW      | 0.069 | 35.56  | 35.56 | 1.015 | 0.944 | -0.087 | 26.94  | 26.94 | 1.017 | 0.944 |
|          | TMLE      | 0.069 | 35.27  | 35.27 | 1.023 | 0.944 | -0.133 | 26.71  | 26.73 | 1.025 | 0.946 |
| C        | KM        | -0.048 | 35.52  | 35.52 | 1.000 | 0.957 | -0.035 | 26.91  | 26.91 | 1.000 | 0.939 |
|          | IPW       | -0.048 | 35.90  | 35.90 | 0.989 | 0.957 | -0.004 | 27.22  | 27.22 | 0.989 | 0.937 |
|          | Adj. IPW  | -0.046 | 36.41  | 36.41 | 0.976 | 0.950 | -0.013 | 27.50  | 27.50 | 0.978 | 0.943 |
|          | AIPW      | -0.046 | 36.05  | 36.05 | 0.985 | 0.954 | -0.048 | 27.23  | 27.23 | 0.988 | 0.939 |
|          | TMLE      | -0.046 | 35.76  | 35.76 | 0.993 | 0.954 | -0.092 | 27.00  | 27.01 | 0.996 | 0.938 |
Table 2 continued

| Scenario | Estimator | Zero treatment effect ($\theta = 0$) | Positive treatment effect ($\theta = 14.9$) |
|----------|-----------|-------------------------------------|------------------------------------------|
|          |           | Bias | Var | MSE | RMSE | CP   | Bias | Var | MSE | RMSE | CP   |
| Informative censoring, i.e., censoring depends on baseline variables |
| A        | KM        | 0.802 | 31.48 | 32.12 | 1.000 | 0.951 | 1.760 | 22.48 | 25.58 | 1.000 | 0.940 |
|          | IPW       | 0.794 | 31.61 | 32.25 | 0.996 | 0.953 | 1.775 | 22.59 | 25.73 | 0.994 | 0.940 |
|          | Adj. IPW  | -0.108 | 29.48 | 29.49 | 1.089 | 0.931 | 0.079 | 22.92 | 22.93 | 1.116 | 0.951 |
|          | AIPW      | -0.045 | 29.22 | 29.22 | 1.099 | 0.947 | 0.097 | 22.44 | 22.44 | 1.140 | 0.947 |
|          | TMLE      | -0.044 | 29.08 | 29.08 | 1.105 | 0.946 | 0.045 | 22.18 | 22.18 | 1.153 | 0.952 |
| B        | KM        | 0.368 | 33.25 | 33.38 | 1.000 | 0.945 | 0.882 | 23.12 | 23.90 | 1.000 | 0.945 |
|          | IPW       | 0.357 | 33.34 | 33.52 | 0.996 | 0.945 | 0.893 | 23.23 | 24.03 | 0.994 | 0.945 |
|          | Adj. IPW  | -0.084 | 33.68 | 33.68 | 0.991 | 0.942 | 0.046 | 24.31 | 24.31 | 0.983 | 0.948 |
|          | AIPW      | -0.050 | 33.36 | 33.36 | 1.000 | 0.943 | 0.056 | 24.13 | 24.13 | 0.990 | 0.940 |
|          | TMLE      | -0.050 | 33.09 | 33.09 | 1.009 | 0.942 | 0.004 | 23.93 | 23.92 | 0.999 | 0.941 |
| C        | KM        | 0.039 | 31.88 | 31.88 | 1.000 | 0.957 | 0.039 | 24.02 | 24.02 | 1.000 | 0.952 |
|          | IPW       | 0.025 | 32.02 | 32.02 | 0.996 | 0.953 | 0.046 | 24.13 | 24.13 | 0.995 | 0.953 |
|          | Adj. IPW  | 0.022 | 32.66 | 32.66 | 0.976 | 0.951 | 0.053 | 24.90 | 24.90 | 0.965 | 0.948 |
|          | AIPW      | 0.041 | 32.51 | 32.51 | 0.980 | 0.957 | 0.051 | 24.77 | 24.77 | 0.970 | 0.949 |
|          | TMLE      | 0.041 | 32.24 | 32.24 | 0.989 | 0.956 | 0.001 | 24.65 | 24.65 | 0.974 | 0.947 |

The bias, variance (VAR), mean squared error (MSE) and coverage probabilities (CP) based on bias-corrected and accelerated bootstrap 95% confidence interval are displayed for the Kaplan–Meier (KM), unadjusted inverse probability weighted (IPW), adjusted IPW (Adj. IPW), augmented IPW (AIPW) and proposed targeted minimum loss based (TMLE) estimator. The relative MSE (RMSE) is the ratio of the MSE for the KM estimator to the other estimators.
| Scenario | Estimator | Zero treatment effect ($\theta = 0$) |  | Positive treatment effect ($\theta = 14.9$) |  |
|----------|-----------|---------------------------------|---|---------------------------------|---|
|          | Bias     | Var   | MSE  | RMSE  | Bias     | Var   | MSE  | RMSE  |
| **Non-informative censoring, i.e., censoring independent of baseline variables** | | | | | | | | |
| A        | KM       | 0.069 | 8.86 | 8.86  | 1.000  | 0.015 | 6.79 | 6.79  | 1.000 |
|          | IPW      | 0.070 | 8.95 | 8.96  | 0.990  | 0.016 | 6.87 | 6.87  | 0.988 |
|          | Adj. IPW | 0.057 | 8.04 | 8.04  | 1.102  | 0.027 | 6.12 | 6.12  | 1.110 |
|          | AIPW     | 0.052 | 7.88 | 7.88  | 1.125  | 0.015 | 6.00 | 6.00  | 1.133 |
|          | TMLE     | 0.051 | 7.81 | 7.81  | 1.134  | 0.060 | 5.95 | 5.95  | 1.142 |
| B        | KM       | 0.022 | 8.92 | 8.92  | 1.000  | 0.060 | 6.68 | 6.68  | 1.000 |
|          | IPW      | 0.022 | 9.01 | 9.01  | 0.990  | 0.029 | 6.76 | 6.76  | 0.989 |
|          | Adj. IPW | 0.019 | 8.77 | 8.77  | 1.018  | 0.033 | 6.60 | 6.60  | 1.012 |
|          | AIPW     | 0.017 | 8.69 | 8.69  | 1.027  | 0.075 | 6.50 | 6.51  | 1.027 |
|          | TMLE     | 0.017 | 8.62 | 8.62  | 1.035  | 0.119 | 6.45 | 6.46  | 1.035 |
| C        | KM       | 0.008 | 8.78 | 8.78  | 1.000  | 0.035 | 6.77 | 6.77  | 1.000 |
|          | IPW      | 0.008 | 8.87 | 8.87  | 0.990  | 0.004 | 6.85 | 6.85  | 0.989 |
|          | Adj. IPW | 0.008 | 8.91 | 8.91  | 0.986  | 0.005 | 6.87 | 6.87  | 0.986 |
|          | AIPW     | 0.009 | 8.82 | 8.82  | 0.996  | 0.048 | 6.80 | 6.80  | 0.996 |
|          | TMLE     | 0.009 | 8.82 | 8.82  | 0.996  | 0.038 | 6.79 | 6.79  | 0.997 |
Table 3 continued

| Scenario | Estimator | Zero treatment effect ($\theta = 0$) | Positive treatment effect ($\theta = 14.9$) |
|----------|-----------|-------------------------------------|---------------------------------------------|
|          |           | Bias      | Var      | MSE      | RMSE     | Bias      | Var      | MSE      | RMSE     |
|          |           |           |          |          |          |           |          |          |          |
| Informative censoring, i.e., censoring depends on baseline variables |
| A        | KM        | 0.797     | 7.78     | 8.42     | 1.000    | 1.646     | 5.65     | 8.36     | 1.000    |
|          | IPW       | 0.790     | 7.82     | 8.44     | 0.997    | 1.661     | 5.68     | 8.44     | 0.991    |
|          | Adj. IPW  | −0.082    | 7.32     | 7.32     | 1.150    | −0.041    | 5.66     | 5.67     | 1.478    |
|          | AIPW      | −0.022    | 7.20     | 7.20     | 1.168    | −0.012    | 5.53     | 5.53     | 1.513    |
|          | TMLE      | −0.023    | 7.15     | 7.15     | 1.178    | −0.057    | 5.48     | 5.48     | 1.526    |
| B        | KM        | 0.407     | 8.08     | 8.24     | 1.000    | 0.863     | 5.76     | 6.50     | 1.000    |
|          | IPW       | 0.396     | 8.12     | 8.27     | 0.997    | 0.875     | 5.78     | 6.55     | 0.993    |
|          | Adj. IPW  | −0.054    | 8.15     | 8.15     | 1.011    | 0.012     | 6.05     | 6.05     | 1.075    |
|          | AIPW      | −0.016    | 8.08     | 8.08     | 1.020    | 0.020     | 5.98     | 5.98     | 1.087    |
|          | TMLE      | −0.016    | 8.02     | 8.02     | 1.028    | −0.024    | 5.93     | 5.93     | 1.097    |
| C        | KM        | −0.012    | 8.12     | 8.12     | 1.000    | −0.006    | 5.85     | 5.85     | 1.000    |
|          | IPW       | −0.025    | 8.16     | 8.16     | 0.995    | 0.002     | 5.88     | 5.88     | 0.995    |
|          | Adj. IPW  | −0.028    | 8.23     | 8.23     | 0.987    | −0.010    | 5.98     | 5.98     | 0.978    |
|          | AIPW      | −0.009    | 8.19     | 8.19     | 0.992    | −0.015    | 5.96     | 5.95     | 0.983    |
|          | TMLE      | −0.009    | 8.12     | 8.12     | 1.000    | −0.061    | 5.90     | 5.91     | 0.991    |

The bias, variance (VAR), and mean squared error (MSE) are displayed for the Kaplan–Meier (KM), unadjusted inverse probability weighted (IPW), adjusted IPW (Adj. IPW), augmented IPW (AIPW) and proposed targeted minimum loss based (TMLE) estimator. The relative MSE (RMSE) is the ratio of the MSE for the KM estimator to the other estimators.
III trial data. The proposed estimator $\hat{θ}_{adj, eff}$ has relative efficiency gains in the range 12–14% compared to the Kaplan–Meier estimator, under non-informative censoring. This means that a prespecified analysis plan using our proposed TMLE could have required roughly 11% ≈ 1 – (1/1.12) fewer patients (55 out of 500) to achieve the same power; alternatively, the trial sample size could be conservatively planned assuming no precision gain, and then using $\hat{θ}_{adj, eff}$ would lead to increased power if baseline variables are prognostic for the outcome. The efficiency gains of $\hat{θ}_{adj, eff}$ are similar under both types of censoring at sample size $n = 500$. However, the gains are larger under informative censoring at $n = 2000$ (reaching 53% in one case); this is due to the bias of the unadjusted estimators (which, unlike the adjusted estimators, are inconsistent) making a substantial contribution to the mean squared error at the larger sample size.

Next consider scenario C, where baseline variables are independent of $T$. For this scenario, all of the estimators are consistent under both censoring distributions. There are small losses in relative MSE for the adjusted estimators, due to their introducing unnecessary variability by adjusting for baseline variables unrelated to the outcome. These precision losses are generally smaller at the larger sample size $n = 2000$ (Table 3) compared to $n = 500$.

The unadjusted IPW estimator has similar bias and variance as the Kaplan–Meier estimator, as predicted by theory. The adjusted IPW estimator is not as efficient as the double robust estimators AIPW and TMLE in scenarios A and B.

The TMLE $\hat{θ}_{adj, eff}$ has similar bias compared to the AIPW estimator. The TMLE variance is slightly smaller, which translates into a relative MSE reduction of about 1% comparing the TMLE to the AIPW estimator in scenarios A and B. This corresponds with a reduction in sample size of about 1%. The cost per patient in the CLEAR III trial was approximately $29,000, so that a 1% reduction in the sample size of 500 gives savings of approximately $143,564. More importantly, it is unethical to run a trial longer and with more patients than absolutely necessary to achieve the research objectives. Our method allowing for a reduction in the sample size may be important in trials with life threatening and debilitating conditions as in the CLEAR III trial.

Other advantages of the TMLE compared to the AIPW estimator are: the TMLE has property (ii), i.e., guaranteed equal or better asymptotic efficiency compared to the Kaplan–Meier estimator under independent censoring; the TMLE is guaranteed to be within the bounds of the parameter space for $θ$. The latter property guarantees that the estimated RMST for each study arm falls in the interval $[0, τ]$ with probability one, which is not guaranteed for the AIPW estimator; an RMST outside the interval $[0, τ]$ would be non-interpretable.

Using the R code in the Web Appendix, computation of the proposed estimator took 3.5 and 16.7 minutes for sample sizes 500 and 2000, respectively, for one of the simulated trials. This computation time includes fitting the initial estimators for the event hazard, as well as the censoring and the treatment mechanism. It was performed using R version 3.2.3 on a MacBook Air with an Intel Core i5 1.3 GHz processor and 4 GB of RAM.
7 Discussion

Under random censoring, our estimator is consistent if either the outcome or censoring model is correctly specified, i.e., our estimator is doubly robust. This is in contrast to the proportional hazard model, which relies exclusively on assumptions on the outcome model. When the dimension of the baseline variables is large relative to the sample size, the curse of dimensionality precludes the use of nonparametric estimators or saturated parametric models (Robins and Ritov 1997). A potential way to address this is to incorporate data-adaptive model selection in constructing the initial estimators in step 1 of the TMLE procedure, such as model stacking (Wolpert 1992) or super learning (van der Laan et al. 2007). The asymptotic properties of the resulting estimator then require conditions (f)–(g) in Theorem 3 of the Web Appendix. These conditions would hold automatically for the MLE in a parametric model, but need to be verified for data-adaptive estimators. van der Laan (2014) proposed an estimator for the case of a cross-sectional study that relaxes assumption (f), and we conjecture that this approach might be generalizable to our problem.

In our presentation of the TMLE algorithm we have assumed that the initial estimators \( \hat{g}_R \) and \( \hat{g}_A \) contain saturated terms for treatment, time, and their interaction. When using data-adaptive methods, such restriction can be avoided by including the aforementioned saturated terms in the logistic regression models (20)–(21) in step 2 of the TMLE algorithm.

Estimators with similar properties may be developed under the estimating equation approach, using the general the general theory presented by Rotnitzky et al. (2012). Their theory, however, requires the use of parametric models for the nuisance parameters \( \hat{g}_R \), \( \hat{g}_A \), and \( h \). In contrast, our estimators can be implemented when these nuisance parameters are estimated based on data-adaptive methods. This is particularly relevant in the context of informative censoring, when the functional relation between time to censoring and baseline covariates is unknown.

Precision gains from adjustment for prognostic baseline variables can be converted into shorter duration trials by using information monitoring. That is, the trial continues until a prespecified information level is achieved. Since improved precision implies (asymptotically) a faster information accrual rate, the trial duration may be shorter.

Our method assumes that censoring is confounded with the time to event only by baseline variables. In the presence of time dependent confounding between censoring and the event time, our proposal may be adapted by augmenting the censoring and outcome models to include time-varying confounders. It may be possible to retain the properties (i)–(iv) in this context by extending the proof techniques from the Web Appendix. These properties are still relevant under time dependent confounding, since the use of proportional hazard models often yields biased estimators in this context, as discussed by Cole et al. (2003).

We defined independent censoring as \( C \perp \perp (T_a, W) \mid A \). Another possible definition of independent censoring, which is more commonly used when discussing the unadjusted estimator, is \( C \perp \perp T_a \mid A \) (which leaves out \( W \) altogether). The latter assumption is weaker (less restrictive) than the former. The covariate adjustment method of Zhang (2014) guarantees enhanced efficiency properties under the latter definition. Our TMLE estimator requires the former definition to achieve the enhanced
efficiency property (ii). On the other hand, our TMLE estimator has the advantage over Zhang (2014) and \( \hat{\theta}_{km} \) of remaining consistent under violations to the assumption that \( C \perp \perp T_a | A \), as long as random censoring holds and at least one of the censoring or survival distributions is consistently estimated.

Most clinical research studies use discrete time scales to measure the time to event. This is the case of our application and simulation studies, in which survival was measured in days. We conjecture that there would not be any technical difficulties in extending our approach to consider a continuous time to event, e.g., by replacing discrete time hazards by their continuous counterpart, as well as replacing certain sums over time by the appropriate martingale integrals (see e.g., Bai et al. 2017). A potential practical limitation is that the software and literature for machine learning based estimation of continuous time hazards (required for the nuisance parameters) is relatively scarce in comparison to that of binary classification, which may be used for estimation of discrete time hazards. Among the few methods that can be used for this problem are (semi)-parametric models such as Cox regression and accelerated failure time models.

If time is measured on a continuous scale, implementation of our methods requires discretization. The specific choice of the discretization intervals may be guided by what is clinically relevant. For example, in clinical applications with time to death outcomes, the clinically relevant scale would typically be a day. In the absence of clinical criteria to guide the choice of discretization level, a concern is that too coarse of a discretization may lead to potentially meaningful information losses. A question for future research is how to optimally set the level of discretization in order to trade off information loss versus estimator precision. Another area for future research is to consider discretization levels that get finer with sample size.

Lastly, the asymptotic properties of our method outlined in Theorems 1 and 2 rely on solving the corresponding score equations up to a factor \( o_P(n^{-1/2}) \) (see the proof of Theorem 3 in the Web Appendix). While it is possible that this is achieved in one iteration of our algorithm, this will not necessarily be the case. Recent ideas in targeted learning (van der Laan and Gruber 2016) may be used to construct an estimator that solves the relevant equations in one step. In the cited paper, the authors introduce the concept of a universal least favorable submodel, in which solving the score equations takes one step. However, current algorithms to estimate the parameter in such submodel rely on recursively updating the initial estimator of the tilting submodel. Therefore, it is unclear to us whether using this method in its current form would yield faster algorithms. Solving the estimating equations in one step may have other advantages such as guaranteed convergence of the algorithm.

Acknowledgements Funding was provided by Patient-Centered Outcomes Research Institute (Grant No. ME-1306-03198), U.S. Food and Drug Administration (US) (Grant No. HHSF223201400113C) and National Institute of Neurological Disorders and Stroke (US) (Grant No. U01NS062851).

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