Chapter 18
RCTs with Time-to-Event Outcomes and Effect Modification Parameters

Ori M. Stitelman, Victor De Gruttola, C. William Wester, Mark J. van der Laan

Current methods used to evaluate effect modification in time-to-event data, such as the Cox proportional hazards model or its discrete time analog the logistic failure time model, posit highly restrictive parametric statistical models and attempt to estimate parameters that are specific to the model proposed. These methods, as a result of their parametric nature, tend to be biased and force practitioners to estimate parameters that are convenient rather than parameters they are actually interested in estimating. The TMLE improves on the currently implemented methods in both robustness, its ability to provide unbiased estimates, and flexibility, allowing practitioners to estimate parameters that directly answer their question of interest.

We apply the methods presented in the previous chapter, as well as introduce two new parameters of interest designed to quantify effect modification, to the Tshepo study. The Tshepo study is an open-label, randomized, $3 \times 2 \times 2$ factorial design HIV study conducted at Princess Marina Hospital in Gaborone, Botswana, to evaluate the efficacy, tolerability, and development of drug resistance to six different first-line combination antiretroviral treatment (cART) regimens. We focus on the effect of two nonnucleoside reverse transcriptase inhibitor (NNRTI)-based cART therapies to which subjects were randomized. The two therapies of interest are efavirenz (EFV) and nevirapine (NVP).

Three statistical questions are of interest:

1. Is there a causal effect of EFV vs. NVP on time to viral failure, death, or treatment modification, or some combination of the three?
2. Does baseline CD4 level modify the effect of EFV vs. NVP on time to viral failure, death, or treatment modification, or some combination of the three?
3. Does the effect of EFV vs. NVP on time to viral failure, death, or treatment modification, or some combination of the three differ by sex?

M.J. van der Laan and S. Rose, *Targeted Learning: Causal Inference for Observational and Experimental Data*, Springer Series in Statistics, DOI 10.1007/978-1-4419-9782-1_18,

Wester et al. (2010) performed an analysis of the Tshepo study using Cox proportional hazards analysis to address statistical questions 1 and 3 above. They concluded that there was no significant difference by assigned NNRTI in time to virological failure. They also presented a slightly less than significant result that women receiving NVP-based cART tended to have higher virological failure rates than the EFV-treated women. Furthermore, they concluded that individuals treated with NVP had shorter times to treatment modification than individuals treated with EFV (this result was highly statistically significant). Using the TMLE, we will readdress these questions as well as explore question 2. The TMLE results will be compared to results from a Cox proportional hazards analysis, and the advantages of using TMLE will be illustrated. This data analysis was originally presented in Stitelman and van der Laan (2011b). We conclude with an appendix presenting extensions of TMLE incorporating time-dependent covariates.

18.1 Data Structure

Time-to-event data capture information about the amount of time, T, it takes for a subject to experience a particular event. Usually one is interested in assessing the effect of a particular treatment, A, on the amount of time, T, it takes for the event of interest to occur. For the analysis performed here we are only concerned with binary levels of treatment, $A \in \{0, 1\}$, and a vector of baseline covariates W. We assume T is discrete and takes on the values $\{1, \ldots, \tau\}$, where τ is the last possible time the subjects are monitored. In the case where T is not discrete, one may discretize time into fine enough cut points as to not lose any signal in the data. The censoring time, C, is the last time at which a subject is observed, which might be marked by the end of the study, or an earlier dropout.

The observed data consist of n i.i.d. replicates of $O = (W, A, \tilde{T}, \Delta)$, where $\tilde{T} = \min(T, C)$ and $\Delta = I(T \leq C)$. Thus $\tilde{T}$ is the last time point observed for a particular individual and Δ is an indicator variable that denotes whether or not the event was observed at that time point. In the observed data, each subject accounts for one line in the data set, and we will refer to this data structure as short-form data structure I. Data structure I in Fig. 18.1 is a sample data set displaying values for four subjects from this observed data structure, and W_1 and W_2 are two sample covariates measured at baseline.

An alternative representation of this data structure, which we refer to as long-form data structure II, is a more appropriate way of thinking about the data for our purposes. Define $N(t) = I(\tilde{T} \leq t, \Delta = 1)$ as the counting process that denotes whether an event has occurred or not and $A(t) = I(\tilde{T} \leq t, \Delta = 0)$ as the counting process that codes right-censoring events. Thus $dN(t) = 0$ for all time points up until there is an observed failure time event, and at time t of the observed event, $dN(t) = 1$. After a censoring event, $dN(t)$ can never jump from 0 to 1 since the event can no longer be observed. Similarly, $dA(t)$ remains 0 for all times the observation is uncensored and $dA(t) = 1$ at the time the observation becomes censored.

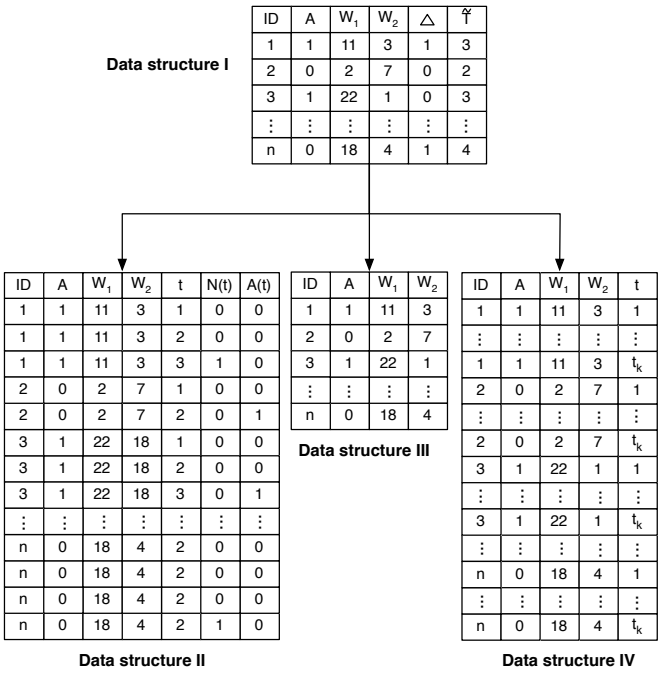

Fig. 18.1 Data structures

Thus, the observed data may be represented in their long form as n i.i.d. observations of $O = (W, A, dN(t), dA(t) : t = 1, \ldots, \tau) \sim P_0$, where P_0 denotes the probability distribution of the observed data structure O. In this representation of the observed data structure, each subject contributes a line of data for each time point at which they were observed up until their event happens, or they are censored. Furthermore, the values measured at baseline, A and W, are just repeated at their initial values for each time point. Data structure II in Fig. 18.1 shows the exact same observations from data structure I, but in their long form.

The subject with ID 1 has $\tilde{T} = 3$ and $\Delta = 1$. This individual was observed for three time periods, and during the third time period the subject had the event of interest. As a result, subject 1 contributes three lines of data to the long form, as can be seen in data structure II in Fig. 18.1. The subject's event process, $N(t)$, remains zero up until time 3 when it jumps to 1, and the subject's censoring process, $A(t)$, remains 0 for all time points since the subject is never right censored. All covariates measured at baseline remain the same for all time points. Subject 2, on the other hand, was right censored at time point 2, so that this subject's event was never observed, resulting in $\tilde{T} = 2$ and $\Delta = 0$. Thus, subject 2 contributes two lines to the data in their long form and $N(t)$ is zero for all t, since the event was not observed, and the censoring-counting process, $A(t)$, jumps to 1 at time 2 since

the subject was censored at that time. A, W_1, and W_2 remain constant at every time point. Contributions from subjects 3 and 4 to the data sets in both the short and long form are included in Fig. 18.1 as additional examples. The data in their long form may be thought of as being conditional on the failure time event or right censoring not having occurred before time t. So each observation contributes a line in the long form of the data for each time point at which the subject has neither experienced the event nor been censored. We also say that, at each time point at which the subject is still at risk of failing or being right censored, it contributes a line of data. Data structure III is used in estimating the treatment mechanism and data structure IV plays a special role in the evaluation of the target parameter. Both will be discussed further later in the chapter.

18.2 Cox Proportional Hazards and Failure Time Models

In 1972, Sir David Cox introduced the Cox proportional hazards model for the estimation of survival curves. The model is based on the proportional hazards assumption and assumes that the effect of treatment and covariates on a hazard follows a particular parametric form. The proportional hazards assumption states that survival curves for different strata must have hazard functions for which their ratio is constant in time.

Even though the Cox proportional hazards model represented a very important breakthrough for analyzing survival data, resulted in important theory, and beautifully generalized multiplicative intensity models for modeling intensities of general counting processes (Andersen et al. 1993), its stringent assumptions make these models susceptible to the same criticism as parametric regression models.

Over 35 years after the introduction of the model, the proportional hazards assumption is still assumed to hold for the majority of data analyses in survival analysis. In fact, there seems to be a common misconception that all semiparametric methods in survival analysis are susceptible to the shortcomings of the Cox proportional hazards model. In this section we will discuss the flaws of the discrete time analogue of the Cox proportional hazards model as well as the Cox proportional hazards model.

It is common in analyses that intend to test whether or not a treatment or exposure, A, has an effect on a particular time-to-event outcome, to assume an a priori specified model for the conditional hazard and to test if the coefficient in front of A in the specified model is different from zero. For continuous time, a Cox proportional hazards model is typically employed, and for discrete failure times, a logistic failure time model is used. It is common practice in both models to model the effect

of time as flexibly as possible and to model the effect of the treatment and covariates, if they are adjusted for, with a linear parametric model.

The following is a typical model for modeling the conditional hazard in discrete time, $P(dN(t) = 1 \mid N(t-1) = 0, A(t-1) = 0, A, W)$:

$$\alpha_1 + \gamma_2 I(t = 2) + \ldots + \gamma_\tau I(t = \tau) + \beta_1 A + \beta_2 W. \tag{18.1}$$

The parameters in the above model for the conditional hazards are then estimated with maximum likelihood estimation, and the p-value for the null hypothesis $H_0 : \beta_1 = 0$ is examined to determine if one can conclude that β_1 is significantly different from zero. Such parameter estimates are contingent on how well the a priori specified model approximates the hazard. However, the model is highly restrictive, and, as a result, the estimate of β_1 may be highly biased with respect to its desired target (presumably, the logarithm of the relative hazard). In most cases, little work is done to assess how well the model does in approximating the true conditional hazard. Even if formal tests are carried out to test the validity of the Cox proportional hazards model, a procedure that reports the test for $H_0 : \beta_1 = 0$ if the null hypothesis of the model is correct is not rejected and reports something else is still subject to severe bias in estimation and assessment of uncertainty. The latter practice, though common, lacks any statistical foundation.

Similarly, the Cox proportional hazards model for continuous failure times specifies the effect due to A and W in terms of a linear model, while it models the baseline hazard as a function of time t nonparametrically. If the model is correct, the coefficient in front of A in the Cox proportional hazards model is the log-relative hazard (RH), where RH is defined as the ratio of the hazard at time t, conditional on $A = 1$, and the hazard at time t, conditional on $A = 0$, within a stratum defined by *any* particular value of W. The Cox proportional hazards model relates the hazard for a particular subject, $\lambda_i(t)$, with baseline data (W_i, A_i), to the baseline hazard, $\lambda_0(t)$, as follows:

$$\lambda_i(t) = \lambda_0(t) e^{\beta_1 A_i + \beta_2 W_i},$$

which may be rearranged in the following way:

$$\log\left[\frac{\lambda_i(t)}{\lambda_0(t)}\right] = \beta_1 A_i + \beta_2 W_i.$$

We will now show how the same parameter under the Cox proportional hazards assumption may be recast in terms of conditional survival probabilities. Let $f(t)$ equal the derivative of the cumulative distribution function $F(t)$ of a continuous survival time:

$$f(t) = \lim_{\delta \to 0}\left(\frac{F(t+\delta) - F(t)}{\delta}\right).$$

Since the survival probability, $S(t)$, equals $1 - F(t)$, the derivative of $S(t)$, $d/dt[S(t)]$, equals $-f(t)$. The hazard, λ, equals $f(t)/S(t)$, which may be rewritten as

$$\lambda(t) = -\frac{d}{dt}[\log S(t)]. \tag{18.2}$$

Solving Eq. (18.2) for $S(t)$ yields

$$S(t) = \exp(-\Lambda(t)), \tag{18.3}$$

where $\Lambda(t) = \int_0^t \lambda(u)\,du)$ is the cumulative hazard. It easily seen that, under the Cox proportional hazards assumption, the ratio of the conditional hazards is equal to the ratio of the conditional cumulative hazards, which is equal to the ratio of log survival probabilities [by (18.3)]. Thus, β_1 may be written in terms of survival probabilities as follows: for any time point t_k

$$\beta_1 = \log\left(\frac{\log S(t_k \mid A = 1, W)}{\log S(t_k \mid A = 0, W)}\right). \tag{18.4}$$

To conclude, β_1 can also be represented as an average over all time points t_k of (18.4) and all covariate values W. Most would agree that it is very difficult to comprehend what the average of the log ratio of log survival probabilities means in terms of the effect of A on the outcome. A parameter β_1 is a parameter only defined on the Cox model, but it can be extended as a parameter in a nonparametric model in many possible ways. It can be represented in terms of an average over time of log hazard ratios or the log of the ratio of the log conditional survival probabilities. These two extensions represent very different parameters for most conditional distributions of T, given (A, W), with very different interpretations, but they happen to be equal to each other for distributions that satisfy the constraints of the Cox proportional hazards model. If one believes the Cox proportional hazards model to be valid, then one also needs to believe that these different representations of β_1 as parameter of the distribution of the data are equal to each other.

In RCTs, the Cox proportional hazards analysis is typically implemented without adjusting for baseline covariates. In this case, the coefficient of the marginal structural Cox proportional hazards model, $\lambda_{T_a}(t) = \lambda_0(t)\exp(\beta a)$, can also be represented, for any weight function $w(t)$, as

$$\beta = \sum_{t_k} w(t_k) \log\left(\frac{\log S_1(t_k)}{\log S_0(t_k)}\right),$$

where $S_a(t_k) = P(T_a > t_k) = E_W S(t_k \mid A = a, W)$ is the treatment-specific survival function. The rationale for using a marginal Cox proportional hazards model $E(dN(t) \mid \tilde{T} \geq t, A) = \lambda_0(t)\exp(\beta A)$ is that (1) individuals have been randomized to treatment groups, and thus those two groups should be reasonably balanced with respect to the levels of all covariates, and (2) censoring is independent of (T, W). Under these assumptions, one indeed has that $E(dN(t) \mid \tilde{T} \geq t, A = a) = P(T_a = t \mid T_a \geq t)$, so that the Cox proportional hazards model for the conditional hazard of T, given A, is equivalent to a Cox proportional hazards marginal structural model for the causal hazard. So under these two assumptions the coefficient β in a Cox

proportional hazards model for the conditional hazard of T, given A, represents a log causal relative hazard.

However, even though treatment/exposure is randomized in RCTs, dependent censoring is often informative, so that by ignoring covariates one may end up with a biased estimate of the causal effect of A on the event of interest. In addition, the estimate of the relative hazard is biased if the effect of A is not constant over time (a violation in the proportional hazards assumption). Thus these estimates can still be very biased, even under randomization, due to dependent censoring or violations in the proportional hazards assumption. In observational studies, practitioners may attempt to adjust for possible confounders by adding them as linear terms in the model. However, this is often done in an ad hoc way and many times covariates are added and removed solely based on how their inclusion in the model affects the estimate of the coefficient β_1 of the treatment A of interest.

Extensions of these methods are also commonly used to assess whether or not a variable V, a single baseline covariate within W, modifies the effect A on the outcome of interest. If the effect of A differs at different levels of V, then V is termed an effect modifier. A typical test for whether V is an effect modifier is to add an interaction term $A \times V$ to the above model and assess whether the coefficient on that term is significant in exactly the same way as was done above for just A.

Whether one adjusts for baseline covariates or not, these methods are usually biased due to the fact that they are dependent on highly restrictive parametric models that are typically not representative of the data-generating distribution. Furthermore, the parameters in these models are difficult to interpret even if the models are correct due to the fact that they were chosen because they are convenient to estimate, as opposed to natural parameters that directly address the questions practitioners are interested in answering.

18.3 Model and Parameters of Interest

We now examine the advantages of defining the parameter of interest as a function of the data-generating distribution, as well as introduce several interesting parameters of interest in time-to-event studies. Rather than choosing the parameter of interest because it is convenient within the chosen model, one can define the parameter of interest as a function of the data-generating distribution, $\Psi(P_0)$. By defining the parameter in this fashion, one can estimate the feature of the data-generating distribution that is of interest. Furthermore, by defining the parameter of interest in this way, it has meaning absent the validity of the Cox proportional hazards model.

The treatment-specific survival curve at a particular time point t_k is a simple example of this type of parameter, $Pr(T_a > t_k)$, where T_a is the counterfactual event time T one would have observed had an individual's treatment been set, possibly contrary to fact, to treatment level a. By formulating a set of causal assumptions through the use of a SCM, as visualized by a causal graph, one may define the distribution of the counterfactual outcomes indexed by an intervention on some treat-

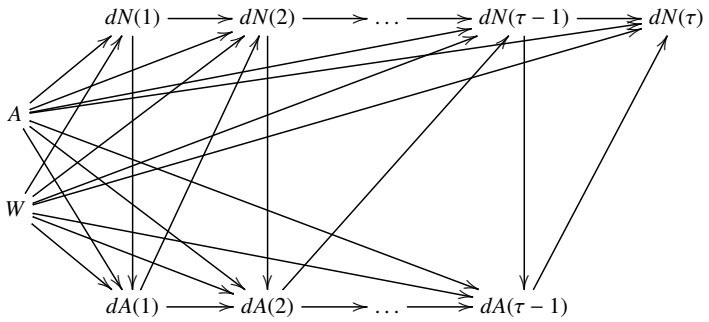

Fig. 18.2 Causal assumptions (exogenous errors omitted for simplicity)

ment and censoring nodes in the SCM. Then one may define a causal parameter as a difference between these counterfactual distributions of the outcome for different interventions on the treatment and censoring nodes.

In order to link the SCM to the observed data, the distribution of the observed data is assumed to be implied by the SCM. The SCM includes the distribution of the error/exogenous nodes and the deterministic functions that define each endogenous node as a function of its parents and a error. Typically, one assumes that the observed data structure corresponds with a subset of the nodes, such as all the endogenous nodes. Under certain causal assumptions one can then show that the causal effect of interest can be identified as a parameter of the distribution of the observed data, $\Psi(P_0)$. Figure 18.2 posits a set of causal assumptions in the form of a causal graph in which our data structure corresponds with the displayed nodes. Exogenous nodes are suppressed for simplicity. This is common practice for displaying that each displayed node has an exogenous node with an arrow going into it and no arrows going into any other nodes.

Necessary conditions typically stated to make causal parameters identifiable may be made through the use of this causal graph, namely, the consistency assumption and CAR assumption. The CAR assumption is arranged by assuming the strong sequential randomization assumption on the intervention nodes of the causal graph. In the analysis presented below, the treatment is in fact randomized; thus there is no arrow from W to A in the causal graph. Note, that simple unobserved nodes that only effect A or the censoring process $dA(t)$, but not the future outcome process $dN(t)$, do not violate these assumptions. This is because such nodes do not produce unblocked backdoor paths to the future outcome process, $dN(t)$.

Another assumption that may not be expressed within the causal graph is necessary in order for a parameter of interest to be identifiable from the observed data. This assumption is known as the positivity assumption, and was discussed in detail in Chap. 10. Suppose that the causal quantity of interest is the additive causal effect $P(T_1 > t_0) - P(T_0 > t_0)$ of treatment on survival at time t_0. The positivity assumption states, in particular, that there is no level of W that is completely predictive of

treatment level A. However, since treatment is randomized, this is not an issue due to the design of the experiment in the Tshepo study. In addition, since we are only interested in the censoring nodes set at value 0, the positivity assumption also states that for all levels of the covariate W, at each time $t \leq t_0$, the conditional hazard of being censored at time t is bounded away from 1.

The causal graph in Fig. 18.2 suggests the following likelihood factorization:

$$P_0(O) = \overbrace{P_0(W)}^{Q_{W,0}} \overbrace{P_0(A)}^{g_{A,0}} \prod_{t=1}^{\tau} \overbrace{P_0(dN(t) \mid \bar{N}(t-1), \bar{A}(t-1), A, W)}^{Q_{dN(t),0}}$$
$$\prod_{t=1}^{\tau} \underbrace{P_0(dA(t) \mid \bar{N}(t), \bar{A}(t-1), A, W)}_{g_{dA(t),0}}.$$

Thus, the likelihood is factorized into a portion Q_0, corresponding to the conditional distributions of the nonintervention nodes, and a portion g_0, corresponding to the conditional distributions of the censoring and treatment nodes. Q_0 is composed of the distribution of the baseline covariates $Q_{W,0}$, and $Q_{dN(t),0}$ the conditional distribution of the binary indicators $dN(t)$, given its parents. We have that g_0 is further factorized into the treatment mechanism, $g_{A,0}$, and censoring mechanism, $g_{dA(t),0}$, which involves the conditional distributions of the binary censoring indicators $dA(t)$, given its parents.

We note that $Q_{dN(t),0}$ and $g_{dA(t),0}$ are identified by the discrete intensities $E_0(dN(t) \mid A, W, \bar{N}(t-1), \bar{A}(t-1)) = I(\tilde{T} \geq t)\bar{Q}_0(t \mid A, W)$ and $E_0(dA(t) \mid A, W, \bar{N}(t), \bar{A}(t-1)) = I(N(t) = 0, A(t-1) = 0)\bar{g}_0(t \mid A, W)$. Note that these two intensities of event process N and censoring process A indeed equal an indicator of being at risk times a function of t, A, W. Under CAR, it follows that $\bar{Q}_0(t \mid A, W) = P_0(T = t \mid T \geq t, A, W)$ equals the conditional hazard of the failure time T, and, similarly, $\bar{g}_0(t \mid A, W) = P_0(C = t \mid C \geq t, A, W)$ equals the conditional hazard of the censoring time C. Let's also define $S_0(t_k \mid A, W) = P_0(T > t_k \mid A, W)$, which is the conditional survival of the event of interest, and can be expressed as a function of the conditional hazard $\bar{Q}_0(t \mid A, W)$ under CAR as $S_0(t_k \mid A, W) = \prod_{t=1}^{t_k} \left(1 - \bar{Q}_0(t \mid A, W)\right)$.

By intervening in the SCM, as visualized by the causal graph, on A and $dA(t)$ by setting treatment A equal to the desired treatment a and setting $dA(t)$ equal to 0, or, equivalently, no censoring for all t, one obtains the distribution of the event process under the desired treatment and without censoring. This counterfactual distribution of the data structure under an intervention can be identified from the observed data, under the stated assumptions, in the g-formula. All of the nodes that are intervened upon in the causal graph are set to their intervened-upon level in the likelihood, and all the conditional distributions for those nodes are removed from the likelihood since they are no longer random variables. The following is the resulting g-computation formula, or distribution of the data (W, T_a) under the intervention:

$$Q_{W,0}(W) \prod_{t=1}^{\tau} Q_{dN(t),0}(dN(t) \mid \bar{N}(t-1), A(t-1) = 0, A = a, W).$$

We can now write the marginal treatment-specific survival probability, $P_0(T_a > t_k)$, in terms of the data-generating distribution, P_0:

$$\Psi_a(P_0)(t_k) = Pr(T_a > t_k) = E_0\left(S_0(t_k \mid A = a, W)\right).$$

Parameters that combine $\Psi_1(P_0)(t_k)$ and $\Psi_0(P_0)(t_k)$ allow one to quantify the effect of a change of A on T. Three examples are the marginal additive difference in the probability of survival, the log relative risk of survival, and the marginal log hazard of survival:

$$\begin{aligned}
\Psi_{RD}(P_0)(t_k) &= \Psi_1(P_0)(t_k) - \Psi_0(P_0)(t_k),\\
\Psi_{RR}(P_0)(t_k) &= \log\left(\frac{\Psi_1(P_0)(t_k)}{\Psi_0(P_0)(t_k)}\right),\\
\Psi_{RH}(P_0)(t_k) &= \log\left(\frac{\log(\Psi_1(P_0)(t_k))}{\log(\Psi_0(P_0)(t_k))}\right).
\end{aligned}$$

For ease of interpretation we prefer the first two of these parameters. However, for completeness, we show that the third parameter, which represents the parameter targeted by a marginal structural Cox proportional hazards model $P(T_a = t \mid T_a \geq t) = \lambda_0(t)\exp(\beta a)$, may also be estimated through the methods presented here. One should note that the parameter $\Psi_{RH}(P_0)(t_k)$ is undefined at t_k for which $P_0(T_a > t_k) = 1$. The above parameters quantify the effect of A at a particular time point, t_k; therefore, averages of the above parameters over a set of time points may also be of interest.

One possible method for estimating the mean counterfactual outcome as expressed in the parameters proposed above is MLE and construct the substitution estimator $\Psi(Q_n) = \psi_n^{MLE}$ according to the mapping $\Psi()$. Thus, it is necessary to estimate $Q_{W,0}$ and $\bar{Q}_0(t \mid A, W)$ and, consequently, its corresponding conditional survival function, $S_0(t_k \mid A, W)$. This estimator is consistent when both of these distributions are estimated consistently. We estimate $Q_{W,0}$ with nonparametric maximum likelihood estimation. In practice, several models have been used for $\bar{Q}_0(t \mid A, W)$. Many practitioners specify a parametric model a priori, often using main terms logistic regression, as in Eq. (18.1), and obtain the maximum likelihood estimate within this highly restrictive model. [Obtaining the estimates of the parameters in Eq. (18.1) can be done by using logistic regression with data structure II.]

This parametric approach almost certainly leads to biased estimates of $\bar{Q}_0(t \mid A, W)$, and thus a biased estimate of $\Psi(Q_0)$, since it is likely that the true $\bar{Q}_0$ is not contained in this highly restrictive model. If the model does not contain the true $\bar{Q}_0$, then the estimates of $\bar{Q}_0$ and $\Psi(Q_0)$ will generally not be consistent. For this reason a nonparametric model for $\bar{Q}_0$ often represents the realistic knowledge about $\bar{Q}_0$. Since this nonparametric model is very large, sieve-based (data-adaptive) maximum likelihood estimation (i.e., loss-based machine learning), involving fine-tuning of the amount of smoothing used, becomes necessary. Many different methods have been developed for estimating the effect of covariates on a binary outcome in the nonparametric model including regression trees, DSA, and k-nearest neigh-

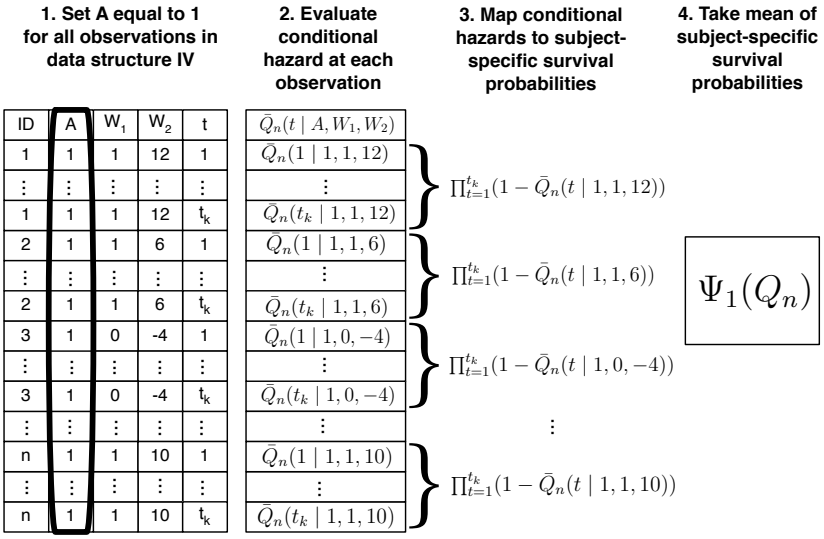

Fig. 18.3 Mapping $\bar{Q}_n$ and $Q_{W,n}$ into $\Psi(Q_n)$

bors. Rudser et al. (2008) used one of these methods, a nonparametric tree estimator, for estimating the survival distribution and subsequently $\Psi(Q_0)$. Even though a single estimator for estimating these distributions in the nonparametric model may yield consistent estimates, super learner will converge to the true distribution at a faster rate.

Once these estimates Q_n are obtained, the MLE of the treatment-specific survival, $\Psi_a(Q_0)(t_k)$ is the substitution estimator obtained by plugging in Q_n:

$$\Psi_a(Q_n)(t_k) = \frac{1}{n}\sum_{i=1}^{n} S_n(t_k \mid A = a, W_i).$$

Figure 18.3 demonstrates how to map $\bar{Q}_n$ and $Q_{W,n}$ into $\Psi_1(Q_n)$, an estimate of the treatment-specific survival curve at $a = 1$ using data structure IV from Fig. 18.1. The MLE of the parameters presented in this section can be generated by combining MLE estimates of the treatment-specific survival curves under alternative treatments.

18.4 Effect Modification Parameters

Parameters that quantify the level of effect modification due to another baseline variable V may also be of interest in studies aimed at assessing the effect of a treat-

ment, A, at different levels of V. However, we must now consider an SCM with an explicit node for the effect modifier V, instead of collapsing it into a single node W. First, let's consider a V that occurs after the baseline covariates W but before treatment and the censoring and event processes. This SCM implies the following factorization of the likelihood:

$$\begin{aligned} P_0(O) = P_0(W)P_0(V \mid W)P_0(A \mid V, W) \\ \times \prod_{t=1}^{\tau} P_0(dN(t) \mid \bar{N}(t-1) = 0, \bar{A}(t-1), A, V, W) \\ \times \prod_{t=1}^{\tau} P_0(dA(t) \mid \bar{N}(t), \bar{A}(t-1) = 0, A, V, W), \end{aligned}$$

and the corresponding g-formula for the intervention $A = a$, $V = v$, and all censoring nodes equal to zero:

$$P_0(W) \prod_{t=1}^{\tau} P_0(dN(t) \mid \bar{N}(t-1), \bar{A}(t-1) = 0, A = a, V = v, W).$$

As before, the MLE only requires an estimate of the marginal distribution of W, and $\bar{Q}_0(t \mid A, W)$. We will define the following parameters of interest to measure the causal effect modification when the effect modifier occurs after W:

$$\Psi_{RD}^{CEM}(P_0) = \sum_{t_k} w(t_k)[(\Psi_{11}(P_0)(t_k) - \Psi_{01}(P_0)(t_k)) - (\Psi_{10}(P_0)(t_k) - \Psi_{00}(P_0)(t_k))], \quad (18.5)$$

$$\Psi_{LR}^{CEM}(P_0) = \sum_{t_k} w(t_k) \left[\log \frac{\log(\Psi_{11}(P_0)(t_k))}{\log(\Psi_{01}(P_0)(t_k))} - \log \frac{\log(\Psi_{10}(P_0)(t_k))}{\log(\Psi_{00}(P_0)(t_k))} \right], \quad (18.6)$$

where $\Psi_{11}(P_0)(t_k)$ is counterfactual survival at t_k setting V to 1 and A to 1, and so on. That is, the first and second subscript code the level a and v for treatment and effect modifier, respectively. Here, $w(t_k)$ are time-varying weights. These weights may be dependent on the question of interest, or they may be set to the reciprocal of an estimate of the variance of the parameter estimate at the particular time, or simply be set to 1. We will weight each time-point-specific estimator by the reciprocal of its estimated variance, to put more emphasis on those time points with more information.

In situations where V is realized before the baseline covariates W, a different SCM must be considered. This SCM implies the following likelihood factorization:

$$\begin{aligned} P_0(O) = P_0(V)P_0(W \mid V)P_0(A \mid V, W) \\ \times \prod_{t=1}^{\tau} P_0(dN(t) \mid \bar{N}(t-1), \bar{A}(t-1), A, V, W) \end{aligned}$$

$$\times \prod_{t=1}^{\tau} P_0(dA(t) \mid \bar{N}(t), \bar{A}(t-1), A, V, W),$$

with the resulting g-formula

$$P_0(W \mid V = v) \prod_{t=1}^{\tau} P_0(dN(t) \mid \bar{N}(t-1), \bar{A}(t-1) = 0, A = a, V = v, W).$$

Characteristics such as sex and gender, which are set at birth, are examples of variables for which V is realized before W. In order to asses the level of effect modification in these situations, an estimate of $P_0(W \mid V = v)$ is needed instead of the marginal distribution $P_0(W)$ of W. The conditional hazard $\bar{Q}_0(t \mid A, W)$ may be estimated as before. The empirical distribution among $V = v$ will be used to estimate $P_0(W \mid V = v)$. We will refer to these causal effect modification parameters as stratified effect modification (SEM) parameters, as they can be expressed as follows:

$$\Psi_{RD}^{SEM}(P_0) = \left[\sum_{t_k} w(t_k)(S_{1|1}(t_k) - S_{0|1}(t_k))\right] - \left[\sum_{t_k} w(t_k)(S_{1|0}(t_k) - S_{0|0}(t_k))\right], \quad (18.7)$$

$$\Psi_{LR}^{SEM}(P_0) = \sum_{t_k} w(t_k)\left[\log\left(\frac{\log(S_{1|1}(t_k))}{\log(S_{0|1}(t_k))}\right) - \log\left(\frac{\log(S_{1|0}(t_k))}{\log(S_{0|0}(t_k))}\right)\right], \quad (18.8)$$

where $S_{1|1}(t_k)$ denotes survival at t_k for individuals with $V = 1$ and treatment set to 1, and so on. These are also counterfactual survival probabilities corresponding with setting $A = a$ and $V = v$. However, we have expressed them as a counterfactual survival probability, $S_{a|v}(t_0)$, conditional on $V = v$, to emphasize the fact that they are different parameters of interest of the data-generating distribution, corresponding to the alternative SCM where V occurs before W.

18.5 The TMLE

The TMLE of the parameters presented in the previous sections improves on the MLE by being consistent when either g_0 or Q_0 is estimated consistently. Thus, the method is double robust. In the TMLE algorithm, an initial estimator of the conditional hazard is obtained, and the algorithm updates it by iteratively adding a time-dependent clever covariate chosen to reduce bias in the estimate of the parameter of interest. This time-dependent clever covariate is a function of time, treatment, and the baseline covariates and requires an estimate of the treatment and censoring mechanisms. The marginal distribution of the covariates is estimated with the empirical distribution and is not updated by the TMLE.

The TMLE involves the construction of an initial estimator P_n^0 of the probability distribution P_0 described by initial estimates $\bar{Q}_n^0(t \mid A, W)$, $g_{A,n}^0$ (using data structure

III), $\bar{g}_n^0(t \mid A, W)$, and the empirical distribution $Q_{W,n}$. The TMLE also requires defining a loss function $L(P)$ for P_0 and a parametric working model $\{P_n^0(\epsilon) : \epsilon\}$ through an initial estimator so that the score $d/d\epsilon L(P_n^0(\epsilon))$ at $\epsilon = 0$ spans the efficient influence curve $D^*(P_n^0)$ at P_n^0 of the target parameter of interest. Our loss function will be the log-likelihood loss function $L(P) = -\log P$. The parametric working model will be selected to only update Q_n^0.

The target parameters $\Psi_1(P_0)(t_k)$ and $\Psi_0(P_0)(t_k)$ have the following two efficient influence curves:

$$D_1^*(P_0) = \sum_{t \le t_k} H_1^*(t, A, W)\left[I(\tilde{T} = t, \Delta = 1) - I(\tilde{T} \ge t)\bar{Q}_0(t \mid A = 1, W)\right] + S_0(t_k \mid A = 1, W) - \Psi_1(P_0)(t_k) \text{ and}$$

$$D_0^*(P_0) = \sum_{t \le t_k} H_1^*(t, A, W)\left[I(\tilde{T} = t, \Delta = 1) - I(\tilde{T} \ge t)\bar{Q}_0(t \mid A = 0, W)\right] + S_0(t_k \mid A = 0, W) - \Psi_0(P_0)(t_k).$$

We select $Q_{W,n}(\epsilon_1) = (1+\epsilon_1 D_{a,W}^*(P_n^0))Q_{W,n}$ as parametric working model for fluctuating the empirical distribution of W, where $D_{a,W}^*(P_n^0) = S_n^0(t_k \mid A = a, W) - \Psi_a(P_n^0)(t_k)$. Note that $D_{a,W}^*(P_0)$ represents the projection of the efficient influence curve $D_a^*(P_0)$ onto the tangent space of the marginal distribution of W. We select the logistic regression model $\text{logit}\,\bar{Q}_n^0(\epsilon_2) = \text{logit}\,\bar{Q}_n^0 + \epsilon_2 H_a^*(P_n^0)$ as parametric working model for fluctuating the conditional hazard, where the clever covariate for the target parameter $\Psi_a(P_0)(t_k)$ is given by

$$H_1^*(P_n^0)(t, A, W) = -\frac{I(A = 1)}{g_{A,n}^0(1 \mid W)\prod_{i=1}^{t-}\left(1 - \bar{g}_n^0(i \mid A, W)\right)}\frac{S_n^0(t_k \mid A, W)}{S_n^0(t \mid A, W)}I(t \le t_k) \text{ and}$$

$$H_0^*(P_n^0)(t, A, W) = -\frac{I(A = 0)}{g_{A,n}^0(0 \mid W)\prod_{i=1}^{t-}\left(1 - \bar{g}_n^0(i \mid A, W)\right)}\frac{S_n^0(t_k \mid A, W)}{S_n^0(t \mid A, W)}I(t \le t_k).$$

This now defines a parametric working model through the conditional distributions $Q_{dN(t),n}^0$ for all $t = 1, \ldots, \tau$. These two working models through the marginal distribution $Q_{W,n}$ and the conditional hazard $\bar{Q}_n^0$ also imply a working parametric model $\{Q_n^0(\epsilon) : \epsilon\}$ through $Q_n^0 = (Q_{W,n}^0, \bar{Q}_n^0)$ indexed by a bivariate $\epsilon = (\epsilon_1, \epsilon_2)$. The working parametric model $\{P_n^0(\epsilon) = (Q_n^0(\epsilon), g_n^0) : \epsilon\}$ through P_n^0 only fluctuates Q_n^0:

$$P_n^0(\epsilon)(O) = Q_{W,n}^0(\epsilon_1)(W)\prod_t Q_{dN(t),n}(\epsilon_2)(dA(t) \mid Pa(A(t))) \times g_{A,n}^0(A \mid W)\prod_t g_{dA(t),n}^0(dA(t) \mid Pa(A(t))).$$

The TMLE of $\Psi_a(P_0)(t_k)$ is now defined by the TMLE algorithm implied by the log-likelihood loss function and this parametric working model $P_n^0(\epsilon)$. The first step of the algorithm computes the maximum likelihood estimator $\epsilon_n = \arg\max_\epsilon \log P_n^0(\epsilon)$. The maximum likelihood estimator of ϵ_1 equals zero. In practice, the maximum likelihood estimator of ϵ_2 is obtained by implementing a univariate logistic regression regressing the binary outcome $dN(t)$ on $H_{a,n}^*(t, A, W)$ using the initial estimate $\bar{Q}_n^0(t \mid A, W)$ as an offset, pooling across the time points t. This results in an update $\text{logit}\bar{Q}_n^1 = \text{logit}\bar{Q}_n^0 + \epsilon_{2n} H_{an}^*$. The first step TMLE of Q_0 is given by $Q_n^1 = (Q_{W,n}, \bar{Q}_n^1)$.

This updating process is iterated until $\epsilon_n \approx 0$. The final TMLE of Q_0 is denoted by $Q_n^* = (Q_{W,n}, \bar{Q}_n^*)$, and the corresponding $P_n^* = (Q_n^*, g_n^0)$ is the TMLE of P_0. The TMLE of $\Psi_a(P_0)(t_k)$ is the substitution estimators based on plugging in the targeted estimator Q_n^*:

$$\Psi_a(Q_n^*)(t_k) = \frac{1}{n} \sum_{i=1}^{n} S_n^*(t_k \mid A = a, W_i),$$

where $S_n^*(t_k \mid A = a, W_i)$ is the survival probability corresponding with $\bar{Q}_n^*$ and $\Psi_a(Q_n^*)(t_k)$ can be constructed as previously shown in Fig. 18.3.

The update is implemented by fitting a univariate logistic regression model of the event process, $N(t)$, on the clever covariate $H_{n,a}^*$ with the initial fit $\bar{Q}_n^0(t \mid A, W)$ as an offset. $\bar{Q}_n^0(\epsilon_n^1)$ is the first-step TMLE of $\bar{Q}_0$, where ϵ_n^1 is the fitted regression coefficient of the clever covariate. This defines the first-step TMLE update P_n^1. Since the time-dependent clever covariate, $H^*(P_n^1)(t, A, W)$, is different under P_n^1 than it is under P_n^0, due to being a function of the estimator of $\bar{Q}_0$, it is necessary to iterate the updating step. The TMLE updating process is detailed in Fig. 18.4.

The above TMLE can be implemented separately for the two target parameters $\Psi_a(P_0)(t_k)$, resulting in a TMLE of any function of these two treatment-specific survival functions. Alternatively, one can construct a single TMLE targeting both target parameters simultaneously. In this case, we select the logistic regression model $\text{logit}\bar{Q}_n^0(\epsilon_2) = \text{logit}\bar{Q}_n^0 + \epsilon_{20} H_0^*(P_n^0) + \epsilon_{21} H_1^*(P_n^0)$ as the parametric working model for fluctuating the conditional hazard. That is, we add the two clever covariates $H_1^*(P_n^0)$ and $H_0^*(P_n^0)$ to the initial estimator of the conditional hazard, one clever covariate for $\Psi_1(P_0)(t_k)$ and one for $\Psi_0(P_0)(t_k)$. The TMLE updates both components $(\epsilon_{20}, \epsilon_{21})$ simultaneously until both components have converged to zero.

The TMLE of $\Psi_{av}(t_k)$ needed for constructing the parameter estimates of target parameters (18.5) and (18.6) may be constructed by treating A and V together as a treatment variable. The treatment mechanism must be replaced by the joint probability of $A = a$ and $V = v$, and the resulting clever covariate is

$$H^*(P_n^0)(t, A, V, W) = -\frac{I(A = a, V = v)}{g_{A,n}^0(A = a, V = v \mid W) \prod_{i=1}^{t-} \left(1 - \bar{g}_n^0(i \mid A, V, W)\right)} \times \frac{S_n^0(t_k \mid A = a, V = v, W)}{S_n^0(t \mid A = a, V = v, W)} I(t \le t_k),$$

and the TMLE is:

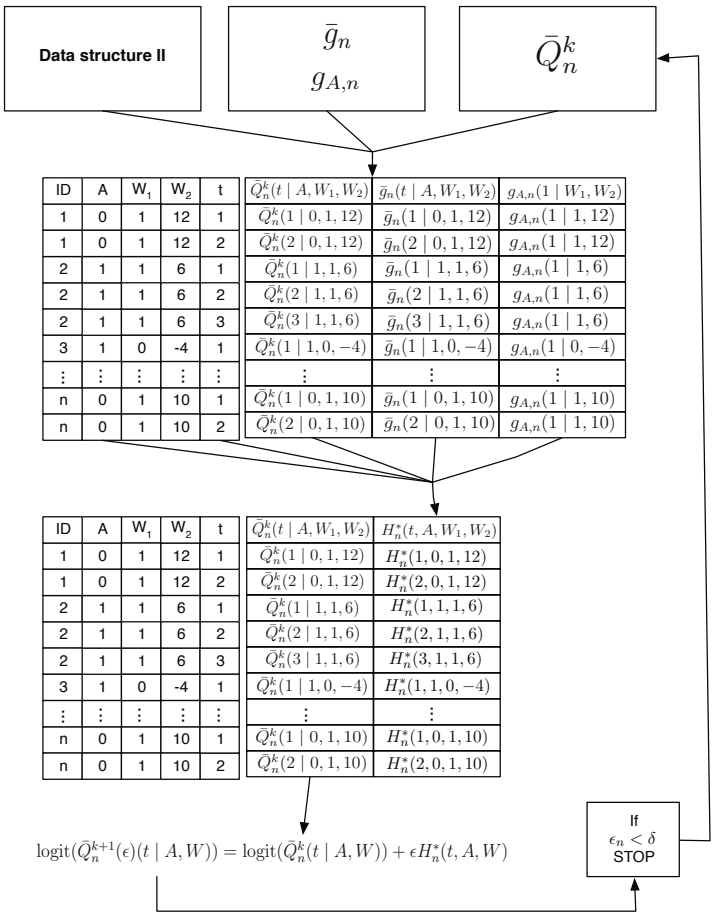

Fig. 18.4 One iteration of the TMLE algorithm

$$\Psi_{av}(Q_n^*)(t_k) = \frac{1}{n}\sum_{i=1}^{n} S_n^*(t_k \mid A = a, V = v, W_i),$$

where S_n^* is now the TMLE of the treatment-specific survival probability at $A = a$ and $V = v$.

The TMLE of $S_{0,a|v}(t_k)$ needed for constructing the parameter estimates of target parameters (18.7) and (18.8) may be constructed in the same way as for one treatment variable A but done separately for each level of V. So the TMLE of $S_{0,a|v}(t_k)$ is the same as the TMLE for $\Psi_a(P_0)(t_k)$ just estimated on a data set that only includes individuals with $V = v$.

There are a few clear advantages of TMLE for time-to-event analysis that are a consequence of the double robustness and local efficiency of the method. First, if

the censoring is independent and treatment is randomized, then the estimator of the parameter of interest is guaranteed to be unbiased since the treatment mechanism $g_{A,0}(A \mid W)$ is known, and the required survivor function corresponding with the censoring mechanism $\bar{g}_0(t \mid A, W) = \bar{g}_0(t)$ can be consistently estimated with the Kaplan–Meier estimator. However, it has also been shown that by estimating these mechanisms, even when they are known, one can improve the efficiency of the estimates by adjusting for empirical confounding. This is done by positing a model for these mechanisms that contains the truth so that the estimates will converge to the truth. For a general account of how estimating the treatment and censoring mechanism can improve efficiency see van der Laan and Robins (2003, Sect. 2.3.7). Second, with informative censoring or observational treatment the double robustness allows one to reduce bias due to the initial estimate of $\bar{Q}_0(t \mid A, W)$ by estimating the treatment mechanism, $g_{A,0}(A, W)$, and censoring mechanism, $\bar{g}_0(t \mid A, W)$, as well as possible.

The TMLE also improves on estimating equation-based techniques, in which case ψ_0 is estimated with the closed-form solution of the efficient influence curve estimating equation $P_n D^*(Q_n^0, g_n^0, \psi) = 0$. This is due to the fact that TMLE is a substitution estimator that obeys the proper bounds of a survival probability. Estimating-equation-based results do not obey these bounds and may even result in estimates of probabilities that don't fall between zero and one. In cases where the treatment mechanism gets very close to zero, or the censoring hazard approximates 1, corresponding with practical violations of the positivity assumption stated above, the estimating-equation-based methods tend to become very unstable. When violations in the positivity assumption are a problem, the estimating-equation-based approaches may not only return estimates that are not a probability, but also suffer drastically in efficiency and not approach the semiparametric efficiency bound. However, the TMLE in such situations is more stable and may still achieve the semiparametric efficiency bound. For more details on how the TMLE compares to estimating-equation-based approaches see Stitelman and van der Laan (2010) and Chap. 20.

Confidence intervals may be constructed by relying on the fact that the TMLE solves the efficient influence curve estimating equation $0 = \sum_{i=1}^{n} D^*(Q_n^*, g_n)(O_i)$, where $D^*(Q_0, g_0) = D^*(Q_0, g_0, \Psi(Q_0))$ is the efficient influence curve for a particular parameter of interest. One can also state that $\Psi(Q_n^*)$ solves the estimating equation in ψ_0: $0 = \sum_i D^*(Q_n^*, g_n, \Psi(Q_n^*))(O_i)$, as defined by this efficient influence curve equation. Under regularity conditions, it can be shown that $\Psi(Q_n^*)$ is asymptotically linear with an influence curve $D^*(Q, g_0, \psi_0) + D_1$ for the case where Q_n^* possibly converges to a misspecified Q, and g_n converges to the true g_0 (van der Laan and Robins 2003, Sect. 2.3.7). If $Q_n = Q_0$, or $g_n = g_0$, then $D_1 = 0$. In addition, if g_n is an ML-based estimator of g_0, then ignoring contribution D_1 results in an asymptotically conservative influence curve and variance estimator. So the asymptotic variance of $n^{1/2}(\psi_{n,a}^* - \Psi_a(P_0))$ may be estimated by $\sigma_n^2 = \frac{1}{n}\sum_{i=1}^{n} D_a^{*2}(P_n^*)(O_i)$, where P_n^* is the TMLE of P_0 and $D_a^*(P_n^*)(O_i)$ the efficient influence curves for the treatment-specific survival curve above evaluated at P_n^*. Now 95% confidence in-

tervals for the treatment-specific survival curve at a particular time point may be constructed as $\psi^*_{n,a} \pm 1.96(\sigma_n/\sqrt{n})$.

Variance estimates for the parameters of interests above that combine $\Psi_1(P_0)(t_k)$ and $\Psi_0(P_0)(t_k)$ may be estimated through the use of the delta method. The resulting efficient influence curves for the parameters of interest presented in Sect. 18.3 are

$$D^*_{RD}(P^*_n)(t_k) = D^*_1(P^*_n)(t_k) - D^*_0(P^*_n)(t_k),$$

$$D^*_{RR}(P^*_n)(t_k) = -\frac{1}{1-\psi^*_{n,1}(t_k)} D^*_1(P^*_n)(t_k) + \frac{1}{1-\psi^*_{n,0}(t_k)} D^*_0(P^*_n)(t_k),$$

$$D^*_{RH}(P^*_n)(t_k) = -\frac{1}{\psi^*_{n,1}(t_k)\log(\hat{\psi}^*_1)} D^*_1(P^*_n)(t_k) + \frac{1}{\psi^*_{n,0}(t_k)\log(\psi^*_{n,0})} D^*_0(P^*_n)(t_k).$$

Confidence intervals may now be constructed for these parameters at a particular time point using the above estimates of the corresponding efficient influence curve. Furthermore, the estimated influence curve for estimates that are means of these parameters may be constructed by taking means of the estimated efficient influence curves over the desired time points.

Appendix A presents an asymptotic linearity result generalized to hold for TMLE when Q^*_n converges to a possibly misspecified Q, and g_n converges to a true conditional censoring/treatment mechanism that adjusts for covariates that predict the residual bias between Q and Q_0. In particular, if either Q^*_n converges to Q_0 or g_n converges to g_0, then, under appropriate regularity conditions, we have that ψ^*_n is asymptotically linear with an influence curve $D(P_0)$:

$$n^{1/2}(\psi^*_n - \Psi(P_0)) = n^{-1/2} \sum_{i=1}^{n} D(P_0)(O_i) + o_p(1),$$

so that, by the central limit theorem,

$$n^{1/2}(\psi^*_n - \Psi(P_0)) \xrightarrow{D} N(0, E(D^2(P_0)(O)),$$

as sample size n converges to infinity.

18.6 Data Application: Tshepo Study

The Tshepo study is a 3-year randomized study using a $3 \times 2 \times 2$ factorial design comparing efficacy and tolerability among different drug regimens. For the purpose of this analysis we focus on the randomization to two NNRTI-based cART therapies: EFV and NVP. The Tshepo study is the first clinical trial evaluating the long-term efficacy and tolerability of EFV- vs. NVP-based cART among adults in Botswana. The study consists of 650 adults ranging in age from 20 to 64. Table 18.1

Table 18.1 Baseline characteristics of Tshepo study

Characteristic		NVP $n = 325$	EFV $n = 325$	Total $n = 650$
Age	Median [IQR]	33.2 [29.0, 38.3]	33.7 [28.8, 39.1]	33.3 [28.9, 38.7]
Male	Count (%)	95 (29.2%)	104 (32.0%)	199 (30.6%)
Weight	Median [IQR]	57.50 [51, 66]	57.0 [50.25, 65.50]	57.0 [51, 66]
BMI	Median [IQR]	21.2 [19.2, 24.3]	21.4 [19.2, 24.1]	21.3 [19.2, 24.3]
HIV-1 RNA (1,000s)	Median [IQR]	183 [63, 466]	204 [85, 499]	195 [70, 477]
CD4+ cell count	Median [IQR]	199 [138, 243]	199 [131, 260]	199 [136, 252]
WHO Clinical Stage 1	Count (%)	90 (27.7%)	108 (33.2%)	198 (30.5%)
WHO Clinical Stage 2	Count (%)	84 (25.8%)	77 (23.7%)	161 (24.8%)
WHO Clinical Stage 3	Count (%)	117 (36.0%)	99 (30.5%)	216 (33.2%)
WHO Clinical Stage 4	Count (%)	25 (7.7%)	33 (10.2%)	58 (8.9%)
Pulmonary TB	Count (%)	27 (8.3%)	32 (9.8%)	59 (9.1%)

displays summary statistics of the baseline characteristics, W, that were collected in the Tshepo study. The outcome of interest is the time to loss of virological response (TLOVR). The only censoring event for this outcome of interest is the end of study, and thus assuming independent censoring is appropriate. The following three questions will be addressed: (1) Is there a causal effect of NNRTI-based cART therapy? (2) Is the effect of NNRTI-based cART therapy modified by gender? (3) Is the effect of NNRTI-based cART therapy modified by baseline CD4 count?

18.6.1 Causal Effect of NNRTI

Table 18.2 presents estimates of the causal effect of taking EFV vs. NVP. The Cox proportional hazards estimate in the first column is the standard analysis performed in assessing the effect of a randomized control trial on a time to event outcome. We present two TMLEs for estimating the mean marginal additive difference in the probability of survival and the mean marginal log relative hazard. This second parameter is an extension of the Cox proportional hazards parameter. The mean is taken over the first 34 months after randomization and the weights are based on the variance of the influence curve. The marginal difference of survival at the final time point, 34 months, is also presented. A positive mean log relative hazard and a negative risk difference corresponds with longer times until the specified outcome for the individuals treated with EFV compared to NVP.

For TLOVR, which includes treatment modification, there is a highly significant causal effect of taking EFV vs. NVP. The TMLE estimates for this outcome are known to be unbiased since treatment is randomized and there is independent censoring (the only censoring event is end of study). Furthermore, the results are consistent with the results presented by Wester et al. (2010), where they concluded

Table 18.2 Causal effect of NNRTI

	Parametric	TMLE		
	Cox PH	Mean RH	Mean RD	RD at $t = 34$
Estimate	0.358	0.451	−0.072	−0.060
SE	0.156	0.165	0.025	0.034
p-value	0.022	0.006	0.003	0.072

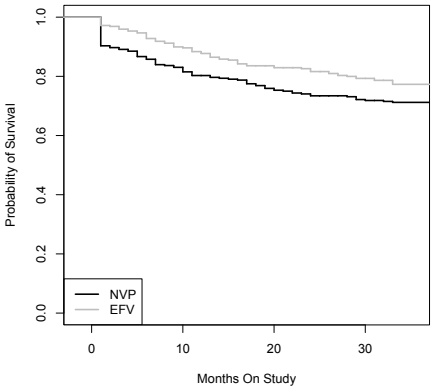

Fig. 18.5 EFV and NVP specific survival curves

that individuals treated with NVP tended to modify treatment sooner than individuals treated with EFV due to the toxicity of NVP.

Figure 18.5 presents the TMLE estimates of the treatment-specific survival curves for TLOVR. Examining the parameter estimates in conjunction with Fig. 18.5 reveals the difficulty in interpreting the Cox proportional hazards parameter (and our TMLE analog) compared to the marginal additive difference in the probability of survival. The mean additive difference is −0.072, which may be interpreted as: on average the EFV specific survival probability is 7.2% higher than the NVP-specific survival probability. A quick examination of Fig. 18.5 verifies this difference in the survival curves. The Cox proportional hazards estimate is 0.358 and would approximate the mean of $\Psi_{RH}(P_0)(t_k)$ over all time points according to the Cox proportional hazards model. This value has no easily interpretable meaning since it is the average of the log of the ratio of log survival probabilities. Alternatively, one could interpret it as an average of the log relative hazards, which requires the user to fully understand the definition of a conditional hazard (like a density). It is clear that when it is positive, the EFV-specific survival curve is larger. However, there is no intuitive meaning gained from the size of the value. In addition, we can see that the TMLE estimates are more statistically significant than the Cox proportional hazards esti-

mates. Efficiency theory specific to the TMLE and simulation results suggest that this gain in significance is due to a reduction in bias from implementing TMLE (van der Laan and Rubin 2006; Moore and van der Laan 2009a). However, it is impossible to validate this claim for TMLE or any other method based on one sample of the data.

18.6.2 Causal Effect Modification by Baseline CD4

Table 18.3 presents the estimates that address whether or not there is a causal effect modification due to CD4 level (high/low) on the effect of cART treatment. The first column is the estimate from the Cox proportional hazards model. All main terms for W were included in the model as well as the interaction term EFV/NVP and the effect modifier CD4 level. The estimate presented is the estimate β_n in front of the cross term, $A \times V$, in the Cox proportional hazards model. The TMLEs presented are the parameters (18.5) and (18.6). The mean is taken over the first 34 months after

Table 18.3 Causal effect modification due to baseline CD4 level

	Parametric	TMLE		
	Cox PH	Mean RH	Mean RD	RD at $t = 34$
Estimate	0.675	0.829	−0.115	−0.144
SE	0.317	0.356	0.051	0.071
p-value	0.033	0.020	0.023	0.043

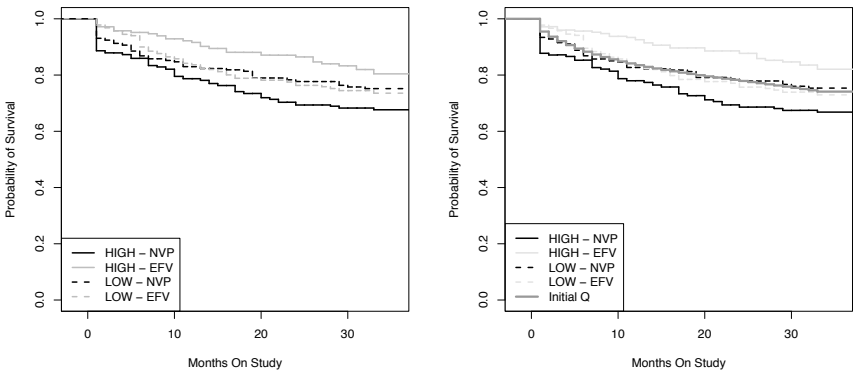

Fig. 18.6 Survival curves for time until viral failure, death, or treatment modification setting NNRTI and CD4. (a) Super learner. (b) Misspecified

randomization, and the weights are based on the variance of the influence curve. The difference in the risk difference at the final time point, 34 months, is also presented. A positive marginal difference in the log relative hazard (18.6), and a negative difference in the risk difference (18.5), indicates that EFV has a larger beneficial causal effect in the high CD4 group than in the low CD4 group.

Causal effect modification by CD4 is significant for all the parameter estimates presented. The Cox proportional hazards estimate is statistically significant; however, as was seen above, the p-value for the TMLE is more significant. These results are consistent with a decrease in bias or increase in efficiency due to using TMLE. Figure 18.6(b) shows the survival curves for TLOVR setting individuals to CD4 level and treatment group. The figure depicts the significant effect modification seen in Table 18.3. Not only is the effect of treatment among setting the individuals to high CD4 different than the effect when setting individuals to low CD4, but the effects are in opposite directions.

Figure 18.6(a) presents the TMLE survival curves where the survival probability at each time point is targeted and the initial estimate of the event hazard is estimated using the super learner. Figure 18.6(b) shows the targeted survival curves when the initial hazard is intentionally misspecified. In fact, the initial estimates for each of the four groups of differing CD4 level and treatment level are not different at all and a main terms logistic model that only accounts for t and t^2 was used. The bolded gray solid line in Fig. 18.6(b) shows the initial estimate of all four survival curves. Super learner was then used to estimate the treatment distribution, and since the only censoring event is the end of study, censoring is known to be independent of the baseline covariates, and Kaplan–Meier was used to estimate the censoring process. Figure 18.6(b) demonstrates that by using TMLE with a completely misspecified initial hazard, the effect modification is recovered, depicted by the separation of the four survival curves. This exemplifies the value of the double robustness of TMLE.

18.6.3 Causal Effect Modification Due to Gender

Table 18.4 present effect modification due to gender on the effect of cART treatment. Main terms were included for A and V, and $A \times V$ was included as well in the Cox proportional hazards model. The estimate is the β_n in front of $A \times V$. The targeted maximum likelihood estimates presented are the stratified effect modification parameters (18.7) and (18.8). The mean is taken over the first 34 months after randomization, and weighting is based on the estimated variance of the influence curve. The difference in the risk difference at the final time point, 34 months, is also presented. A negative marginal difference in the log relative hazard (18.8), and a positive difference in the risk difference (18.7), indicates that EFV has a larger beneficial causal effect for females. The treatment effect modification by gender on TLOVR is statistically significant for all three TMLE estimates and the Cox proportional hazards estimate. In fact, it is highly significant for the mean difference in

Table 18.4 Effect modification due to gender

	Parametric	TMLE		
	Cox-PH	Mean RH	Mean RD	RD at $t = 34$
Estimate	−0.952	−0.816	0.116	0.193
SE	0.353	0.329	0.035	0.054
p-value	0.007	0.013	0.001	0.000

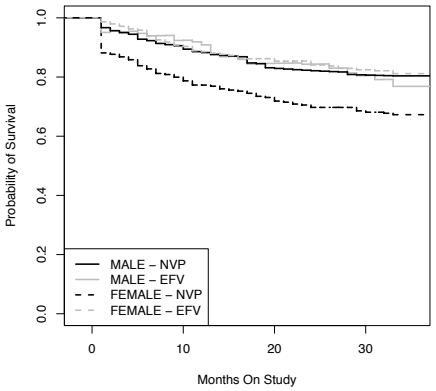

Fig. 18.7 Survival curves for time to viral failure, death, or treatment modification setting NNRTI and gender

the marginal log hazard of survival, and the difference in the marginal log hazard of survival at $t_k = 34$. Figure 18.7 shows the survival curves for the TLOVR outcome.

18.7 Discussion

The three statistical questions of interest presented in the introduction of this chapter may now be answered based on the TMLE methods and results presented above:

1. *Is there a causal effect of EFV vs. NVP on time to viral failure, death, or treatment modification?* There appears to be a causal effect of EFV vs. NVP on TLOVR. This suggests that viral failure, death, treatment modification or a combination of the three differs between individuals treated with EFV vs. NVP. The average risk difference in survival probability over the first 34 months after randomization is −7.2%.
2. *Does baseline CD4 level modify the effect of EFV vs. NVP on time to viral failure, death, or treatment modification?* Baseline CD4 level does modify the effect of EFV vs. NVP on time until TLOVR. EFV tends to be favorable compared to NVP for individuals at high CD4 levels. At low CD4 levels there is not much

of a difference in the treatment-specific survival curves (Fig. 6(a)). For TLOVR, the average risk difference between the effect in the high CD4 group vs. the low CD4 group is 12% (p-value = 0.023). One possible explanation for this is that the side effects associated with taking NVP were considered more acceptable for people with lower CD4 level so treatment was not modified. Healthier people would modify treatment because the advantages of treatment do not offset the risk of the side effects.

3. *Does the effect of EFV vs. NVP on time to viral failure, death, or treatment modification or some combination of the three differ by sex?* Gender does modify the effect of EFV vs. NVP on the time until TLOVR. Women tend to have more favorable outcomes using EFV, while males tend to have more favorable outcomes with NVP. For TLOVR, the average causal risk difference between the effect in the males vs. the females is 12% (p-value = 0.001). A possible reason for this result is that female NVP users tend to modify their treatment at a higher rate than the other groups. Based on Fig. 18.7, the major difference in the modification rate tends to occur right after starting the NVP therapy.

In addition to answering these statistical questions, the results illustrate the advantages of using TMLE over Cox proportional hazards regression for causal effects. The parameters estimated using TMLE are much easier to interpret than the parameter estimated using Cox regression. Furthermore, TMLE is double robust and locally efficient resulting in advantages over Cox regression in both producing unbiased estimates and gaining efficiency. The double robustness was illustrated by Fig. 6(b), where the effect modification due to CD4 level was regained after starting with an initial estimate of the four CD4/treatment-specific survival curves that was the same for all four combinations of CD4/treatment. The overall efficiency gains and bias reductions may not be directly exhibited through a single data analysis, as done here, but previous theoretical results and simulations have exhibited these advantages. Since TMLE targets the parameter of interest and, rather than relying on an a priori specified model to estimate the conditional hazard, it produces consistent estimates of a specified parameter of interest under very unrestrictive model assumptions, whereas the Cox proportional hazards estimate is only consistent if the Cox proportional hazards model and its restrictive parametric assumptions are true. For these reasons, the parameter estimates and significance levels produced by the TMLE should be considered more reliable than those produced using Cox proportional hazards.

Appendix

TMLE incorporating time-dependent covariates. In the Tshepo study, time-dependent measurements on viral load and CD4 count over time until end of follow-up were collected. The analysis presented in this chapter ignored these measurements. A general roadmap and algorithm for constructing TMLE based on general longitudinal data structures has been developed in van der Laan (2010a,b), is also

presented in Appendix A, and demonstrated in Part VIII. This type of TMLE, with an enhanced implementation maximizing computational speed, has been fully implemented and evaluated in an upcoming article by Stitelman and van der Laan (forthcoming, 2011). The implementation can be easily adapted to handle general longitudinal data structures and target parameters, such as the causal effect of a dynamic treatment regimen on survival. In this upcoming article and corresponding technical report (forthcoming, 2011), full simulations and data analysis of the Tshepo study will be presented. It provides a TMLE of the causal effect of treatment on the survival function utilizing both the baseline covariates and the measured time-dependent covariates to improve efficiency as well as remove bias due to informative dropout. In this chapter appendix, we present preliminary results from this upcoming article, demonstrating the additional gains obtained by using a TMLE that incorporates the time-dependent covariates, and demonstrating the gain of TMLE relative to current practice in terms of IPCW estimation for dealing with time-dependent covariates.

We present the results of simulation studies that compare the bias and efficiency of six different estimators of the treatment specific survival curve $S_1(t_0)$: baseline TMLE, baseline IPCW, baseline A-IPCW, time-dependent TMLE, time-dependent IPCW, and time-dependent EE. Baseline refers to the data structure that excludes the time-dependent covariates, and EE is an an abbreviation for an estimating equation based estimator we developed for the complete longitudinal data structure [it can be viewed as an A-IPCW of the type presented in van der Laan and Robins (2003), but it is based on the representation of the efficient influence curve as used in the TMLE].

The EE involves representing the efficient influence curve for the longitudinal data structure as an estimating function in the target parameter ψ_0 and defining the estimator as the solution of the corresponding estimating equation, estimating the nuisance parameters with the initial estimators as used in the TMLE. No similar estimating equation based estimators have gained traction in the literature due to the computational difficulties of constructing such an estimate when there are many time points and intermediate variables. The algorithm proposed in the forthcoming article by Stitelman and van der Laan make the estimation of such an estimator computationally feasible. The EE is like the TMLE in that it is a double robust locally efficient estimator, but the TMLE is also a substitution estimator, while the EE is not. The time-dependent IPCW is defined as the empirical mean of

$$D_{IPCW}(O) = \frac{I(T > t_0, A = 1, C > t_0)}{\bar{G}_n(t_0- \mid X, A = 1) g_n(A \mid W)},$$

where g_n is an estimator of the treatment mechanism g_0, conditional on baseline covariates, $\bar{G}_n(t- \mid X, A = 1) = \prod_{t<t_0}(1 - \lambda_n(t \mid X, A = 1)$ is the estimator of the survivor function of censoring, conditional on baseline treatment, baseline covariates, and time-dependent covariates, and $\lambda_n(t \mid X, A = 1)$ is the conditional hazard of censoring at time t, adjusting for the observed past up to time $t-$.

The goal of the first set of simulations was to illustrate the bias reduction that occurs when one adjusts for time-dependent covariates that impact dropout beyond the effect of the baseline covariates on time to dropout. The second set of simulations show that if censoring is noninformative, a TMLE and EE incorporating the available time-dependent covariates improve efficiency relative to an estimator that ignores the time-dependent covariates, even though in this independent censoring scenario the latter is still a valid asymptotically linear estimator. Furthermore, our simulations also demonstrate that a locally efficient double-robust substitution estimator (time dependent TMLE) performs better in finite samples than both a locally efficient double-robust nonsubstitution estimator (time-dependent EE) and the current standard for accounting for time-dependent covariates (time-dependent IPCW). In fact, the simulations suggest that the benefit of targeted learning increases quickly, and dramatically, when the complexity (e.g., dimension of data structure) of the estimation problems increases.

In our simulations we simulated a longitudinal data structure

$$O = (W(0), A(0), N(1), W_4(1), W_5(1), A(1)..., N(K), W_4(K), W_5(K), A(K), N(K+1)),$$

for $t = 1, ..., K+1$. Here $W(0) = (W_1(0), W_2(0), W_3(0), W_4(0), W_5(0))$ are the baseline covariates, $A(0)$ is the binary baseline treatment randomized with probability 0.5, $N(t)$ is the indicator of observing a failure time event at time t, $A(t)$ is the indicator of observing a censoring event at time t, and $W_4(t)$ and $W_5(t)$ are the continuous time-dependent covariates. In each simulation, 100 simulated data sets with sample size $n = 500$ were generated, the treatment specific survival curve $S_1(t_0)$ at time point $t_0 = 3$ was estimated using each of the six different estimators, and estimates of bias and MSE were recorded. The true treatment specific survival $S_1(t_0)$ for each simulation equals 0.469. All six estimators were supplied consistent estimators of the hazards of censoring and failure, while the conditional distributions of the time-dependent covariates were estimated inconsistently by discretizing the continuous covariates ($W_4(t)$, $W_5(t)$), coding the discretized covariates with binary indicators, and estimating the conditional distribution of the binary indicators with logistic parametric regression. Each estimator was evaluated using the same estimators Q_n and g_n (for each simulation) so that any difference in their performance may not be attributed to how Q_0 and g_0 were estimated.

Simulations with informative censoring. The precise data-generating mechanism is described as follows.

(1) Drawing baseline covariates $W(0)$ involved first generating from a mean-zero multivariate normal and truncating any component from above by 2 and from below by -2. The covariance matrix was defined as 1 on the diagonal and 0.2 off the diagonal.
(2) The two time-dependent covariates $W_4(t)$ and $W_5(t)$ were generated as follows:

$$W_4(t) = 0.2A(0) + 0.5W_1(0) - 0.4W_2(0) - 0.4W_3(0) + 2W_4(t-1) + 2W_5(t-1) + U_4$$
$$W_5(t) = 0.1A(0) + 0.1W_1(0) + 0.1W_2(0) - 0.4W_3(0) + 2W_4(t) + 2W_5(t-1) + U_5,$$

Table 18.5 Simulation results for low and highly informative censoring

	Time-dependent			Baseline		
	TMLE	EE	IPCW	TMLE	A-IPCW	IPCW
Low informative						
Mean of Estimates	0.471	0.471	0.451	0.469	0.469	0.469
MSE	0.00070	0.00073	0.00127	0.00082	0.00081	0.00093
Highly informative						
Mean of Estimates	0.472	0.472	0.172	0.436	0.437	0.394
MSE	0.00066	0.00067	0.08864	0.00215	0.00210	0.00773

where U_4 and U_5 are i.i.d. $N(0, \sigma = 0.4)$.

(3) The event indicators, $N(t)$, were generated as Bernoulli indicators with probability defined by the following conditional hazard of time to failure T:

$$\lambda_T(t) = \text{expit}(-3+0.3A(0)+0.3W_1(0)-0.3W_2(0)-0.3W_3(0)+2W_4(t-1)+2W_5(t-1)).$$

(4) The censoring indicators, $A(t)$, were generated as Bernoulli indicators with probability defined by the following conditional hazard for censoring for the low and highly informative censoring case, respectively:

$$\begin{aligned}\lambda_C(t) = \text{expit}(&-4 + 0.8A(0) + 0.3W_1(0)\\ &-0.3W_2(0) - 0.3W_3(0) - 0.01W_4(t) - 0.01W_5(t-1)),\\ \lambda_C(t) = \text{expit}(&-4 + 0.8A(0) + 0.3W_1(0)\\ &-0.3W_2(0) - 0.3W_3(0) - 0.1W_4(t) - 0.1W_5(t-1)).\end{aligned}$$

Table (18.5) presents the results for this simulation. The incorporation of the time-dependent covariates results in an important bias reduction (and MSE) for the TMLE and EE estimators. In the low informative censoring simulation, the time-dependent IPCW estimator has an MSE that is 1.8 times larger than the MSE of the time-dependent TMLE and EE estimator. In the highly informative censoring scenario, the MSE of the time-dependent IPCW estimator is 134 (!) times larger than the MSE of the time-dependent TMLE and EE estimator. The latter demonstrates a complete breakdown of the IPCW estimator, reflecting that it is simply a very unreliable estimator, even though it represents current practice.

Simulations with independent censoring. The data-generating distribution was the same as above, except the censoring mechanism was modified. The hazard of censoring was only a function of time, such that censoring was independent of the evolving processes, but three different hazards were considered, representing different levels of independent censoring: no censoring, medium censoring, and high censoring. In the first scenario, each individual was left uncensored. In the second and third scenario each subject was censored with either 20% probability (medium) or 60% probability (high).

Table 18.6 Simulation results for independent censoring

	Time-dependent			Baseline		
	TMLE	EE	IPCW	TMLE	A-IPCW	IPCW
No censoring						
Mean of Estimates	0.469	0.469	0.469	0.468	0.468	0.469
MSE	0.00047	0.00047	0.00054	0.00048	0.00048	0.00054
Medium censoring						
Mean of Estimates	0.467	0.467	0.470	0.469	0.469	0.468
MSE	0.00063	0.00086	0.00203	0.00093	0.00093	0.00169
High censoring						
Mean of Estimates	0.476	0.477	0.477	0.464	0.464	0.466
MSE	0.00111	0.00315	0.00566	0.00180	0.00181	0.00417

The results are presented in Table 18.6. We know that under independent censoring all six estimators are consistent. Indeed, the results demonstrate that all estimators are unbiased across the three simulations, so that the estimators only differ in their efficiency (i.e., variance). Under no censoring, all estimators behave similarly, with the exception of the IPCW estimators that are somewhat inefficient. Gains in efficiency due to incorporation of the time-dependent covariates can only be expected if a significant proportion of the subjects are right censored, since an efficient estimator treats a censored subject that is very sick at the censoring time differently than a censored subject that was relatively healthy at the censoring time. Indeed, the table shows that as the amount of independent censoring increases, the IPCW estimators become increasingly inefficient relative to the efficient TMLE and EE estimators.

It is also of interest to note that, under high censoring, the time-dependent TMLE is 1.6 times more efficient than the baseline TMLE. This demonstrates the substantial gain in efficiency one can obtain by utilizing time-dependent covariates. Furthermore, under high censoring, the locally efficient double-robust nonsubstitution estimator (time-dependent EE) has an MSE of almost three (!) times the MSE of the locally efficient double-robust substitution estimator (time-dependent TMLE). This demonstrates the enormous importance of being a substitution estimator. This gain is most likely due to estimated censoring probabilities that are empirically imbalanced across strata of the covariates, so that the estimators behave similarly, as in a highly informative censoring simulation. We repeatedly observed the problem with nonsubstitution estimators when there is strong confounding in a variety of situations. Finally, it is noteworthy that the time-dependent IPCW estimator has an MSE that is 5 times larger than the MSE of the time-dependent TMLE.