Chapter 17
RCTs with Time-to-Event Outcomes

Kelly L. Moore, Mark J. van der Laan

RCTs are often designed with the goal of investigating a causal effect of a new treatment drug vs. the standard of care on a time-to-event outcome. Possible outcomes are time to death, time to virologic failure, and time to recurrence of cancer. The data collected on a subject accumulates over time until the minimum of the time of analysis (end of study), the time the subject drops out of the study, or until the event of interest is observed. Typically, for a large proportion of the subjects recruited into the trial, the subject is right censored before the event of interest is observed, i.e., the time of analysis or the time the subject drops out of the study occurs before the time until the event of interest. The dropout time of the subject can be related to the actual time to failure one would have observed if the person had not dropped out prematurely. In this case, the standard unadjusted estimator of a causal effect of treatment on a survival time, such as the difference of the treatment-specific Kaplan–Meier survival curves at a particular point in time, is not only inefficient by not utilizing the available covariate information, but it is also biased due to informative dropout.

The TMLE can be applied to the estimation of the causal effect of the treatment on a survival outcome in an RCT, incorporating covariates for the purpose of more efficient estimation, without the risk of inducing bias, and reducing bias due to informative dropout. In this chapter we only consider the utilization of the baseline covariates. We present the TMLE of a causal effect of treatment on survival, as well as a simulation study. In the next chapter, we will present an RCT data analysis, including more complicated target parameters incorporating effect modification, but based on the same right-censored data structure. This next data application chapter also provides a detailed discussion of the flaws of current practice based on applications of Cox proportional hazards statistical models. We also encourage readers to study the previous chapter, which introduces many topics related to right censoring and time-to-event data.

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_17,

17.1 Data, Likelihood, and Model

We assume that in the study protocol, each patient is monitored at K clinical visits. At each visit, an outcome is evaluated as having occurred or not occurred. Let T represent the first visit at which the event was reported and thus can take values $\{1, ..., \tau\}$. The censoring time C is the first visit when the subject is no longer enrolled in the study. Let $A \in \{0, 1\}$ represent the treatment assignment at baseline and W represent a vector of baseline covariates. The observed data structure is: $O = (W, A, \tilde{T}, \Delta) \sim P_0$, where $\tilde{T} = \min(T, C)$, $\Delta = I(T \leq C)$ is the indicator that subject was not censored, and P_0 denotes the true probability distribution of O.

Let $N(t) = I(\tilde{T} \leq t, \Delta = 1)$ and $A(t) = I(\tilde{T} \leq t, \Delta = 0)$ denote the indicators that jumps at an observed failure time and observed censoring time, respectively. We can represent O as the following longitudinal data structure: $O = (W, A, (N(t), A(t) : t = 1, \ldots, K))$. The likelihood of O can be represented accordingly, and is given by

$$P_0(O) = Q_{W,0}(W) g_{A,0}(A \mid W) \times \prod_{t=1}^{\tau} Q_{dN(t),0}(dN(t) \mid Pa(dN(t))) \prod_{t=1}^{\tau} g_{dA(t),0}(dA(t) \mid Pa(A(t))),$$

where $Pa(dN(t)) = (W, A, \bar{N}(t-1), \bar{A}(t-1))$ denotes the history available before $dN(t)$ is realized, and similarly, $Pa(A(t)) = (W, A, \bar{N}(t), \bar{A}(t-1))$ denotes the parent set for the censoring indicator $A(t)$. Here $Q_{dN(t),0}$ and $g_{A(t),0}$ denote the conditional probability distributions of the binary indicators $dN(t)$ and $dA(t)$, respectively.

The intensity of the counting process $N()$ is defined as $E_0(dN(t) \mid Pa(dN(t)))$, and can be represented as

$$E_0(dN(t) \mid Pa(dN(t)) = I(\tilde{T} \geq t) \bar{Q}_0(t \mid A, W),$$

where $\bar{Q}_0(t \mid A, W) = E_0(dN(t) \mid \tilde{T} \geq t, A, W)$. Similarly, the intensity of $A(t)$, $E_0(dA(t) \mid Pa(dA(t)))$, can be represented as

$$E_0(dA(t) \mid Pa(dA(t))) = I(A(t-1) = 0, N(t) = 0) \bar{g}_0(t \mid A, W),$$

where $\bar{g}_0(t \mid A, W) = E_0(dA(t) \mid N(t) = A(t-1) = 0, W, A)$. Thus, $Q_{dN(t),0}$ and $g_{A(t),0}$ are identified by $\bar{Q}_0(t \mid A, W)$ and $\bar{g}_0(t \mid A, W)$, respectively. To conclude, the likelihood of O is parameterized by the marginal distribution of W, the treatment mechanism $g_{A,0}$, the conditional probabilities $\bar{Q}_0$ for the binary indicator $dN(t)$, and censoring mechanism $g_{A(t),0}$. Let $Q_0 = (Q_{W,0}, \bar{Q}_0)$.

The statistical model for P_0 is defined by possible knowledge of the censoring mechanism $g_{A(t),0}$, a known treatment mechanism $g_{A,0}$, and a nonparametric statistical model for $Q_0 = (Q_{W,0}, \bar{Q}_0)$. We assume an SCM:

$$W = f_W(U_W),$$
$$A = f_A(W, U_A),$$

$$dN(t) = f_{dN(t)}(Pa(dN(t)), U_{dN(t)}), t = 1, \ldots, K,$$
$$dA(t) = f_{dA(t)}(Pa(dA(t)), U_{dA(t)}), t = 1, \ldots, K.$$

This SCM allows us to define counterfactual failure times $T_a = T_{a,\bar{A}=\bar{0}}$ corresponding with the intervention $A = a$ and $A(t) = 0$ for all $t = 1, \ldots, \tau$. Thus T_1 represent a patient's time to the occurrence of the failure event had the patient, possibly contrary to fact, been assigned to the treatment group, and was also not right censored. Let T_0 likewise represent the time to the occurrence of the event had the patient been assigned to the control group, also not right censored.

17.2 Causal Quantity, Identifiability, and Statistical Parameter

We can then define our causal effect of treatment on survival at time t_0 as

$$\psi_0^F = P_0(T_1 > t_0) - P_0(T_0 > t_0) \equiv S_1(t_0) - S_0(t_0).$$

We assume that treatment A is randomized in the sense that A is conditionally independent of (T_0, T_1), given W, and that $\min_a g_{A,0}(a \mid W) > 0$ a.e., which is true in an RCT. In addition, we assume that for each $t = 1, \ldots, \tau$, the censoring indicator $A(t)$ is conditionally independent of (T_0, T_1), given $Pa(A(t))$ (e.g., for each t, the unobserved exogenous error $U_{dA(t)}$ is independent of the exogenous errors $(U_{dN(s)} : s > t)$), and the following positivity assumption holds:

$$\bar{G}_0(t_0 \mid A, W) \equiv \prod_{t=1}^{t_0} (1 - \bar{g}_0(t \mid A, W)) > 0 \text{ a.e.}$$

Under these assumptions, it follows that the causal effect is identified from the true observed data distribution P_0:

$$\psi_0^F = \Psi(Q_0) \equiv E_{W,0}[S_0(t_0 \mid A = 1, W) - S_0(t_0 \mid A = 0, W)],$$

where $S_0(t_0 \mid A, W) = P_0(T > t_0 \mid A, W)$ is the conditional survival function of T, given A, W. The latter conditional survival function $S_0(t_0 \mid A, W)$ is identified by the conditional hazard $\bar{Q}_0(t \mid A, W) = P_0(T = t \mid T \geq t, A, W)$ through the product-integral relation between a survival function and a hazard:

$$S_0(t_0 \mid A, W) = \prod_{t=1}^{t_0} (1 - \bar{Q}_0(t \mid A, W)).$$

Here we used that under the stated sequential independence assumption on the censoring indicators, the conditional hazard of T, given (A, W), is indeed given by $\bar{Q}_0$.

Let $\Psi_a(P_0) = S_a(t_0)$ denote the target parameters of P_0 that map into the desired treatment-specific survival function $S_a(t_0)$, indexed by treatment group $a \in \{0, 1\}$.

The additive causal effect on survival at t_0 is thus given by

$$\Psi(P_0) = \Psi_1(P_0) - \Psi_0(P_0) = S_1(t_0) - S_0(t_0).$$

Similarly, the causal relative risk at t_0 is given by

$$\frac{S_1(t_0)}{S_0(t_0)},$$

and the causal odds ratio at t_0 is given by

$$\frac{S_1(t_0)(1 - S_0(t_0))}{S_0(t_0)(1 - S_1(t_0))},$$

where these parameters are all defined as simple functions of $\Psi_a(P_0)$. We will present the TMLE targeting both $(S_0(t_0), S_1(t_0))$, so that this also yields the TMLE procedure for these other causal measures of the treatment effect on survival.

Positivity

It is important to note that the TMLE, like other estimators, relies on the assumption that each subject has a positive probability of being observed (i.e., not censored) up till time t_0+. More formally, this assumption is $\bar{G}(t_0 \mid A, W) > 0$ a.e. This identifiability assumption for the target parameter $S_1(t_0) - S_0(t_0)$ has been addressed as an important assumption for right-censored data (Robins and Rotnitzky 1992). One is alerted to such violations by observing very small probabilities of remaining uncensored based on the estimated censoring mechanism, i.e., there are patients with a probability of censoring of almost one given their observed past at a time $t < t_0$. We recommend the parametric bootstrap method for assessing bias in the estimator due to practical or theoretical violation of the positivity assumption, as presented in Chap. 10.

17.3 Efficient Influence Curve

The efficient influence curve of $\Psi_a : \mathcal{M} \to \mathbb{R}$ at P_0, for any model on the treatment mechanism and censoring mechanism, is given by

$$D_a^*(P_0) = \sum_{t=1}^{\tau} I(\tilde{T} \geq t) H_a^*(t, A, W)(dN(t) - \bar{Q}_0(t \mid A, W)) + S_0(t_0 \mid A = 1, W) - S_0(t_0 \mid A = 0, W) - \Psi_a(P_0),$$

where, for $a \in \{0, 1\}$,

$$H_a^*(t,A,W) = -\left(\frac{I(A=a)}{g_{A,0}(a \mid W)\bar{G}_0(t_- \mid A=a,W)}\right)\left(\frac{S_0(t_0 \mid A=a,W)}{S_0(t \mid A=a,W)}\right) I(t \le t_0).$$

Note that the efficient influence curve for parameters that are a function of $S_1(t_0)$ and $S_0(t_0)$ can be obtained by application of the δ-method to the efficient influence curves D_1^* and D_0^*. For example, the efficient influence curve for the parameter $\Psi(P_0) = S_1(t_0) - S_0(t_0)$ is given by $D_1^* - D_0^*$.

This formula for the efficient influence curve is derived in van der Laan and Rubin (2007) and Moore and van der Laan (2009a). We also refer readers to Appendix A, and Chapter 3 in van der Laan and Robins (2003). The general formula for this time-dependent covariate $H_0^*(t,A,W)$ to update an initial hazard fit was provided in van der Laan and Rubin (2007) and is given by

$$H^*(t,A,W) = \frac{D^{FULL}(A,W,t \mid P_0) - E_{P_0}[D^{FULL}(A,W,T \mid P_0) \mid A,W,T>t)]}{\bar{G}_0(t_0 \mid A,W)},$$

where D^{FULL} is the efficient influence curve of the parameter of interest in the nonparametric model for the full-data structure (W,A,T) in which there is no right censoring. For example, the full-data estimating function for $\Psi_1(P_0)(t_0)$ and $\Psi_0(P_0)(t_0)$ is given by $I(T_1 > t_0) - S_1(t_0)$ and $I(T_0 > t_0) - S_0(t_0)$. Substitution of this full-data estimating function for D^{FULL} in the general formula yields the expression above.

17.4 TMLE of Additive Effect on Survival at a Fixed End Point

The first step of the TMLE involves determining an initial estimator P_n^0 of the P_0 of O, identified by an estimator $\bar{Q}_n^0(t \mid A,W)$, an estimator $g_{A,n}(A \mid W)$ of the treatment mechanism, an estimator $\bar{g}_n(t \mid A,W)$ of the censoring mechanism, and the empirical probability distribution $Q_{W,n}$ of $W_1,...,W_n$. The second step involves defining a loss function $L(P)$, and a fluctuation parametric working model $P_n^0(\epsilon)$ whose score (with respect to the loss function) at $\epsilon = 0$ equals the efficient influence curve $D_a^*(P_n^0)$ of the target parameter $\Psi_a(Q_0)$. As loss function we select the log-likelihood loss function $-\log P$. We recommend the use of super learning in the estimator $\bar{Q}_n(t \mid A,W)$ of the hazard $\bar{Q}_0(t \mid A,W)$. The marginal distribution of W is estimated with the empirical probability distribution of $W_1,\ldots,W_n$.

In order to fluctuate $\bar{Q}_n^0$, we will use as fluctuation parametric working model

$$\text{logit}\bar{Q}_n^0(\epsilon)(t \mid A,W) = \text{logit}\ \bar{Q}_n^0(t \mid A,W) + \epsilon H_{a,n}^*(t,A,W),$$

where the estimated time-dependent clever covariate is given by

$$H_{a,n}^*(t,A,W) = \left(\frac{I(A=a)}{g_{A,n}(a \mid W)\bar{G}_n(t_0 \mid A=a,W)}\right)\left(\frac{S_n^0(t_0 \mid A=a,W)}{S_n^0(t \mid A=a,W)}\right) I(t \le t_0).$$

In addition, let $Q_{W,n}(\epsilon) = (1 + \epsilon Q^0_{W,n})D_2(Q^0_n)$ be a parametric working fluctuation model with score at $\epsilon = 0$ equal to $D_2(Q^0_n) = S^0_n(t_0 \mid 1, W) - S^0_n(t_0 \mid 0, W) - \Psi_a(Q^0_n)$. The corresponding fluctuation parametric working model for P^0_n is given by

$$P^0_n(\epsilon)(O) = Q^0_{W,n}(\epsilon_1)(W)g_{A,n}(A \mid W) \times \prod_t g_{A(t),n}(A(t) \mid Pa(A(t))) \prod_t Q^0_{dN(t),n}(\epsilon_2)(dN(t) \mid Pa(dN(t))),$$

where

$$\{Q^0_{dN(t),n}(\epsilon_2) : \epsilon_2\}$$

is the fluctuation working model implied by the fluctuation model $\{\bar{Q}^0_n(\epsilon) : \epsilon\}$ through the hazard fit $\bar{Q}^0_n$.

The TMLE procedure is now defined. One computes the maximum likelihood estimator $\epsilon_n = (\epsilon_{1,n}, \epsilon_{2,n})$, which maximizes $\epsilon \to P_n \log P^0_n(\epsilon)$. Since the empirical distribution of W is a nonparametric maximum likelihood estimator, it follows that $\epsilon_{1,n} = 0$. The maximum likelihood estimator $\epsilon_{2,n}$ can be estimated with univariate logistic regression software, using $\bar{Q}^0_n$ as an offset, applied to a pooled repeated measures sample in which each subject contributes a line of data for each time point t with $t \leq \tilde{T}$. The univariate logistic regression software can be invoked simply ignoring the repeated measures structure of the data. This now defines an updated estimator $P^1_n = P^0_n(\epsilon_n)$, defined by the update $Q^1_n = Q^0_n(\epsilon_n)$ of Q^0_n.

The above steps for evaluating ϵ_n, and thereby obtaining the updated hazard fit $\bar{Q}^1_n(t \mid A, W)$, correspond with a single iteration of the targeted maximum likelihood algorithm. In the second iteration, the updated $\bar{Q}^1_n(t \mid A, W)$ now plays the role of the initial fit, and the clever time-dependent covariate $H^*_a(t, A, W)$ is then reevaluated with the updated $S^1_n(t \mid A, W)$ based on $\bar{Q}^1_n(t \mid A, W)$, and ϵ_n is estimated again.

This updating process for $\bar{Q}_n$ is iterated until $\epsilon_{2,n} \approx 0$; let's denote its limit by $\bar{Q}^*_n$. The latter represents the TMLE of the conditional hazard $\bar{Q}_0$. Let $Q^*_n = (Q_{W,n}, \bar{Q}^*_n)$ be the corresponding TMLE of Q_0, and P^*_n is defined as the updated data-generating distribution corresponding with Q^*_n and the initial (nonupdated) estimator $g_n = (g_{A,n}, \bar{g}_n)$ of the treatment mechanism and right-censoring mechanism. The TMLE of $\psi_{a,0} = S_a(t_0)$ is the corresponding substitution estimator

$$\psi^*_{a,n} = \Psi_a(P^*_n) = \Psi_a(Q^*_n) = \frac{1}{n}\sum_{i=1}^n S^*_n(t_0 \mid A = a, W_i).$$

The TMLE can now be implemented separately for each treatment group $a \in \{0, 1\}$. The TMLE of the bivariate parameter $(S_0(t_0), S_1(t_0))$ follows the same algorithm as described above for $S_a(t_0)$, but one now adds both time-dependent clever covariates $H^*_{0,n}$ and $H^*_{1,n}$ to the logistic regression working model for fluctuating $\bar{Q}^0_n$:

$$\text{logit}(\bar{Q}^0_n(\epsilon_2)(t \mid A, W)) = \text{logit}\bar{Q}^0_n(t \mid A, W) + \epsilon_{2,1}H^*_{1,n}(t, A, W) + \epsilon_{2,0}H^*_{0,n}(t, A, W).$$

The fluctuation fit $\epsilon_{2,n} = \{\epsilon_{2,1,n}, \epsilon_{2,0,n}\}$ is now obtained by fitting a logistic regression in the covariates $\text{logit}\bar{Q}_n^0(t \mid A, W)$, $H^*_{1,t_0}(t, A, W)$ and $H^*_{0,t_0}(t, A, W)$, where the coefficient in front of $\text{logit}\bar{Q}_n^0$ is fixed at one, and the intercept is set to zero. Again, the updating of $Q_{W,n}$ does not occur. This TMLE $Q_n^* = (Q_{W,n}, \bar{Q}_n^*)$, whose hazard fit $\bar{Q}_n^*$ is now targeted to both treatment-specific survival functions, results in targeted maximum likelihood substitution estimators for any function of $(S_1(t_0), S_0(t_0))$.

For example, the TMLE of $\psi_0 = S_1(t_0) - S_0(t_0)$ is defined as the substitution estimator

$$\psi_n^* = \Psi(Q_n^*) = \frac{1}{n}\sum_{i=1}^{n}\left[S_n^*(t_0 \mid 1, W_i)) - S_n^*(t_0 \mid 0, W_i)\right].$$

One can also target the TMLE directly toward the desired function $g(S_0(t_0), S_1(t_0))$ of $(S_0(t_0), S_1(t_0))$ by adding a single time-dependent clever covariate defined by

$$H^* = \frac{d}{dS_0(t_0)}g(S_0(t_0), S_1(t_0))H_0^* + \frac{d}{dS_1(t_0)}g(S_0(t_0), S_1(t_0))H_1^*.$$

All three types of TMLEs of $S_1(t_0) - S_0(t_0)$ [target $S_a(t_0)$ separately, target both $(S_0(t_0), S_1(t_0))$, and target $S_1(t_0) - S_0(t_0)$] are double robust and asymptotically efficient, as stated below.

17.5 Statistical Properties

Consider the parameter $\Psi(Q_0)$. The targeted maximum likelihood estimate $P_n^* \in \mathcal{M}$ of P_0 solves the efficient influence curve estimating equation, given by

$$\sum_{i=1}^{n} D^*(g_n, Q_n^*, \Psi(Q_n^*))(O_i) = 0,$$

which is the optimal estimating equation for the parameter of interest. It has been shown that $E_0 D^*(g, Q, \Psi(Q_0)) = 0$ if either the conditional hazard $\bar{Q}$ and marginal Q_W is correctly specified, or the treatment g_A and censoring mechanism $\bar{g}$ is correctly specified: (1) $Q_W = Q_{W,0}$, $\bar{Q} = \bar{Q}_0$ or (2) $g = g_0$ (Moore and van der Laan 2009a). Since the treatment mechanism is known in an RCT and the marginal distribution of W is consistently estimated with the empirical distribution, the consistency of the TMLE $\psi_n^*(t_0)$ of $\Psi(Q_0)$ in an RCT relies only on consistent estimation of either the censoring survival function $\bar{G}_0(\cdot \mid A, W)$ or the conditional survivor function $S_0(\cdot \mid A, W)$. In particular, when there is no right censoring or censoring is independent so that $\bar{G}_0(t \mid A, W) = \bar{G}_0(t \mid A)$ can be consistently estimated with the Kaplan–Meier estimator, the TMLE ψ_n^* is consistent, even when the estimator $S_n^*(\cdot \mid A, W)$ of $S_0(\cdot \mid A, W)$ is inconsistent (e.g., if it relies on a misspecified statistical model).

17.6 Variance Estimator

Let P_n^* represent the TMLE of P_0 and $IC_n = D^*(P_n^*)$ be the corresponding estimate of the efficient influence curve. Under the assumption that the censoring mechanism is consistently estimated, one can conservatively estimate the asymptotic variance of $\sqrt{n}(\psi_n^* - \psi_0)$ with $\sigma_n^2 = 1/n \sum_{i=1}^n IC_n^2(O_i)$. In this case, the true influence curve of ψ_n^* is given by $D^*(Q^*, g_0, \psi_0)$ minus its projection onto the tangent space of the model used for g_0. Given a specified model for g_0, this influence curve can be explicitly determined as well. The bootstrap provides an alternative method for estimating the variance of the TMLE.

17.7 Simulations

Data were simulated to mimic an RCT in which the goal was to determine the effectiveness of a new drug in comparison to the current standard of care on survival as measured by an occurrence of an event (e.g., particular marker falling below a given level) at 6 months into treatment. For each recruited subject, the probability of receiving the new treatment was 0.5. At baseline, two covariates were measured, and both are negatively correlated with survival time with a univariate correlation of around −0.5 and −0.6. For example, these two covariates might represent age in years and weight gain in the year prior to baseline. Specifically, 1000 samples of size 500 were generated based on the following data-generating distribution, where time is discrete and takes values $t \in \{1, ..., 9\}$:

$$\begin{aligned} P(A = 1) &= 0.5, \\ W_1 &\sim U(2, 6), \\ W_2 &\sim N(10, 10), \\ \bar{Q}_0(t \mid A, W) &= \frac{I(t < 9)}{1 + \exp(-(-8 - 0.75A + 0.3W_1^2 + 0.25W_2))} + I(t = 9), \end{aligned}$$

where $\bar{Q}_0(t \mid A, W)$ is the conditional hazard of the survival time.

Censoring times were generated according to two different mechanisms, which we will refer to as uninformative censoring and informative censoring, respectively. The two censoring mechanisms were set such that approx. 27% and 20% of the observations were censored, respectively.

Under the uninformative censoring mechanism, the hazard for censoring is given by $\lambda_C(t) = 0.15$. Under the informative censoring mechanism, the hazard for censoring depends on A and W_1, where the treated subjects ($A = 1$) had a much higher hazard of censoring for high levels of W_1 than the untreated subjects, whereas the untreated subjects had a much higher hazard for censoring than the treated subjects for low levels of W_1. Specifically, the hazard of censoring is defined as follows: $\lambda_C(t = 1 \mid A, W) = 0$, and, for $t \in 2, ..., 9$

$$\lambda_C(t \mid A, W_1) = \begin{cases} 0.25 \text{ if } W_1 > 4.5 \text{ and } A = 1, \\ 0.20 \text{ if } 4.5 \leq W_1 > 3.5 \text{ and } A = 1, \\ 0.05 \text{ if } 3.5 \leq W_1 > 2.5 \text{ and } A = 1, \\ \quad 0 \text{ if } W_1 > 3.5 \text{ and } A = 0, \\ 0.25 \text{ if } 3.5 \leq W_1 > 2.5 \text{ and } A = 0, \\ 0.05 \text{ if } W_1 \leq 2.5. \end{cases}$$

If censoring and failure times were the same, the subject was considered uncensored. The target parameter of interest was the difference $S_1(6) - S_0(6)$ in survival at $t_0 = 6$. The TMLE was applied with three types of initial estimator for the conditional hazard. The first estimator was fitted with a correctly specified logistic regression. The second estimator was fitted according to a misspecified logistic regression, by including only a main term for A and W_1. The third estimator was fitted according to a misspecified logistic regression that only included a main term for A and W_2. In the uninformative censoring mechanism simulation, the censoring mechanism was consistently estimated with the Kaplan–Meier estimator. In the informative censoring mechanism simulation, the censoring mechanism was consistently estimated with a logistic regression model. For comparison, these TMLEs were compared with the the unadjusted estimator of the treatment effect defined as the difference of the two treatment-specific Kaplan–Meier estimators at $t = 6$.

The estimators were compared using a relative efficiency (RE) measure based on the MSE, computed as the MSE of the Kaplan–Meier estimates divided by the MSE of the targeted maximum likelihood estimates. Thus a value greater than one indicates a gain in efficiency of the TMLE over the unadjusted estimator. In addition, we report the percent bias, proportion of rejected tests (PR) for testing the null hypothesis of no treatment effect, and the coverage of the 95% confidence intervals.

Table 17.1 Power and efficiency comparison of TMLE and Kaplan–Meier estimator of additive causal effect on survival. The initial estimator of the failure time hazard was based on a correctly specified logistic regression (TMLE_C), misspecified logistic regression that included only a main term for treatment and W_1 (TMLE_{M1}), and misspecified logistic regression that included only a main term for treatment and W_2 (TMLE_{M2}). KM is unadjusted Kaplan–Meier estimate

Uninformative censoring	% Bias	PR	95%	RE
KM	2	0.32	0.95	1.00
TMLE_C	1	0.75	0.94	2.82
TMLE_{M1}	3	0.44	0.95	1.36
TMLE_{M2}	2	0.40	0.94	1.27
Informative censoring	**% Bias**	**PR**	**95%**	**RE**
KM	24	0.47	0.93	1.00
TMLE_C	−3	0.72	0.94	2.94
TMLE_{M1}	−3	0.38	0.94	1.45
TMLE_{M2}	−2	0.37	0.94	1.31

Table 17.1 provides the results for the simulations. In the uninformative censoring simulation, the results show the expected gain in efficiency of the TMLE relative to the unbiased unadjusted estimator. When the initial hazard is consistently estimated, the gain in power for the targeted maximum likelihood estimate was as high as 75% − 32% = 43%. Although the gains are more modest when the initial hazard is misspecified, the gain in power was still 12% for the TMLE over the unadjusted estimator. The relative efficiency is 2.8 for the targeted maximum likelihood estimate using a consistently estimated hazard over the Kaplan–Meier-based estimator, demonstrating the reduction in variance due to the full utilization of the available covariates. In the informative censoring simulation, the unadjusted estimate is severely biased ($\approx 24\%$), whereas the targeted maximum likelihood estimate remains consistent. In such a setting, one must account for the informative censoring as the results from the unadjusted method are completely unreliable.

17.8 Discussion

The TMLE is a robust and efficient estimator of the causal effect of treatment on survival in RCTs. Under uninformative censoring, the validity of the TMLE in an RCT does not require any assumptions. The advantage of the TMLE relative to the unadjusted estimator in an RCT is twofold. The first is the potential efficiency gains over the unadjusted estimator due to utilization of covariates. The second is that the TMLE accounts for informative censoring and is thereby a less biased estimator than the unadjusted estimator.

The simulation results demonstrate the importance of the initial estimator of the failure time hazard, and that, for full utilization of available covariate information, data-adaptive machine learning algorithms should be applied as long as the algorithm is specified a priori. However, even misspecified parametric regression working models for the conditional hazard of the failure time result in gains in efficiency and power. The ideal approach includes an aggressive machine learning algorithm such as super learning to obtain an initial estimator of the conditional hazard of the failure time, and the subsequent targeted maximum likelihood bias reduction step based on a data-adaptive estimator of the censoring mechanism within a realistic model for the censoring mechanism. These two steps combined provide valid statistical inference for the treatment effect with potentially large gains in power and bias over a procedure that ignores covariates.

17.9 Notes and Further Reading

Portions of this chapter were adapted from Moore and van der Laan (2009c), and the TMLE we present is also discussed in Moore and van der Laan (2009a). A general approach to constructing locally efficient double robust estimators that are

guaranteed to improve on the unadjusted estimator can be found in van der Laan and Robins (2003), which is based on the original estimating equation methodology (Robins 1993; Robins and Rotnitzky 1992; Rubin and van der Laan 2008), grounded in empirical efficiency maximization. This reference also provides an overview of the literature on development of estimators based on right-censored data structures. In particular, we refer to Hubbard et al. (1999), who provide and implement nonparametric locally efficient estimation of the treatment-specific survival distribution with right-censored data and covariates in observational studies based on estimating equation methodology.

Covariate adjustment with time-to-event outcomes using Cox proportional hazards statistical models (e.g., Hernández et al. 2006), analogous to logistic linear regression for fixed-endpoint outcomes, relies on parametric assumptions for asymptotic validity of the effect estimates. In addition, the method estimates a conditional (on covariates W) effect rather than a marginal effect on survival. Lu and Tsiatis (2008) demonstrated how the efficiency of the logrank test in an RCT can be improved with covariate adjustment based on estimating equation methodology. Their method, which does not make assumptions beyond those of the logrank test, is more efficient and was shown to increase power over the logrank test. A nonparametric method for a covariate-adjusted method that uses logrank or Wilcoxon scores was proposed in Tangen and Koch (1999) and explored via simulation studies in Jiang et al. (2008). Adjusting for covariates instead of using the logrank test, with respect to power, is also discussed in Akazawa et al. (1997).