CONTINUOUS-TIME TARGETED MINIMUM LOSS-BASED ESTIMATION OF INTERVENTION-SPECIFIC MEAN OUTCOMES

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This paper generalizes the targeted minimum loss-based estimation (TMLE) framework to allow for estimating the effects of time-varying interventions in settings where both interventions, covariates, and outcome can happen at subject-specific time-points on an arbitrarily fine time-scale. TMLE is a general template for constructing asymptotically linear substitution estimators for smooth low-dimensional parameters in infinite-dimensional models. Existing longitudinal TMLE methods are developed for data where observations are made on a discrete time-grid.

We consider a continuous-time counting process model where intensity measures track the monitoring of subjects, and focus on a low-dimensional target parameter defined as the intervention-specific mean outcome at the end of follow-up. To construct our TMLE algorithm for the given statistical estimation problem we derive an expression for the efficient influence curve and represent the target parameter as a functional of intensities and conditional expectations. The high-dimensional nuisance parameters of our model are estimated and updated in an iterative manner according to separate targeting steps for the involved intensities and conditional expectations.

The resulting estimator solves the efficient influence curve equation. We state a general efficiency theorem and describe a highly adaptive lasso estimator for nuisance parameters that allows us to establish asymptotic linearity and efficiency of our estimator under minimal conditions on the underlying statistical model.

1. Introduction. We consider a continuous-time longitudinal data structure of $n \in \mathbb{N}$ independent and identically distributed observations of a multivariate process on a bounded interval of time $[0, \tau]$ with distribution P_0 belonging to a semiparametric statistical model $\mathcal{M}$. We are interested in assessing the effect of interventions on an outcome of interest under interventions that can happen at arbitrary points in time and are subject to time-

dependent confounding. Our focus is on the construction of an asymptotically efficient substitution estimator of intervention-specific mean outcomes represented as a parameter $\Psi : \mathcal{M} \to \mathbb{R}$.

In all that follows, we use the words 'intervention' and 'treatment' synonymously. Recent developments in the field of causal inference have produced numerous methods to deal with effects of time-varying treatments in presence of time-varying confounding (Robins, 1986, 1987, 1989b,a, 1992, 1998, 2000a,b; Bang and Robins, 2005; Robins et al., 2008; van der Laan, 2010a,b; Petersen et al., 2014). These methods deal with settings with a fixed number of time-points at which subjects of a population are all measured and can be intervened upon.

In the present work we consider a continuous-time model, utilizing a counting process framework (Andersen et al., 1993) where intensity processes define the rate of a finite number of continuous monitoring times for each subject conditional on their observed history, see Figure 1. Our approach is closely related to the work of Lok (2008) and of Røysland (2011, 2012), who propose continuous-time versions of structural nested models and marginal structural models (Robins, 1989b,a, 1992, 1998, 2000b,a; Robins et al., 2008), respectively, using counting processes and martingale theory. Our parameter $\Psi(P_0)$ is defined via the g-computation formula (Robins, 1986) in terms of interventions on the product integral representing the data-generating distribution.

To estimate $\Psi(P_0)$, we proceed on the basis of the targeted minimum loss-based estimation (TMLE) framework (van der Laan and Rubin, 2006; van der Laan and Rose, 2011, 2018). TMLE is a general methodology for constructing regular and asymptotically linear substitution estimators for smooth low-dimensional parameters in infinite-dimensional models, combining flexible ensemble learning and semiparametric efficiency theory in a two-step procedure. The earliest of the TMLE developments for estimation of effects of time-varying treatments in longitudinal data structures (LTMLE) involve full likelihood estimation and targeting (van der Laan, 2010a,b; Stitelman et al., 2012) whereas the later (van der Laan and Gruber, 2012; Petersen et al., 2014) are based on the techniques of sequential regression originating from Bang and Robins (2005). All these methods rely on a discrete timescale.

To construct our continuous-time TMLE algorithm we derive an expression for the efficient influence curve. The efficient influence curve is the canonical gradient of the functional Ψ and is a central component in the construction of locally efficient estimators of a target parameter in general (Bickel et al., 1993). Semiparametric efficiency theory yields that, given a statistical

model and a target parameter, a regular and asymptotically linear estimator is efficient if and only if its influence curve is equal to the efficient influence curve. Our estimation procedure is based on a representation of the target parameter in terms of intensities and conditional expectations for which we need initial estimators and a targeting updating algorithm. We propose such a targeting algorithm based on separate targeting steps for the intensities and for the conditional expectations that are iterated until convergence. The resulting estimator solves the efficient influence curve equation.

Our TMLE relies on initial estimators for the intensities and the conditional expectations that constitute our nuisance parameters. The TMLE framework allows us to take advantage of flexible and data-adaptive nuisance parameter estimation through super learning (van der Laan et al., 2007). A super learner is based on a library of candidate estimators for each nuisance parameter, and uses cross-validation to select either the best performing estimator or the best weighted combination of estimators. The general oracle inequality for cross-validation shows that the super learner performs asymptotically as well as the best combination of estimators in the library (van der Laan and Dudoit, 2003; van der Vaart et al., 2006). In particular, we discuss the highly adaptive lasso (HAL) (van der Laan, 2017) for all likelihood components. If this HAL estimator is included in the library of the super learner used for initial estimation, we can show that our TMLE estimator is asymptotically linear and efficient under minimal conditions on the model $\mathcal{M}$.

Our methods extend the existing longitudinal TMLE (LTMLE) to the continuous-time case. While the theory and asymptotic performance of LTMLE remain valid on any arbitrarily fine time-scale as long as it is discrete, we note the following. Sequential regression based LTMLE works by iterating through a sequence of regressions across all time-points and has been a popular choice over the full likelihood-based LTMLE that requires modeling of densities of potentially high-dimensional covariates. Our framework provides a unified methodology that covers both the continuous and the discrete-time case, where intensities of monitoring times are modeled separately and the regression approach can be used to deal with high-dimensional covariates. The substantial difference between LTMLE and our continuous-time TMLE lies in the limitation of LTMLE that one needs sufficiently many events at each time-point to fit the regressions. In contrast, our method can be applied when there are monitoring times with few events, or just one event.

1.1. *Motivating applications.* The methods developed here are applicable to a large variety of problems in pharmacoepidemiology. In this field
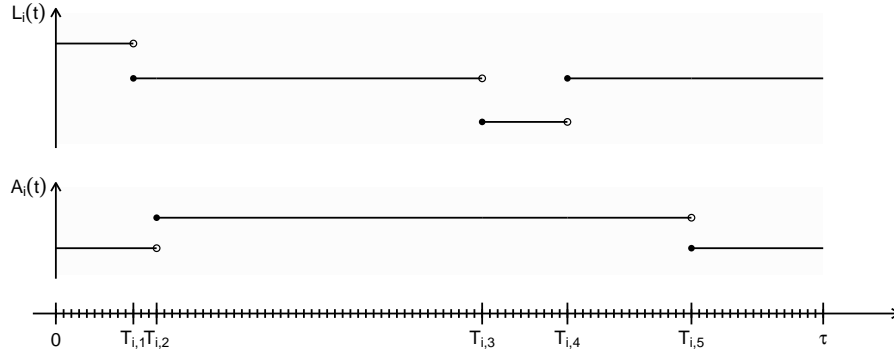
FIG 1. *Observations measured on a continuous scale, with five random time-points $T_{i,1}, \ldots, T_{i,5}$ between time 0 and time τ, referred to as monitoring times, where actual changes for the given subject i are measured. In this illustration, the process $L_i(t)$ changes at times $T_{i,1}$, $T_{i,3}$, and $T_{i,4}$ where it jumps between three different states and the process $A_i(t)$ changes at times $T_{i,2}$ and $T_{i,5}$ where it jumps from one state to another and back again.*

of research, hazard ratios are often used as measures of the association of time-dependent exposure with time-to-event outcomes (see, e.g., Andersen et al., 2013; Karim et al., 2016; Kessing et al., 2019). However, the interpretation of hazard ratios as the measure of causal treatment effects is hampered for many reasons (Hernán, 2010; Martinussen et al., 2018). Furthermore, the time-dependent Cox model cannot be used in the presence of time-dependent confounding (Robins, 1986). In many applications, it is thus of great interest to formulate and estimate statistical parameters under hypothetical treatment interventions that have a causal interpretation under the right assumptions.

Specifically, it may be of interest to assess the effect of a (dynamic) drug treatment regime on the τ-year risk of death. As an example, let $N^a(t)$ denote the process counting visits to a medical doctor who can prescribe the drug. Let the process $A(t)$ be information on the type and dose level of the drug prescribed at patient-specific times $T_1^a < T_2^a < \ldots < T_{N^a(\tau)}^a$ during the study period $[0, \tau]$. Further, let $N^\ell(t)$ denote the process counting doctor visits where health information $L(t)$ is collected. At visit T_k^a, the doctor considers the baseline characteristics L_0 of the patient, the treatment so far $\{(N^a(t), A(t)) : t \in [0, T_{k-1}^a]\}$, and evaluates changes of covariates $\{(N^\ell(t), L(t)) : t \in [0, T_k^a)\}$ to decide to continue or to change the treatment. We are interested in the result of a hypothetical experiment that we would have liked to have conducted but did not. In our example, the causal effect

resulting from such a hypothetical experiment could be the difference of the τ-year risk of death under different (dynamic) treatment regimes.

A treatment regime is any a priori defined rule which can be applied at doctor visits during the study period to decide if the treatment should be changed or continued. For example, the intervention could state that the patient stays on an initially randomized drug throughout the entire study period. A dynamic treatment regime is an example of an adaptive intervention which allows the decision to depend on the current history of the patient. The rule could be that whenever the measurement of a blood marker value exceeds a certain threshold the dose level of the drug should be adapted. By comparison of the effects of different regimes we may further learn optimal strategies for treatment interventions based on patients' medical past. In this article, we focus on interventions of the treatment process keeping the doctor visits where they naturally occur, that is, we consider interventions on $A(t)$ but not on $N^a(t)$ or $N^\ell(t)$.

The data analysis is complicated by the fact that the observed data are subject to time-dependent confounding: at any point in time, doctors and patients make treatment decisions for reasons depending on treatment and covariate history. Furthermore, past treatment may further influence future values of covariates, such as biomarkers and diagnoses, and future treatment decisions. Additionally, a proportion of subjects in the population may be lost to follow-up (censored) which can likewise depend on prior treatment decisions and covariate values. Our estimation framework allows us to control for the history of all observed time-varying covariates and treatment choices that we believe could be predictive of both treatment decisions and censoring, and of the risk of death. Importantly, the estimated effects of the hypothetical interventions can be interpreted causally when neither the treatment decision nor the censoring mechanism depend on any unrecorded health information. Specifically, this entails that the observed history at any point in time is sufficient to predict the next treatment decision and the censoring at that time, or, in other words, that there is no unmeasured confounding.

1.2. *Organization of article.* The article is organized as follows. We first define the statistical estimation problem. Section 2 introduces the continuous-time longitudinal setting and presents the model of a single subject along with the likelihood. In particular, Section 2.2 defines interventions on the likelihood, Section 2.4 defines the target parameter, and Section 2.5 provides the efficient influence function for the estimation problem. In Section 2.4.1, we briefly review the assumptions under which the target parameter identifies the causal effect of interest. Section 3 presents a representation

of the target parameter in terms of intensities and conditional expectations for which we need to construct an estimation procedure. Section 4 states a general theorem for asymptotically efficient substitution estimation. Section 5 introduces targeted minimum loss-based estimation (TMLE) for the considered estimation problem. Section 6 describes initial estimation of the likelihood components needed for the targeting updating steps and for estimation of the target parameter that fulfills the criteria of the efficiency theorem. Section 7 presents a particular TMLE algorithm for estimation of the target parameter in the continuous-time setting that involves separate targeting for conditional expectations and intensities, pooled over time. Section 8 reviews inference for the TMLE estimator. Section 9 presents the results of a simulation study as a demonstration of the methods and a proof-of-concept. Section 10 closes with a discussion. The supplementary material provides proofs of main results, further characterization of the initial estimation based on the highly adaptive lasso, and an overview of notation and algorithms.

2. Formulation of the statistical estimation problem. We start out defining the data structure, the statistical estimation problem and the target parameter. An overview of our notation can be found in Appendix C.1.

2.1. *Notation and setup.* We represent the subject-specific information in terms of a counting process model (Andersen et al., 1993). Suppose $n \in \mathbb{N}$ subjects of a population are followed in a bounded interval of time $[0, \tau]$. Let (N^a, N^ℓ, N^c, N^d) be a multivariate counting process generating random times at which treatment, covariates, censoring status and survival status may change. At jump times of N^a we observe changes in a treatment regime $A(t)$ taking values in finite set $\mathcal{A}$ and at jump times of N^ℓ we observe changes of a covariate vector $L(t)$ with values in a compact subset of $\mathbb{R}^d$. The processes N^c and N^d count changes in censoring status, and death status, respectively. Furthermore, L_0 denotes a vector of baseline covariates measured at time 0, and Y a real valued outcome variable measured at time τ. We assume that there are no events at time zero, and that realizations of all processes are càdlàg functions on $[0, \tau]$. Let $(\mathcal{F}_t)_{t \geq 0}$ denote the filtration generated by the history of the observed processes up to time t. Specifically, we have $\mathcal{F}_0 = \sigma(L_0)$.

Let $T_1^a < T_2^a < \ldots < T_{N^a(\tau)}^a$ and $T_1^\ell < T_2^\ell < \ldots < T_{N^\ell(\tau)}^\ell$ be the random times at which the treatment regime A and the covariate process L may change, and let T^c and T^d be the right-censoring time and the survival time, respectively. By definition, $N^a(t)$ and $N^\ell(t)$ are the subject-specific counts of

treatment and covariate monitoring times in $[0, t]$. The actual end of follow-up for a subject is $\min(T^c, T^d, \tau)$ and the total number of unique event times before time t is,

$$(1) \quad K(t) = \#\big\{\{T_1^a, \ldots, T_{N^a(t)}^a\} \cup \{T_1^\ell, \ldots, T_{N^\ell(t)}^\ell\} \cup \{T^c \wedge T^d \wedge t\}\big\}.$$

For each subject, the number $K(\tau)$ of change points of the multivariate counting process on $[0, \tau]$ is finite.

For $x = a, \ell, d, c$, we denote by Λ_0^x the cumulative intensity that characterizes the compensator of N^x. We further denote by $M^x = N^x - \Lambda_0^x$ the corresponding martingale. Heuristically, we have that

$$P(N^x(dt) = 1 \mid \mathcal{F}_{t-}) = \mathbb{E}[N^x(dt) \mid \mathcal{F}_{t-}] = d\Lambda_0^x(t \mid \mathcal{F}_{t-}),$$

where the increment $N^x(dt)$ is non-zero and equal to 1 if and only if there is a jump of N^x in the infinitesimal interval $[t, t + dt)$ (Andersen et al., 1993; Gill, 1994).

We assume that the processes A and L only change at monitoring times. The distribution of the treatment $A(t)$ at any time t where $N^a(t)$ jumps is denoted $\pi_{0,t}(a \mid \mathcal{F}_{t-}) = P(A(t) = a \mid \mathcal{F}_{t-})$, $a \in \mathcal{A}$, and the distribution of covariates $L(t)$ at any time t where $N^\ell(t)$ jumps is characterized by a conditional density $\mu_{0,t}(\ell \mid \mathcal{F}_{t-})$ with respect to a dominating measure ν_L. We assume that $A(t) = A(t-)$ and $L(t) = L(t-)$ otherwise. Lastly, the probability distribution of baseline covariates L_0 is characterized by the density μ_{0,L_0} with respect to a dominating measure ν_{L_0}.

2.1.1. *Observations.* For subject i, with $i = 1, \ldots, n$ independent subjects, let $\{T_{i,k}\}_{k=1}^{K_i(t)}$ denote the ordered set of unique event times up to time t. The observed data for subject i in a bounded interval $[0, t]$, $t \leq \tau$, is given by:

$$(2)$$
$$\bar{O}_i(t) = \big\{\big(L_{0,i}, s, N_i^a(s), A_i(s), N_i^\ell(s), L_i(s), N_i^d(s), N_i^c(s)\big) : s \in \{T_{i,k}\}_{k=1}^{K_i(t)}\big\}.$$

We also use the shorthand notation $O_i = \bar{O}_i(\tau)$ and denote by $\mathcal{O}$ the space where O_i takes its values. Let $\mathbb{P}_n$ denote the empirical distribution of the data $\{O_i\}_{i=1}^n$. For a dataset with n observations, we use

$$(3) \qquad\qquad\qquad 0 = t_0 < t_1 < \cdots < t_{\kappa_n}$$

with $\kappa_n = \sum_{i=1}^n K_i(\tau)$, to denote the ordered sequence of unique times of changes $\cup_{i=1}^n \cup_{k=1}^{K_i(\tau)} \{T_{i,k}\}$.

The distribution P_0 of the observed data O factorizes according to the time-ordering, going from one infinitesimal time interval to the next with $d\Lambda_0^x(t \,|\, \mathcal{F}_{t-})$ representing the conditional probability of an event of N^x in $[t, t+dt)$, for $x = a, \ell, d, c$ (Andersen et al., 1993, Section II.7). Accordingly, we express the likelihood as

$$
(4)
$$
$$
dP_0(O) =
$$
$$
\mu_{0,L_0}(L_0) \prod_{t \in (0,\tau]} \left(d\Lambda_0^\ell(t \,|\, \mathcal{F}_{t-}) \, \mu_{0,t}(L(t) \,|\, \mathcal{F}_{t-}) \right)^{N^\ell(dt)} \left(1 - d\Lambda_0^\ell(t \,|\, \mathcal{F}_{t-}) \right)^{1 - N^\ell(dt)}
$$
$$
\prod_{t \in (0,\tau]} \left(d\Lambda_0^a(t \,|\, \mathcal{F}_{t-}) \, \pi_{0,t}(A(t) \,|\, \mathcal{F}_{t-}) \right)^{N^a(dt)} \left(1 - d\Lambda_0^a(t \,|\, \mathcal{F}_{t-}) \right)^{1 - N^a(dt)}
$$
$$
\prod_{t \in (0,\tau]} \left(d\Lambda_0^c(t \,|\, \mathcal{F}_{t-}) \right)^{N^c(dt)} \left(1 - d\Lambda_0^c(t \,|\, \mathcal{F}_{t-}) \right)^{1 - N^c(dt)}
$$
$$
\prod_{t \in (0,\tau]} \left(d\Lambda_0^d(t \,|\, \mathcal{F}_{t-}) \right)^{N^d(dt)} \left(1 - d\Lambda_0^d(t \,|\, \mathcal{F}_{t-}) \right)^{1 - N^d(dt)},
$$

with $\prod$ denoting the product integral (Gill and Johansen, 1990; Andersen et al., 1993, Section II.6). A particularly nice aspect of the product-integral representation is that it gives a unified presentation for the discrete and the continuous time case.

2.2. *Interventions.* We are interested in estimating the effect of dynamic treatment regimes (Robins, 2002; Murphy et al., 2001; Hernán et al., 2006; van der Laan and Petersen, 2007) corresponding to hypothetical experiments, under hypothetical interventions, where data had been generated differently. An intervention defines a rule specifying treatment at each intervention time point given the data so far. In our setting, we allow the number and schedule of the intervention time-points to be subject-specific and to occur in continuous time. We thus distinguish between interventions that control the treatment decision mechanism, but not the conditional distribution governing the schedule of the intervention time points, and interventions that control the distribution of treatment decisions as well as the distribution of the intervention times. In our motivating pharmacoepidemiological applications from Section 1.1, an intervention only on the treatment decision mechanism could for example specify a treatment regime where a particular drug treatment should be continued or discontinued, while the frequency of doctor visits are kept as they would naturally occur for the subjects of the population had they followed that treatment regime. In addition to the treatment regimes of interest, interventions always control the

censoring mechanism, such that, in the hypothetical experiment, all subjects are followed for the entire study period $[0, \tau]$.

The observed data are generated by the distribution P_0 which factorizes as displayed in (4). We define interventions directly on P_0, by replacing a subset of its components by an intervention-specific choice. To formulate this, we decompose the observed data distribution P_0 into two parts which we refer to as the interventional part (G_0) and the non-interventional part (Q_0), respectively. We parametrize P_0 accordingly,

$$dP_0 = dP_{Q_0, G_0} = \prod_{t \in [0, \tau]} dQ_{0,t}\, dG_{0,t},$$

with $dG_{0,t}(o)$ and $dQ_{0,t}(o)$ denoting the conditional measures, given the observed history, corresponding to the interventional part and the non-interventional part at time t, respectively. We use $g_{0,t}$ to denote the density of $G_{0,t}$ and likewise $q_{0,t}$ to denote the density of $Q_{0,t}$, both with respect to appropriate dominating measures.

Now, an intervention involves replacing G_0 by some G^* encoding how treatment and censoring is generated conditional on the available history in the hypothetical experiment. In its generality, this is what is referred to as a *randomized plan* in Gill and Robins (2001, Sections 6 and 7), or a *stochastic* intervention (Robins et al., 2004; Dawid and Didelez, 2010), but it includes *static* and *dynamic* interventions (Hernán et al., 2006; Chakraborty and Moodie, 2013) plans as special cases as we explain below. Which components we include in G_0, and thus intervene upon, depends on what kinds of effects we are interested in and thus what scientific question we wish to address. Consider the following options.

DEFINITION 1 (Interventions on treatment assigned). *An intervention on treatment assigned involves replacing $\pi_{0,t}$ by some choice π_t^*. Thus, the interventional part includes the treatment and the censoring mechanism:*

$$(5) \qquad dG_{0,t}(O) = \big(\pi_{0,t}(A(t) \,|\, \mathcal{F}_{t-})\big)^{N^a(dt)} \big(d\Lambda_0^c(t \,|\, \mathcal{F}_{t-})\big)^{N^c(dt)} \\ \big(1 - d\Lambda_0^c(t \,|\, \mathcal{F}_{t-})\big)^{1 - N^c(dt)}.$$

The intervention prevents censoring and specifies the treatment regime π_t^*, such that

$$dG_t^*(O) = \big(1 - N^c(t)\big)\, \pi_t^*(A(t) \,|\, \mathcal{F}_{t-}).$$

The distribution of the intervention times is not intervened upon, i.e., Λ_0^a is included in the non-interventional part.

When the interventional treatment distributions are degenerated and, for example, set to a single value $a^* \in \mathcal{A}$ throughout the entire study period,

$$\pi_t^*(A(t) \,|\, \mathcal{F}_{t-}) = \mathbb{1}\{A(t) = a^*\}. \tag{6}$$

We refer to π_t^* as a static intervention since it deterministically sets $A(t) = a^*$ (at treatment monitoring times). A dynamic intervention, on the other hand, defines π_t^* that assigns $A(t)$ deterministically dependent on the subject's observed past.

DEFINITION 2 (Intervention on treatment and schedule). *The interventional part includes the treatment, the schedule of intervention times, and the censoring mechanism:*

$$dG_{0,t}(O) = \big(d\Lambda_0^a(t \,|\, \mathcal{F}_{t-}) \,\pi_{0,t}(A(t) \,|\, \mathcal{F}_{t-})\big)^{N^a(dt)} \big(1 - d\Lambda_0^a(t \,|\, \mathcal{F}_{t-})\big)^{1-N^a(dt)}$$
$$\big(d\Lambda_0^c(t \,|\, \mathcal{F}_{t-})\big)^{N^c(dt)} \big(1 - d\Lambda_0^c(t \,|\, \mathcal{F}_{t-})\big)^{1-N^c(dt)}.$$

The intervention prevents censoring and specifies a treatment regime by π_t^* and $\Lambda^{a,*}$, such that,

$$dG_t^*(O) = \big(1 - N^c(t)\big) \big(d\Lambda^{a,*}(t \,|\, \mathcal{F}_{t-}) \,\pi_t^*(A(t) \,|\, \mathcal{F}_{t-})\big)^{N^a(dt)}$$
$$\big(1 - d\Lambda^{a,*}(t \,|\, \mathcal{F}_{t-})\big)^{1-N^a(dt)}.$$

An intervention on the schedule of treatment decisions involves replacing the intensity Λ_0^a by some choice $\Lambda^{a,*}$. In the context of the applications described in Section 1.1, this could be to decrease or increase the frequency of doctor visits, for instance to ensure at least a monthly visit.

To focus our presentation, we continue with $dG_{0,t}$ as defined by (5) according to Definition 1, considering interventions only on the treatment decision π_t and on the censoring mechanism Λ^c. Note that this defines the non-interventional part as

$$dQ_{0,t}(O) = \big(d\Lambda_0^a(t \,|\, \mathcal{F}_{t-})\big)^{N^a(dt)} \big(1 - d\Lambda_0^a(t \,|\, \mathcal{F}_{t-})\big)^{1-N^a(dt)}$$
$$\big(d\Lambda_0^\ell(t \,|\, \mathcal{F}_{t-}) \,\mu_{0,t}(L(t) \,|\, \mathcal{F}_{t-})\big)^{N^\ell(dt)} \big(1 - d\Lambda_0^\ell(t \,|\, \mathcal{F}_{t-})\big)^{1-N^\ell(dt)}$$
$$\big(d\Lambda_0^d(t \,|\, \mathcal{F}_{t-})\big)^{N^d(dt)} \big(1 - d\Lambda_0^d(t \,|\, \mathcal{F}_{t-})\big)^{1-N^d(dt)},$$

for $t > 0$.

2.3. *Statistical model.* Let $\mathcal{Q}$ denote the parameter set for the non-interventional part $Q = (\mu_t, \Lambda^a(t), \Lambda^\ell(t), \Lambda^d(t))_{t \in [0,\tau]}$ and $\mathcal{G}$ the parameter set for the interventional part $G = (\pi_t, \Lambda^c(t))_{t \in [0,\tau]}$. We consider a statistical model $\mathcal{M}$ as follows:

$$(7) \qquad \mathcal{M} = \left\{ P \,:\, dP = dP_{Q,G} = \prod_{t \in [0,\tau]} dQ_t dG_t, \ G \in \mathcal{G}, \ Q \in \mathcal{Q} \right\}.$$

In Section 6 we summarize results that require Q, G to be contained in the set of càdlàg functions, i.e., functions that are right-continuous with left-hand limits, with bounded sectional variation norm. For now we leave $\mathcal{Q}, \mathcal{G}$ unspecified.

2.4. *Target parameter.* Suppose an intervention G^* is given. We define the post-interventional distribution for any $P \in \mathcal{M}$ by replacing G by G^* in $P_{Q,G}$. The resulting P_{Q,G^*} is commonly referred to as the *g-computation formula* (Robins, 1986; Gill and Robins, 2001). We will also denote this by P^{G^*}. Based on the data $O = \bar{O}(\tau)$, our overall aim is to estimate the expectation of the outcome of interest Y under the g-computation formula. That is, we are interested in the parameter $\Psi^{G^*} : \mathcal{M} \to \mathbb{R}$ given by

$$(8) \qquad \Psi^{G^*}(P) = \mathbb{E}_{P^{G^*}}\left[Y\right] = \int_{\mathcal{O}} y \prod_{t \in [0,\tau]} dQ_t(o) \, dG_t^*(o),$$

where the notation $\mathbb{E}_{P^{G^*}}$ refers to the expectation operator with respect to the post-interventional measure $P^{G^*} = P_{Q,G^*}$.

In this paper we focus on an all-cause mortality outcome, $Y = N^d(\tau)$, so that (8) is the expected risk of dying by time τ under the distribution defined by the g-computation formula. We emphasize, however, that in principle Y can be defined as any mapping of the observed past $\mathcal{F}_\tau$ as long as Y takes value in a compact set. We denote by $\psi_0 := \Psi^{G^*}(P_0)$, the true value of the target parameter. The target parameter is identifiable from the observed data under the following positivity assumption.

ASSUMPTION 1 (Positivity). *We assume absolute continuity of P_{Q,G^*} with respect to $P_{Q,G}$, i.e., $P_{Q,G^*} \ll P_{Q,G}$. This implies existence of the Radon-Nikodym derivative $dP_{Q,G^*}/dP_{Q,G} = \prod_{s < \tau} dG_s^*/dG_s$.*

The g-computation formula arising from replacing the observed G_0 by G^* and the resulting target parameter in (8) are well-defined statistical quantities by Assumption 1.

2.4.1. *Causal parameter and causal interpretability.*   Causal interpretability of the g-computation formula in the setting of discrete data is provided by Robins' work (Robins, 1986, 1987, 1989b) under the assumptions of no unmeasured confounding and positivity (for a nice review, see, Hernan and Robins, 2020, Part III). This work is further generalized by Gill and Robins (2001) to continuously varying covariates and treatments. Our setting differs from theirs in that subjects are measured at random times on a continuous scale: Our g-computation formula is represented as a product integral over times where something actually happens, whereas the g-computation formula of Gill and Robins (2001) consists of a finite product over times of a discrete grid. Nevertheless, note that the counting processes only have finitely many changes in the compact time interval $[0, \tau]$, and that interventions on the treatment decision are in fact only applied at a finite number of (random) times. Thus, the 'traditional' causal assumptions as stated by Gill and Robins (2001) can be applied at the random times to ensure the causal interpretation of the g-computation formula (Gill and Robins, 2001, Theorem 2).

Particularly, consider G^* that defines an intervention on the treatment assigned according to a distribution π_t^*. Let O^{G^*} be the counterfactual random variable representing the data that would have been observed, had G^* been adhered to rather than the factual G throughout the follow-up period. The causal parameter of interest is $\mathbb{E}[Y^{G^*}]$, the expected value of Y when imposing the intervention G^*. For our setting with random treatment monitoring times, $T_1^a < T_2^a < \ldots < T_{N^a(\tau)}^a$, we formulate the no unmeasured confounding assumption for the treatment decision as follows:

ASSUMPTION 2 (No unmeasured confounding). $Y^{G^*} \perp\!\!\!\perp A(T_k^a) \,|\, \bar{O}(T_k^a-)$, for all $k = 1, \ldots, N^a(\tau)$.

Assumption 1 and Assumption 2 together yield that our target parameter identifies the expected value of the counterfactual outcome, i.e., $\bar{\Psi}^{G^*}(P) = \mathbb{E}[Y^{G^*}]$, had the treatment decisions been governed by π_t^*.

In settings where one intervenes not only on the treatment decisions but also on the mechanism of the timing of treatment monitoring, an additional assumption equivalent to Assumption 2 is needed. Specifically, causal interpretability of $\Psi^{G^*}(P)$ is in that case achieved if the counterfactual outcome Y^{G^*} is independent of the time to the next treatment monitoring event conditional on the observed history up to any event time T_k.

Generally in our considered framework, note that the observed history at any time includes information on the A and L processes only at previous monitoring times. In medical applications, the treatment process A and

certain types of L processes will often be piecewise constant in time. For example, L could count hospital admissions with a certain medical diagnosis. However, other types of variables, such as blood pressure, may change continuously in time. The causal interpretation in our setup requires in particular that all changes that relate to treatment decisions are captured at the subject-specific monitoring times.

2.5. *Canonical gradient.* The canonical gradient of the pathwise derivative of the target parameter characterizes the information bound of the estimation problem relative to the statistical model $\mathcal{M}$ (Bickel et al., 1993). The canonical gradient is also known as the *efficient influence curve*. The following theorem provides a representation of the canonical gradient for our statistical model $\mathcal{M}$ and target parameter $\Psi^{G^*} : \mathcal{M} \to \mathbb{R}$. We will use this representation to construct an asymptotically efficient estimator.

We follow a general recipe to derive our expression for the canonical gradient. For this, consider the submodel $\mathcal{M}_G \subset \mathcal{M}$ that assumes G to be known and let $\mathscr{T}_G(P)$ denote the tangent space at P in the submodel $\mathcal{M}_G$. The canonical gradient can be found as the projection of any other gradient of the pathwise derivative of $\Psi : \mathcal{M}_G \to \mathbb{R}$ at P onto the tangent space $\mathscr{T}_G(P)$ (van der Laan and Robins, 2003). Thus, we need to characterize the tangent space $\mathscr{T}_G(P)$ and construct an initial gradient to project onto $\mathscr{T}_G(P)$. Note that the tangent space $\mathscr{T}_G(P)$ is generated by fluctuations only of the conditional distributions of Q since G is known. To construct an initial gradient, we can use the influence curve of an inverse probability weighted estimator of ψ_0 in $\mathcal{M}_G$. The detailed derivations can be found in Appendix A.

THEOREM 1 (Canonical gradient). *The canonical gradient $D^*(P)$ at P in $\mathcal{M}$ can be represented as follows:*

$$
\begin{aligned}
D^*(P) = {} & \mathbb{E}_{P^{G^*}}[Y \mid \mathcal{F}_0] - \Psi^{G^*}(P) \\
& + \int_0^\tau \prod_{s<t} \frac{dG_s^*}{dG_s} \Big(\mathbb{E}_{P^{G^*}}[Y \mid L(t), N^\ell(t), \mathcal{F}_{t-}] - \mathbb{E}_{P^{G^*}}[Y \mid N^\ell(t), \mathcal{F}_{t-}] \Big) N^\ell(dt) \\
& + \int_0^\tau \prod_{s<t} \frac{dG_s^*}{dG_s} \Big(\mathbb{E}_{P^{G^*}}[Y \mid \Delta N^\ell(t) = 1, \mathcal{F}_{t-}] - \mathbb{E}_{P^{G^*}}[Y \mid \Delta N^\ell(t) = 0, \mathcal{F}_{t-}] \Big) M^\ell(dt) \\
& + \int_0^\tau \prod_{s<t} \frac{dG_s^*}{dG_s} \Big(\mathbb{E}_{P^{G^*}}[Y \mid \Delta N^a(t) = 1, \mathcal{F}_{t-}] - \mathbb{E}_{P^{G^*}}[Y \mid \Delta N^a(t) = 0, \mathcal{F}_{t-}] \Big) M^a(dt) \\
& + \int_0^\tau \prod_{s<t} \frac{dG_s^*}{dG_s} \Big(1 - \mathbb{E}_{P^{G^*}}[Y \mid N^d(t) = 0, \mathcal{F}_{t-}] \Big) M^d(dt).
\end{aligned}
$$

We here follow notation of Andersen et al. (1993) and use Δ to denote the difference operator defined by $\Delta X = X - X_-$ for a càdlàg process X.

3. Representation of the target parameter by iterated expectations. Estimation of the target parameter requires evaluation of a large integral. We here present a parametrization of the target parameter in terms of a nested sequence of conditional expectations which is central for our estimation procedure. As for the discrete-time analogue (Bang and Robins, 2005; Robins, 2000b), the parametrization is defined backwards through time, starting at the end of the study period τ. The main difference to the discrete-time representation is that the time-points where events happen are random.

The notation that we present in this section will be used throughout the remainder of the paper. For $P \in \mathcal{M}$ and a fixed regime G^* according to Definition 1, we define for $t \in [0, \tau]$:

(9)
$$Z_t^{G^*} := \mathbb{E}_{PG^*} \left[Y \mid L(t), N^\ell(t), N^a(t), N^d(t), \mathcal{F}_{t-} \right] = \int Y \prod_{s \geq t} dG_s^* \prod_{s > t} dQ_s.$$

Note that the conditioning set of $Z_t^{G^*}$ excludes the interventional part at time t. We further denote the conditional expectation where $L(t)$ has been integrated out by:

(10)
$$Z_{t,L(t)}^{G^*} := \mathbb{E}_{PG^*} \left[Y \mid N^\ell(t), N^a(t), N^d(t), \mathcal{F}_{t-} \right]$$
$$= \mathbb{E}_{PG^*} \left[Z_t^{G^*} \mid N^\ell(t), N^a(t), N^d(t), \mathcal{F}_{t-} \right]$$
$$= \int \left(\int Y \prod_{s \geq t} dG_s^* \prod_{s > t} dQ_s \right) d\mu_{0,t}(L(t) \mid \mathcal{F}_{t-}).$$

The notation using the subscript '$L(t)$' in $Z_{t,L(t)}^{G^*}$ to refer to $L(t)$ being integrated out follows the notation of van der Laan and Gruber (2012).

LEMMA 1.   *Define, for any $P \in \mathcal{M}$:*

(11) $$\mathbf{Z} = \mathbf{Z}(P) := \left(Z_t^{G^*}, Z_{t,L(t)}^{G^*}, \Lambda^\ell(t), \Lambda^a(t), \Lambda^d(t) \right)_{t \in [0,\tau]}.$$

Particularly, let $\mathbf{Z}_0 = \mathbf{Z}(P_0)$. The target parameter Ψ^{G^*} defined in (8) can be represented as a functional of P only through $\mathbf{Z}$.

PROOF.   See Appendix A.8.   □

In line with the sequential regression representation of Bang and Robins (2005), we may thus utilize that $\boldsymbol{Z}$ rather than P itself can be used to evaluate the target parameter. Our aim is to estimate $\boldsymbol{Z}$ in an optimal way. The canonical gradient presented in Theorem 1 can be represented as a functional of $\boldsymbol{Z}$ and G; this will guide the construction of estimators for $\boldsymbol{Z}$ as a result of our efficiency theorem in Section 4.

4. Efficiency theorem for substitution estimation. In the previous section we have demonstrated that the target parameter can be represented as a functional of $P \in \mathcal{M}$ through $\boldsymbol{Z}$. We define a substitution estimator of the target parameter $\psi_0 = \Psi(P_0)$ based on an estimator $\hat{\boldsymbol{Z}}_n$ for $\boldsymbol{Z}_0$. The following theorem states the general conditions for asymptotic efficiency of such substitution estimation of ψ_0. Particularly, efficient estimation requires estimation of the relevant parts of the data-generating distribution that enter the expression of the efficient influence curve. Thus, an efficient estimator $\hat{P}_n$ is characterized by both $\hat{\boldsymbol{Z}}_n$ and $\hat{G}_n$. The proof of the theorem follows proofs in similar work (see, e.g., van der Laan and Rubin, 2006; van der Laan, 2017; van der Laan and Rose, 2011, Theorem A.5), is short and relies on an analysis of the separate terms of a von Mises expansion of the target parameter. In Section 6 we summarize results on initial estimators that meet the regularity conditions under minimal smoothness conditions on $\mathcal{M}$. Throughout we use the notation $Pf = \int f dP$ and $\|f\|_P = \sqrt{Pf^2}$.

We show in Appendix A.7 that the difference $\Psi^{G^*}(P) - \Psi^{G^*}(P_0)$ admits the following presentation:

$$(12) \qquad \Psi^{G^*}(P) - \Psi^{G^*}(P_0) = -P_0 D^*(P) + R_2(P, P_0), \qquad P \in \mathcal{M},$$

where $D^*(P)$ is the canonical gradient and the second-order remainder $R_2(P, P_0)$ is given by:

$$
\begin{aligned}
R_2(P, P_0) &= \Psi^{G^*}(P) - \Psi^{G^*}(P_0) + P_0 D^*(P) \\
(13) \qquad &= \int_0^\tau \int_\mathcal{O} Y \frac{1}{\bar{g}_t} \left(\bar{g}_{0,t} - \bar{g}_t \right) \prod_{s \leq \tau} dG_s^* \prod_{s < t} dQ_{0,s} \left(dQ_{0,t} - dQ_t \right) \prod_{s > t} dQ_s.
\end{aligned}
$$

Here we have used the notation:

$$\bar{g}_t = \prod_{s < t} g_s, \quad \text{and,} \quad \bar{g}_{0,t} = \prod_{s < t} g_{0,s},$$

with g_t being the density of the interventional part dG_t as defined in Section 2.2.

THEOREM 2.   *Consider an estimator $\hat{P}_n$ for P_0, such that*

(14)
$$\mathbb{P}_n D^*(\hat{P}_n) = o_P(n^{-1/2}).$$

If the following conditions 1 and 2 hold true,

Condition 1) $R_2(\hat{P}_n, P_0) = o_P(n^{-1/2})$,

Condition 2) $D^*(\hat{P}_n)$ *belongs to a Donsker class, and* $P_0\big(D^*(\hat{P}_n) - D^*(P_0)\big)^2$ *converges to zero in probability,*

then

$$\Psi^{G^*}(\hat{P}_n) - \Psi^{G^*}(P_0) = \mathbb{P}_n D^*(P_0) + o_P(n^{-1/2}),$$

that is, $\Psi^{G^*}(\hat{P}_n)$ is asymptotically linear at P_0 with influence curve $D^*(P_0)$ and is thus asymptotically efficient among all locally regular estimators at P_0.

PROOF. The proof of the theorem relies on the expansion (12). Applying the representation at $\hat{P}_n^*$ and using Equation (14) from the theorem yields

$$\Psi^{G*}(\hat{P}_n) - \Psi^{G*}(P_0) = (\mathbb{P}_n - P_0)D^*(\hat{P}_n) + R_2(\hat{P}_n, P_0) + o_P(n^{-1/2}).$$

It is now a result of empirical process theory (see, e.g., van der Vaart, 2000, Lemma 19.24) that condition 2 implies

$$(\mathbb{P}_n - P_0)\big(D^*(\hat{P}_n) - D^*(P_0)\big) = o_P(n^{-1/2}),$$

which finishes the proof.   □

If we are able to construct estimators $\hat{P}_n$ that meet the conditions of Theorem 2 and solve Equation (14), the so-called efficient influence curve equation, then the resulting substitution estimator $\Psi^{G^*}(\hat{P}_n)$ is asymptotically linear and efficient. In the following, we comment on conditions 1 and 2.

REMARK 1 (Second-order remainder).   *The second-order remainder expressed in (13) displays a double robustness structure (van der Laan and Robins, 2003) in the sense that,*

$$R_2(P, P_0) = 0 \quad if \quad \bar{g}_t = \bar{g}_{0,t} \quad or \quad q_t = q_{0,t}.$$

When $\bar{g}_t$ is bounded away from zero, the product structure of the remainder $R_2(P, P_0)$ yields, by use of the Cauchy-Schwartz inequality, an upper bound in terms of the $L_2(P_0)$-norm of $(\bar{g}_{0,t} - \bar{g}_t)$ and the $L_2(P_0)$-norm of $(q_{0,t} - q_t)$:

$$\int_0^\tau \|\bar{g}_{0,t} - \bar{g}_t\|_{P_0} \|q_{0,t} - q_t\|_{P_0}\, dt.$$

Here we have further used that $Y \in [0, 1]$. The required convergence rate $R_2(\hat{P}_n, P_0) = o_P(n^{-1/2})$ will for example be achieved if we estimate both parts at a rate faster than $o_P(n^{-1/4})$. In Section 6 we apply recent results on highly adaptive lasso (HAL) estimation (van der Laan, 2017) to show that such estimators do exist.

REMARK 2 (Donsker class conditions). In Section B.1 we give conditions under which $D^*(\hat{P}_n) \in \mathscr{F}$ where $\mathscr{F} = \{D^*(P) : P\}$ is a Donsker class. The key is that there is a finite number of monitoring times per subject, so that any subject contributes with finitely many terms to the likelihood. Then the canonical gradient can be written as a well-behaved mapping of the nuisance parameters such that Donsker properties of the nuisance parameters will translate into Donsker properties of the efficient influence curve. An important Donsker class is the class of càdlàg functions with finite variation.

Theorem 2 tells us what we need for efficient estimation of our target parameter. The next sections deal with construction of such an estimator.

5. Targeted minimum loss-based estimation (TMLE). We present a TMLE procedure for the construction of an estimator that will satisfy the conditions of Theorem 2. In summary, this consists of, first, constructing initial estimators for the components of $\boldsymbol{Z}$ and G, and, second, setting up an algorithm for performing an update of the collection of initial estimators that guarantees that it solves the efficient influence curve equation (14).

We also refer to the second step as the targeting step or the targeting algorithm. It involves for each component of $\boldsymbol{Z}$ a choice of a loss function and a corresponding path indexed by $\varepsilon \in \mathbb{R}$ through the initial estimator of that component such that the generated score at $\varepsilon = 0$ gives a desired part of the canonical gradient. The general targeting algorithm involves iterative updating steps that are repeated until convergence, at which point the efficient influence curve equation (14) is solved.

A certain amount of extra notation is needed. For $t \in (0, \tau]$, we define the "clever weights" as the Radon-Nikodym derivative

$$(15) \qquad h_t^{G^*} = \prod_{s < t} \frac{dG_s^*}{dG_s},$$

that only depends on the G-part of the likelihood, and the "clever covariates",

$$(16) \qquad h_t^{\ell} = \mathbb{E}_{PG^*}[Y \mid \Delta N^{\ell}(t) = 1, \mathcal{F}_{t-}] - \mathbb{E}_{PG^*}[Y \mid \Delta N^{\ell}(t) = 0, \mathcal{F}_{t-}],$$

$$(17) \qquad h_t^{a} = \mathbb{E}_{PG^*}[Y \mid \Delta N^{a}(t) = 1, \mathcal{F}_{t-}] - \mathbb{E}_{PG^*}[Y \mid \Delta N^{a}(t) = 0, \mathcal{F}_{t-}],$$

$$(18) \qquad h_t^{d} = 1 - \mathbb{E}_{PG^*}[Y \mid N^{d}(t) = 0, \mathcal{F}_{t-}],$$

that only depend on $\boldsymbol{Z}$. This now allows us to write the canonical gradient as,

$$
\begin{aligned}
D^*(P) &= Z_{t=0}^{G^*} - \Psi^{G^*}(P) \\
(19) \qquad &+ \int_0^{\tau} h_t^{G^*} \big(Z_t^{G^*} - Z_{t,L(t)}^{G^*}\big) dN^{\ell}(t) + \sum_{x \in \{a,\ell,d\}} \int_0^{\tau} h_t^{G^*} h_t^x \, dM^x(t).
\end{aligned}
$$

In the following, we define loss functions and one-dimensional parametric submodels for each component of $\boldsymbol{Z}$ such that the scores are equal to the respective terms of (19). These will be used to construct our targeting algorithm in Section 7. We consider each term of (19) separately and define loss functions and submodels for $Z_{t,L(t)}^{G^*}$ (Section 5.1) and for each of the conditional intensities Λ^x, $x = a, \ell, d$ (Section 5.2).

Before we do so, we remark upon another particular approach taken in the discrete-time setting (van der Laan, 2010a; Stitelman et al., 2012) that could also be applied to our problem. Note that, in this paper, we focus on the parametrization of the target parameter Ψ^{G^*} in terms of $\boldsymbol{Z}$ as presented in Section 3, but we could instead construct initial estimators for all likelihood components, i.e., all conditional densities and intensities, and construct a targeted updating step for each of these components as is done in the discrete-time case. Here we focus on $\boldsymbol{Z}$ rather than the full likelihood so that we can avoid targeting the conditional density of the potential high-dimensional $L(t)$. This will make the targeting step simpler and computationally more efficient.

5.1. *Loss function and submodel for $Z_{t,L(t)}^{G^*}$.* We need a loss function and a submodel for $Z_{t,L(t)}^{G^*}$ such that the score of the submodel equals the first term of (19). This term consists of an integral over a difference between $Z_t^{G^*}$ and $Z_{t,L(t)}^{G^*}$; thus, we will define our loss function and submodel for $Z_{t,L(t)}^{G^*}$ for a given $Z_t^{G^*}$. Particularly, we define the time-point specific logarithmic loss for $Z_{t,L(t)}^{G^*}$, indexed by $Z_t^{G^*}$:

$$
\mathscr{L}_{t,Z_t^{G^*}}\big(Z_{t,L(t)}^{G^*}\big) = Z_t^{G^*} \log Z_{t,L(t)}^{G^*} + \big(1 - Z_t^{G^*}\big) \log \big(1 - Z_{t,L(t)}^{G^*}\big).
$$

With this loss function, the parametric submodel

$$\text{logit } Z_{t,L(t)}^{G^*}(\varepsilon) = \text{logit } Z_{t,L(t)}^{G^*} + \varepsilon h_t^{G^*},$$

has the desired property that

$$\frac{d}{d\varepsilon} \mathscr{L}_{t,Z_t^{G^*}}\left(Z_{t,L(t)}^{G^*}(\varepsilon)\right)\Big|_{\varepsilon=0} = h_t^{G^*}\left(Z_t^{G^*} - Z_{t,L(t)}^{G^*}\right).$$

Correspondingly, we define the integrated loss for $\bar{Z}_{\tau,L(\tau)}^{G^*} = (Z_{s,L(s)}^{G^*} : 0 \leq s \leq \tau)$, indexed by $\bar{Z}_\tau^{G^*} = (Z_s^{G^*} : 0 \leq s \leq \tau)$,

$$\bar{\mathscr{L}}_{\bar{Z}_\tau^{G^*}}\left(\bar{Z}_{\tau,L(\tau)}^{G^*}(\varepsilon)\right) = \int_0^\tau \mathscr{L}_{t,Z_t^{G^*}}\left(Z_{t,L(t)}^{G^*}(\varepsilon)\right) dN^\ell(t),$$

for which we have that

$$\frac{d}{d\varepsilon}\bar{\mathscr{L}}_{\bar{Z}_\tau^{G^*}}\left(\bar{Z}_{\tau,L(\tau)}^{G^*}(\varepsilon)\right)\Big|_{\varepsilon=0} = \int_0^\tau \frac{d}{d\varepsilon}\mathscr{L}_{t,Z_t^{G^*}}\left(Z_{t,L(t)}^{G^*}(\varepsilon)\right)\Big|_{\varepsilon=0} dN^\ell(t)$$

$$= \int_0^\tau h_t^{G^*}\left(Z_t^{G^*} - Z_{t,L(t)}^{G^*}\right) dN^\ell(t),$$

which, as we wanted, equals the first term of the part of the canonical gradient expressed in (19).

5.2. *Loss function and submodel for the intensities* $\Lambda^x(t)$. We consider the case that Λ^x is absolutely continuous and denote by λ^x the intensity rate such that $\Lambda^x(t \mid \mathcal{F}_{t-}) = \int_0^t \lambda^x(s \mid \mathcal{F}_{s-})ds$. For each $x = a, \ell, d$, we specify a proportional hazard type submodel for Λ^x with time-dependent covariates as follows:

$$(20) \qquad d\Lambda^x(t;\varepsilon) = d\Lambda^x(t)\exp(\varepsilon h_t^{G^*} h_t^x),$$

together with the partial log-likelihood loss function:

$$\mathscr{L}_x(\Lambda^x) = \log\left(\prod_{t\in[0,\tau]} \left(\lambda^x(t)\right)^{N^x(dt)}\left(1 - d\Lambda^x(t)\right)^{1-N^x(dt)}\right)$$

$$= \int_0^\tau \log \lambda^x(t) \, dN^x(t) - \int_0^\tau d\Lambda^x(t).$$

For this pair of submodel and loss function we have the desired property
that

$$
\begin{aligned}
\frac{d}{d\varepsilon}\, \mathscr{L}_x(\Lambda^x(\,\cdot\,;\varepsilon)) \Big|_{\varepsilon=0} &= \frac{d}{d\varepsilon}\left(\int_0^\tau \left(\log \lambda^x(t) + \varepsilon h_t^{G^*} h_t^x \right) dN^x(t) - \right. \\
&\qquad\qquad \left. \int_0^\tau \exp\left(\varepsilon h_t^{G^*} h_t^x \right) d\Lambda^x(t) \right) \Big|_{\varepsilon=0} \\
&= \int_0^\tau h_t^{G^*} h_t^x\, dN^x(t) - \int_0^\tau h_t^{G^*} h_t^x\, d\Lambda^x(t) \\
&= \int_0^\tau h_t^{G^*} h_t^x \left(dN^x(t) - d\Lambda^x(t) \right),
\end{aligned}
$$

is equal to the corresponding terms of the canonical gradient as expressed in
(19).

6. Initial estimation of nuisance parameters. To carry out our targeting algorithm, we need initial estimators for the following time-sequences of conditional densities, conditional expectations, and conditional intensities:

$$
\begin{aligned}
\text{(21)} \qquad & G = \left(\pi_t, \Lambda^c(t) \right)_{t\in[0,\tau]}, \qquad \text{and,} \\
& \boldsymbol{Z} = \left(Z_t^{G^*}, Z_{t,L(t)}^{G^*}, \Lambda^\ell(t), \Lambda^a(t), \Lambda^d(t) \right)_{t\in[0,\tau]}.
\end{aligned}
$$

To establish conditions 1 and 2 of Theorem 2 under as weak as possible restrictions on our model $\mathcal{M}$, which in turn yields the asymptotic efficiency of our TMLE estimator, we propose highly adaptive lasso (HAL) estimation (van der Laan, 2017) for each of the quantities displayed in (21). In the present work, the aim of introducing HAL estimation is mainly theoretical; we can apply earlier results established by van der Laan (2017) on convergence properties for the HAL estimator under one key assumption that the nuisance parameters can be parametrized by functions that are càdlàg with finite sectional variation norm.

We refer to Appendix B for a more detailed characterization of HAL estimation and specifically the conditions on our model $\mathcal{M}$ that are sufficient to establish asymptotic efficiency of the TMLE estimator when initial estimators are constructed using HAL. The present section gives a short account of the HAL results that can be summarized as follows:

1. The nuisance parameters that characterize the statistical model $\mathcal{M}$ can be discontinuous or non-differentiable, we only need them to be parametrizable by functions that are càdlàg and have finite sectional variation norm. Such functions generate a signed measure (Gill et al.,

1995; van der Laan, 2017) and can be represented in terms of its measures over sections (Gill et al., 1995) corresponding to an infinite linear combination of indicator basis functions.

2. The HAL estimator is defined as the minimizer of the loss-specific empirical risk over the space of càdlàg functions with sectional variation norm bounded by a constant. In practice this can be solved by L_1-penalized (Lasso) regression (Tibshirani, 1996) where indicator basis functions are the covariates and the point-mass assigned to support points are the corresponding coefficients. Specifically, the sectional variation norm equals the sum of the absolute values of the coefficients, i.e., the L_1-norm of the vector of coefficients.

3. The highly adaptive lasso estimators attain the sufficient $n^{-1/4}$ convergence rate (a rate that has been further improved to $n^{-1/3} \log(n)^{d/2}$ for dimension d by Bibaut and van der Laan, 2019). Thus, by Remark 1 on the double robustness of the estimation problem, the use of HAL for estimation of the nuisance parameters in (21) allows us to establish condition 1 of Theorem 2.

4. The class of functions that are càdlàg and have finite sectional variation norm is a Donsker class and the canonical gradient is a well-behaved mapping of the nuisance parameters. This yields that $D^*(P) \in \mathscr{F}$ where $\mathscr{F} = \{D^*(P) : P\}$ is a Donsker class and thus provides the basis to establish condition 2 of Theorem 2.

To further optimize the estimation of the quantities in (21), we may use a super learner that selects the best performing estimator from a prespecified library of candidate algorithms by minimizing the cross-validated empirical risk. See Appendix C for a short description. The super learner performs asymptotically no worse than any algorithm included in its library, a property known as the oracle inequality (van der Laan and Dudoit, 2003; van der Vaart et al., 2006). Accordingly, a super learner that includes the HAL estimator in its library will converge at the same rate as the HAL estimator. From an applied perspective, the super learner has the advantages that it protects against model misspecification, compared to a single parametric model, and may improve efficiency compared to a single non-parametric model.

7. Targeting algorithm. Based on the loss functions and submodels defined in Sections 5.1–5.2, we here present a targeting algorithm for updating the collection of initial estimators for $\boldsymbol{Z}_0$ for a given estimator $\hat{G}_n$ for G_0 on $[0, \tau]$. We index the initial estimator for $\boldsymbol{Z}$ by $m = 0$ as follows:

$$\hat{\boldsymbol{Z}}_n^{m=0} = \left(\hat{Z}_{t,m=0}^{G^*}, \hat{Z}_{t,L(t),m=0}^{G^*}, \hat{\Lambda}_{m=0}^{\ell}(t), \hat{\Lambda}_{m=0}^{a}(t), \hat{\Lambda}_{m=0}^{d}(t) \right)_{t \in [0,\tau]}.$$

Our targeting algorithm involves separate updating steps for current estimators $\hat{Z}^{G^*}_{t,L(t),m}$ and $\hat{\Lambda}^x_m(t)$, $x = a, \ell, d$, from m to $m + 1$, $m = 0, 1, \ldots$, carried out simultaneously for all time-points. Our algorithm is overall centered around the representation of the target parameter by iterated expectations that we introduced in Section 3, with the separate updating steps ensuring that we solve the individual terms of the efficient influence curve equation. To describe the algorithm, recall that, as introduced in Display (3),

$$0 = t_0 < t_1 < \cdots < t_{\kappa_n},$$

denotes the ordered sequence of unique times of changes $\cup^n_{i=1} \cup^{K_i(\tau)}_{k=1} \{T_{i,k}\}$ across all subjects of the dataset. Evaluated at time t_r, the conditional expectations $Z^{G^*}_t$ and $Z^{G^*}_{t,L(t)}$ from Section 3 can be written:

$$(22) \qquad Z^{G^*}_{t_r} = \mathbb{E}_{P^{G^*}}[Y \mid L(t_r), N^\ell(t_r), N^a(t_r), N^d(t_r), \mathcal{F}_{t_{r-1}}],$$

$$(23) \qquad Z^{G^*}_{t_r, L(t_r)} = \mathbb{E}_{P^{G^*}}[Y \mid N^\ell(t_r), N^a(t_r), N^d(t_r), \mathcal{F}_{t_{r-1}}].$$

Further, at each t_r, we need to estimate the sequence of conditional expectations:

$$(24) \qquad \mathbb{E}_{P^{G^*}}[Y \mid N^a(t_r), N^d(t_r), \mathcal{F}_{t_{r-1}}],$$

$$(25) \qquad \mathbb{E}_{P^{G^*}}[Y \mid N^d(t_r), \mathcal{F}_{t_{r-1}}],$$

$$(26) \qquad \mathbb{E}_{P^{G^*}}[Y \mid \mathcal{F}_{t_{r-1}}].$$

Based on current estimators $\hat{\boldsymbol{Z}}^m_n$, we construct estimators for (22)–(26) for all $r = 1, \ldots, \kappa_n$, which further yield estimators for $\hat{h}^\ell_{t_r,m}, \hat{h}^a_{t_r,m}, \hat{h}^d_{t_r,m}$ for the clever covariates $h^\ell_{t_r}, h^a_{t_r}, h^d_{t_r}$. A more detailed description of this procedure is given in Appendix C.2. Estimators $\hat{h}^{G^*}_{t_r}$, $r = 1, \ldots, \kappa_n$, for the clever weights are obtained by substituting the estimator $\hat{G}_n$ for G in (15).

7.1. *Updating the estimator for $Z^{G^*}_{t_r,L(t_r)}$.* The updating step for the time-sequence $(\hat{Z}^{G^*}_{t_r,L(t_r),m})_{1 \leq r \leq \kappa_n}$ of estimators for the conditional expectations (23) is defined according to the loss function and submodel from Section 5.1, given the estimated clever weights $(\hat{h}^{G^*}_{t_r})_{1 \leq r \leq \kappa_n}$, as:

$$\hat{\bar{Z}}^{G^*}_{\tau,L(\tau),m+1} := \hat{\bar{Z}}^{G^*}_{\tau,L(\tau),m}(\hat{\varepsilon}_n).$$

Here, $\hat{\varepsilon}_n$ is estimated from the data by:

$$\hat{\varepsilon}_n := \underset{\varepsilon}{\operatorname{argmin}} \, \mathbb{P}_n \, \bar{\mathscr{L}}_{\hat{\bar{Z}}^{G^*}_{\tau,m}} \big(\hat{\bar{Z}}^{G^*}_{t_r,L(t_r),m}(\varepsilon) \big),$$

and the now updated estimators $\hat{\bar{Z}}^{G^*}_{\tau,L(\tau),m+1} = \big(\hat{Z}^{G^*}_{t_r,L(t_r),m+1}\big)_{1 \le r \le \kappa_n}$ solves the desired part of the efficient influence curve equation

$$\mathbb{P}_n \int_0^\tau \hat{h}^{G^*}_t \big(\hat{Z}^{G^*}_{t,m} - \hat{Z}^{G^*}_{t,L(t),m+1}\big) \, dN^\ell(t) = 0.$$

Notably, this updating step is carried out only at subject-specific time-points $t_r \in \{T^\ell_1, \ldots, T^\ell_{N^\ell(\tau)}\}$, where changes in $L(t)$ are observed.

7.2. *Updating the estimators for the intensities.* For each of $x = \ell, a, d$, the updating step for the current estimator $\hat{\Lambda}^x_m$ for the intensity Λ^x uses the estimated time-sequence of clever weights $(\hat{h}^{G^*}_{t_r})_{1 \le r \le \kappa_n}$ and the time-sequence $(\hat{h}^x_{t_r,m})_{1 \le r \le \kappa_n}$ of current estimators for the relevant clever covariate. Based on the loss function and submodel as defined in Section 5.2, $\hat{\varepsilon}_x$ is now estimated from the observed data by:

$$\hat{\varepsilon}_x := \underset{\varepsilon}{\operatorname{argmax}} \; \mathbb{P}_n \, \mathscr{L}_x\big(\hat{\Lambda}^x_m(\,\cdot\,;\varepsilon)\big).$$

We denote the corresponding updated intensity by $\hat{\Lambda}^x_{m+1} = \hat{\Lambda}^x_m(\,\cdot\,;\hat{\varepsilon}_x)$, which now solves

$$\mathbb{P}_n \int_0^\tau \hat{h}^{G^*}_t \hat{h}^x_{t,m} \big(dN^x(t) - d\hat{\Lambda}^x_{m+1}(t)\big) = 0,$$

the equation of interest.

7.3. *Iterating the targeting steps.* The updated estimators for $Z^{G^*}_{t,L(t)}$ and the intensities across time yield updated estimators for the sequence of conditional expectations (22)–(26) and thus for the clever covariates. This process constitutes the targeting iteration from m to $m+1$, corresponding to updating $\hat{\boldsymbol{Z}}^m_n$ into $\hat{\boldsymbol{Z}}^{m+1}_n$. The process is now repeated iteratively for $m = 0, 1, 2, \ldots$, moving from a current collection of estimators $\hat{\boldsymbol{Z}}^m_n$ to an updated collection of estimators $\hat{\boldsymbol{Z}}^{m+1}_n$. At each step m, the efficient score equation is evaluated

$$\mathbb{P}_n D^*(\hat{\boldsymbol{Z}}^m_n, \hat{G}_n) = \mathbb{P}_n \left(\hat{Z}^{G^*}_{0,m} + \int_0^\tau \hat{h}_t \big(\hat{Z}^{G^*}_{t,m} - \hat{Z}^{G^*}_{t,L(t),m}\big) \, dN^\ell(t) \right.$$
$$\left. + \sum_{x \in \{a,\ell,d\}} \int_0^\tau \hat{h}_t \, \hat{h}^x_{t,m} \big(dN^x(t) - d\hat{\Lambda}^x_m(t)\big) \right) - \Psi^{G^*}(\hat{\boldsymbol{Z}}^m_n),$$

and the iterations from m to $m+1$ are continued until

$$\big| \mathbb{P}_n D^*(\hat{\boldsymbol{Z}}^m_n, \hat{G}_n) \big| \le s_n,$$

for some choice of stopping criterion $s_n = o_P(n^{-1/2})$. We can for example use $s_n = \sigma/(n^{-1/2}\log n)$, where σ^2 is the variance of the efficient influence function which we can estimate by substituting the current estimators $\hat{\boldsymbol{Z}}_n^m$. Letting $m^* := \min(m \,:\, |\,\mathbb{P}_n D^*(\hat{\boldsymbol{Z}}_n^m, \hat{G}_n)\,| \le s_n)$, we denote the final estimator by $\hat{\boldsymbol{Z}}_n^* = \hat{\boldsymbol{Z}}_n^{m^*}$, where

$$\hat{\boldsymbol{Z}}_n^{m^*} = \left(\hat{Z}_{t,m^*}^{G^*}, \hat{Z}_{t,L(t),m^*}^{G^*}, \hat{\Lambda}_{m^*}^{\ell}(t), \hat{\Lambda}_{m^*}^a(t), \hat{\Lambda}_{m^*}^d(t) \right)_{t\in[0,\tau]}.$$

8. Inference for the targeted substitution estimator. In Section 6 we have summarized results that yield the existence of initial estimators that fulfill the regularity conditions of Theorem 2. In Section 7 we have presented a targeting algorithm that maps the initial estimator $\hat{\boldsymbol{Z}}_n^{m=0}$ into a targeted estimator $\hat{\boldsymbol{Z}}_n^*$ that solves the efficient influence curve equation (14). In the end we estimate the target parameter by:

$$\hat{\psi}_n^{G^*} = \mathbb{P}_n \, \hat{Z}_{t=0,m^*}^{G^*},$$

but we note that $\hat{\psi}_n^{G^*}$ is equal to the substitution estimator $\Psi^{G^*}(\hat{P}_n^*)$, where $\hat{P}_n^*$ is characterized by $(\boldsymbol{Z}_n^*, \hat{G}_n)$. Specifically, the components of $\hat{\boldsymbol{Z}}_n^*$ are compatible with a probability distribution $\hat{P}_n^*$ whose conditional expectations of Y given the relevant histories coincide with those of $\hat{\boldsymbol{Z}}_n^*$.

Theorem 2 implies asymptotic efficiency of $\hat{\psi}_n^{G^*}$, and we can use the asymptotic normal distribution

$$\sqrt{n}\left(\Psi^{G^*}(\hat{P}_n^*) - \Psi^{G^*}(P_0)\right) \xrightarrow{\mathcal{D}} \mathcal{N}(0, P_0 D^*(P_0)^2),$$

to provide an approximate two-sided confidence interval. Here

$$(27) \qquad\qquad \hat{\sigma}_n^2 := \mathbb{P}_n\{D^*(\hat{P}_n^*)\}^2,$$

can be used to estimate the variance of the TMLE estimator.

9. Empirical study. We demonstrate our methods by describing the application to simulated data, using the proposed algorithm to estimate the contrast between a treatment rule that sets $A(t) = 1$ and a treatment rule that sets $A(t) = 0$. One could think of a randomized trial where subjects in the study population are initially randomized to receive treatment or no treatment, but may switch treatment over time depending on the value of time-varying covariates. This is a setting where a standard Cox regression, as mentioned in Section 1.1, does not apply. Our focus is here to confirm our theory by evaluating the targeting algorithm, and, further, to compare our new algorithm to the existing longitudinal TMLE (LTMLE).

We consider a setting where subjects of a population are followed for τ days of follow-up time. On any given day, subjects may change treatment, covariates, may be lost to follow-up (right-censored), or may experience the outcome of interest. Both the treatment and the censoring mechanisms are subject to time-dependent confounding. The data are simulated such that the number of monitoring times per subject are approximately the same across different τ. Thus, the larger τ is, the less events are observed at single monitoring times. Throughout we let $n = 1,000$. Instructions on how to reproduce the simulations are available on GitHub (https://github.com/helenecharlotte/Web-appendix-continuous-time-TMLE).

9.1. *Setup.* In all simulations, we generate data from a sequence of logistic regressions allowing time-varying treatment and covariates to affect one another, keeping effects time-constant. Throughout, we let $L_0 \in \{1, \ldots, 6\}$, $A_0 \in \{0, 1\}$, $A(t) \in \{0, 1\}$ and $L(t) \in \{0, 1\}$. We draw observations A_0 such that large values of L_0 increase the probability of $A_0 = 1$. Subjects for which $A_0 = 0$ and with current covariate value equal to 1 are more likely to begin treatment by time t. Further, current treatment increases the probability of $L(t) = 1$. Both the baseline treatment A_0 and the time-varying treatment $A(t)$ have a negative main effect on the outcome process $N^d(t)$. Moreover, A_0 has a different effect within levels of $L(t)$, and $L(t)$ has a positive main effect. At last, the censoring process $N^c(t)$ depends on both A_0 and current covariates.

9.2. *Parameter of interest.* Our parameter of interest is the contrast between the intervention-specific mean outcomes under the regime that imposes $A(t) = 1$ (subjects adhering to treatment) to the regime that imposes $A(t) = 0$ (subjects adhering to no treatment). Both regimes also impose no censoring throughout follow-up. Thus, our interventions are specified as follows, following Definition 1:

Intervention 0: $\quad dG_t^0(O) = \big(1 - A(t)\big)^{N^a(dt)}\big(1 - N^c(t)\big),$

Intervention 1: $\quad dG_t^1(O) = \big(A(t)\big)^{N^a(dt)}\big(1 - N^c(t)\big).$

We let ψ^1 denote the intervention-specific mean outcome under Intervention 1 and ψ^0 the intervention-specific mean outcome under Intervention 0. Our target parameter is the corresponding difference:

$$\Psi(P) = \int Y \, dP_{Q,G^1} - \int Y \, dP_{Q,G^0} = \psi^1 - \psi^0.$$

LTMLE	$\tau = 5$	$\tau = 30$	$\tau = 50$	contTMLE	$\tau = 5$	$\tau = 30$	$\tau = 50$
ψ_0	-0.135	-0.138	-0.148	ψ_0	-0.135	-0.138	-0.148
$\hat{\psi}_{n,M}^{\mathrm{ltmle}}$	-0.135	-0.136	-0.149	$\hat{\psi}_{n,M}^{*}$	-0.137	-0.137	-0.147
Bias	-0.001	0.002	-0.001	Bias	-0.001	0.001	0.001
Cov (95%)	0.941	0.972	0.986	Cov (95%)	0.947	0.956	0.953
$\sqrt{\mathrm{MSE}}$	0.034	0.048	0.039	$\sqrt{\mathrm{MSE}}$	0.033	0.034	0.035
$\hat{\sigma}_{n,M}$	0.034	0.051	0.052	$\hat{\sigma}_{n,M}$	0.033	0.035	0.034

TABLE 1

Results from a simulation study with $\tau = 5, 30, 50$ days of follow-up. Left: Results from applying existing LTMLE software. Right: Results from applying our algorithm (contTMLE). The row ψ_0 shows the true value of the target parameter, and the rows $\hat{\psi}_{n,M}$ and $\hat{\sigma}_{n,M}$ show averages of estimates across the $M = 1000$ simulation repetitions.

As usual, the true value is denoted by $\psi_0 = \Psi(P_0)$. There is no unmeasured confounding, so that our parameter can be interpreted causally as the treatment effect we would see in the real world if subjects had been treated ($A(t) = 1$) compared to not ($A(t) = 0$). Note that $\psi_0 < 0$ reflects a protecting effect of the treatment. Throughout, we estimate ψ_0^1 and ψ_0^0 separately and report results for the estimated difference $\psi_0 = \psi_0^1 - \psi_0^0$.

9.3. *Simulations.* Overall, we seek to investigate the following:

1. The distribution of $\sqrt{n}\,(\hat{\psi}_n^* - \psi_0)$ under correctly specified parametric models for initial estimation of the nuisance parameters.
2. Comparison to LTMLE estimation when data are given on a discrete grid with small τ.
3. Robustness properties of our TMLE estimator: What happens when we misspecify the distribution of, for example, the outcome process.

As in Section 8, we use σ^2 to denote the variance of the canonical gradient and $\hat{\sigma}_n^2$ its estimator. We are generally interested in the coverage of confidence intervals based on $\hat{\sigma}_n^2$.

Comparison to LTMLE. For small τ, we can compare our estimation procedure to the results from the existing LTMLE implementation (Lendle et al., 2017). Table 1 shows the results of estimating the contrast $\psi_0 = \psi_0^1 - \psi_0^0$ when $\tau = 5$ and when $\tau = 50$, using LTMLE and using our algorithm. The table illustrates the deterioration of LTMLE when τ increases; for the simulations with $\tau = 50$, the estimated standard error from LTMLE is completely off.

Correctly specified initial estimation				Misspecified initial estimation			
	$\tau = 30$	$\tau = 50$	$\tau = 100$		$\tau = 30$	$\tau = 50$	$\tau = 100$
ψ_0	-0.138	-0.148	-0.130	ψ_0	-0.138	-0.148	-0.130
$\hat{\psi}_{n,M}^{\text{init}}$	-0.138	-0.147	-0.129	$\hat{\psi}_{n,M}^{\text{init}}$	-0.119	-0.135	-0.128
$\hat{\psi}_{n,M}^{*}$	-0.137	-0.147	-0.129	$\hat{\psi}_{n,M}^{*}$	-0.138	-0.147	-0.129
Bias (init)	0.000	0.001	0.001	Bias (init)	0.019	0.013	0.001
Bias (tmle)	0.001	0.001	0.001	Bias (tmle)	0.000	0.001	0.000
Cov (95%)	0.956	0.953	0.945	Cov (95%)	0.936	0.955	0.944
$\sqrt{\text{MSE}}$	0.034	0.035	0.035	$\sqrt{\text{MSE}}$	0.035	0.033	0.034
$\hat{\sigma}_{n,M}$	0.035	0.034	0.034	$\hat{\sigma}_{n,M}$	0.035	0.034	0.034

TABLE 2

Results from a simulation study with $\tau = 30, 50, 100$ days of follow-up. The initial estimator is denoted $\hat{\psi}_n^{\text{init}}$ and the targeted estimator is denoted $\hat{\psi}_n^{*}$. Left: Results from applying our algorithm with correctly specified initial estimation. Right: Results from applying our algorithm with misspecified initial estimation. The row ψ_0 shows the true value of the target parameter, and the rows $\hat{\psi}_{n,M}^{*}$, $\hat{\psi}_{n,M}^{\text{init}}$ and $\hat{\sigma}_{n,M}$ show averages of estimates across the $M = 1000$ simulation repetitions. As desired, the targeting algorithm corrects the bias of the initial estimator. It is further noted that the results for the TMLE estimator with misspecified and correctly specified initial estimation are very similar.

Performance of estimation and double robustness. We investigate the distribution of $\sqrt{n}\,(\hat{\psi}_n^{*} - \psi_0)$ under correctly specified and misspecified parametric models used for the initial estimation. For the latter, we leave out all time-varying variables when estimating the outcome distribution. Table 2 shows the results of estimating the contrast $\psi_0 = \psi_0^1 - \psi_0^0$ with $\tau = 30, 50, 100$ days of follow-up. In the last setting, LTMLE cannot be applied due to too few events at single monitoring times. The results in the table illustrate that our algorithm achieve appropriate coverage across τ, and that the targeting step of our algorithm removes bias from the initial estimation. In these simulations we further see that our TMLE estimation based on misspecified initial estimators is able to achieve very similar results to our TMLE estimators based on correctly specified initial estimators.

9.4. *Conclusions on the empirical findings.* Based on our simulations we draw the following conclusions:

1. The confidence intervals based on the estimate of the efficient influence curve have valid coverage in the simulations when the initial estimation is correctly specified.
2. Our new estimation algorithm produces similar results to the existing LTMLE for the settings where LTMLE applies. When τ gets larger, and thus observation sparsity increases, LTMLE breaks down.

3. Misspecification of the Q-part of the likelihood, such as the distribution
   of the outcome process, leads to biased initial estimation. This bias is
   corrected for by our targeting procedure.

10. Discussion. The current paper lays the groundwork for targeted
minimum loss based estimation of intervention-specific mean outcomes based
on a continuous-time counting process model. Our generalization of the
TMLE methodology is motivated by the problems arising when estimat-
ing interventional effects from observational data, where observations are
made without a schedule and potentially over very long time horizons. We
have developed our TMLE based on a continuous-time model to cover any
time-scale. The advantage is that we can track the information of changes in
continuous time, hereby preserving the original time-order of treatment and
covariates.

We have derived the efficient influence function for the estimation prob-
lem, and we have proposed a particular targeting algorithm to construct an
estimator that solves the efficient influence curve equation. Contrary to the
existing discrete-time longitudinal TMLE method (LTMLE) that involves a
regression step separately for every time-point, even if nothing is observed at
that time-point, our proposed TMLE algorithm allows us to smooth infor-
mation across time. In a sense, the estimation procedure we have presented
amounts to doing a sequential regression for each infinitesimal time interval,
but simultaneously by pooling over all t.

A substantial advantage of the proposed setting for estimation of inter-
ventional effects is that it provides a framework for studying various types of
interventions. In this paper, we have focused on interventions on censoring
(Λ^c) and treatment decision (π_t), and in our simulations we considered only
an intervention that imposed 'treatment' compared to 'no treatment'. As
discussed in Section 1.1 and Section 2.2, other interventions on treatment
decision and interventions on the treatment monitoring intensity Λ^a are pos-
sible within the same framework: The targeting procedure remains the same,
although, for the latter, Λ^a is taken out of the non-interventional part, and
thus out of the targeting procedure. In future work we will consider stochastic
and optimal interventions (Murphy, 2003, 2005; Hernán et al., 2006; Zhang
et al., 2013, 2012) both on the treatment decision and on the treatment mon-
itoring. One intervention of interest could be to replace Λ^a by $\Lambda^{a,*}$ that only
depends, for example, on the time since last treatment monitoring to ensure
a regime where subjects are monitored regularly.

It is evident from the general analysis of TMLE that the performance
of the final estimator depends on how well the nuisance parameters are es-

timated. In the continuous-time setting, the nuisance parameters comprise regressions of the intensity of changes and regressions of the time-dependent means. We have shown that we can construct HAL estimators for all required components such as to fulfill the conditions needed for asymptotic efficiency. To improve the estimation of nuisance parameters, it is desirable to set up large libraries consisting of flexible models and estimators for the conditional means and intensities that can then be fed into the super learner. In general, one should adapt the choices to the application at hand, considering the length of the time interval, the marginal intensity rates of the changes of action and covariates as well as the sample size and outcome prevalence.

We further point out that our targeting algorithm does not depend on the conditional density μ_t of the covariates $L(t)$; although we may use μ_t to provide an initial estimator for the conditional expectations, we are not committed to doing so. The fact is that it can be a big advantage to avoid estimation of μ_t altogether. In future work we investigate in more detail how to construct an estimator, for instance based on inverse probability weighted regression, that we map into an estimator that fulfills the representation in terms of iterated expectations of Lemma 1.

Future work will further deal with a general implementation of our TMLE procedure, beyond the simple settings of our simulation study. In addition to the applications outlined in Section 1.1, another important area of application is that of randomized trials where subjects crossover, start additional treatment and drop out. Here our methods can be applied to supplement the intention-to-treat analysis.

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SUPPLEMENTARY MATERIAL

APPENDIX A: ANALYSIS OF THE ESTIMATION PROBLEM

The first part of this appendix (Sections A.1–A.4) is concerned with the derivation of the canonical gradient as presented in Theorem 1. In the second part, we compute the second-order remainder (Sections A.6–A.7) and prove Lemma 1 from Section 3 (Section A.8). We refer to the main text with respect to notation; additional notation is introduced in the sections of the appendix where necessary.

A.1. Canonical gradient. An estimator is asymptotically efficient if and only if it is regular and asymptotically linear with influence curve equal to the canonical gradient. This makes the canonical gradient a central component in the construction of an asymptotically efficient estimator (Bickel et al., 1993; van der Vaart, 2000; Tsiatis, 2007). We here derive the canonical gradient for our statistical model $\mathcal{M}$ and target parameter $\Psi^{G^*} : \mathcal{M} \to \mathbb{R}$. In the following, consider the submodel $\mathcal{M}_G \subset \mathcal{M}$ that assumes G to be known and let $\mathscr{T}_G(P)$ denote the tangent space at P in the submodel $\mathcal{M}_G$. To derive the canonical gradient, we characterize the tangent space $\mathscr{T}_G(P)$ and construct an initial gradient of the pathwise derivative of $\Psi^{G^*} : \mathcal{M}_G \to \mathbb{R}$ at P. Relying on the factorization of any $P \in \mathcal{M}$ into a G-part and a Q-part, the canonical gradient can then be found as the projection of the initial gradient onto the tangent space $\mathscr{T}_G(P)$ (van der Laan and Robins, 2003). Note that the tangent space $\mathscr{T}_G(P)$ is generated by fluctuations of the conditional distributions of Q only since G is known. We deal with this in Section A.3. Furthermore, to construct an initial gradient, we can use the influence curve of any regular and asymptotically linear (RAL) estimator of $\Psi^{G^*} : \mathcal{M}_G \to \mathbb{R}$. In Section A.2, we construct an inverse probability weighted estimator (Hernán et al., 2000, 2002, 2001; van der Laan and Robins, 2003), the influence curve of which we will use as an initial gradient. In Section A.4 we provide projection formulas and in Section A.5 we collect the results of the lemmas of Section A.4 to provide the final proof of Theorem 1.

A.2. Initial gradient. To obtain an initial gradient, we construct an asymptotically linear estimator given the submodel $\mathcal{M}_G \subset \mathcal{M}$ that assumes that G is known and derive its influence function. To this end, we note the

following representation of the target parameter, for any $P \in \mathcal{M}$,

$$
\begin{aligned}
\Psi^{G^*}(P) = \mathbb{E}_{P^{G^*}}\big[Y\big] &= \int y \prod_{t \in [0, \tau]} dQ_t(o) \, dG_t^*(o) \\
&= \int y \prod_{t \leq \tau} dG_t^*(o) \frac{dG_t(o)}{dG_t(o)} \, dQ_t(o) \\
&= \int \left(y \prod_{t \leq \tau} \frac{dG_t^*(o)}{dG_t(o)} \right) \prod_{t \leq \tau} dG_t(o) \, dQ_t(o) \\
&= \mathbb{E}\left[Y \prod_{t \leq \tau} \frac{dG_t^*(O)}{dG_t(O)} \right].
\end{aligned}
$$

This suggests that we can estimate $\Psi^{G^*} : \mathcal{M}_G \to \mathbb{R}$ with an inverse probability weighted estimator as follows:

$$
(28) \qquad \hat{\psi}_{n,\mathrm{IPW}}^{G^*} := \mathbb{P}_n\left(\prod_{t \leq \tau} \frac{dG_t^*}{dG_t} Y \right) = \frac{1}{n} \sum_{i=1}^{n} \prod_{t \leq \tau} \frac{dG_t^*(O_i)}{dG_t(O_i)} Y_i
$$

The IPW estimator as written in (28) is a sample mean. It follows then directly that it is a linear (and thereby also asymptotically linear) estimator at any $P \in \mathcal{M}_G$ with influence curve:

$$
(29) \qquad D_{\mathrm{IPW}}^{G^*}(P)(O) = \prod_{t \leq \tau} \frac{dG_t^*(O)}{dG_t(O)} Y - \Psi^{G^*}(P).
$$

Since $D_{\mathrm{IPW}}^{G^*}(P)$ is an influence curve of a RAL estimator of Ψ^{G^*} in $\mathcal{M}_G$, we can derive the canonical gradient by projecting $D_{\mathrm{IPW}}^{G^*}(P)$ onto $\mathscr{T}_G(P)$.

A.3. Tangent space.   In the following we characterize the tangent space $\mathscr{T}_G(P)$. Based on the factorization of the probability distribution of the observed data, such that the likelihood from Display (4) of Section 2.1.1 consists of separate terms for each of μ_{L_0}, $(\mu_t)_{t \geq 0}$ and Λ^x, $x = a, \ell, d$, the tangent space $\mathscr{T}_G$ is given as the orthogonal sum of the individual tangent spaces:

$$
(30) \qquad \mathscr{T}_G = \mathscr{T}_{\mu_0} \oplus \mathscr{T}_\mu \oplus \mathscr{T}_{\Lambda^a} \oplus \mathscr{T}_{\Lambda^\ell} \oplus \mathscr{T}_{\Lambda^d}.
$$

In the following, $L_2(P)$ is used to denote the Hilbert space of measurable functions $h : \mathcal{O} \to \mathbb{R}$ with $Ph^2 < \infty$. The following lemmas characterize the tangent spaces in (30). The notation $h \in \sigma(X)$, for some random variable X, means that h is measurable with respect to the σ-algebra generated by X, and can thus be written as a function of X.

Lemma 2. *The tangent space $\mathscr{T}_{\mu_{L_0}}$ associated with the density μ_{L_0} of L_0 is given by:*

$$\mathscr{T}_{\mu_{L_0}}(P) = \left\{ h \in \mathcal{F}_0 \ : \ \mathbb{E}_P[h] = 0 \right\} \cap L_2(P).$$

Proof. We put no restrictions on the density μ_{L_0}, so the corresponding tangent space $\mathscr{T}_{\mu_{L_0}}$ is the entire Hilbert space of measurable square-integrable functions of L_0 with mean zero (van der Vaart (2000), Example 25.16). $\qquad\square$

Lemma 3. *The tangent space $\mathscr{T}_\mu$ associated with the conditional density μ_t of $L(t)$ is given by:*

$$\mathscr{T}_\mu(P) = \left\{ \int_0^\tau h_t\, N^\ell(dt) \ : \ h_t \in \sigma(L(t), N^\ell(t), \mathcal{F}_{t-}) \ \wedge \right.$$
$$\left. \mathbb{E}_P\big[h_t \,\big|\, N^\ell(t), \mathcal{F}_{t-}\big] = 0 \right\} \cap L_2(P).$$

Proof. Consider the parametric submodel:

$$\mu_{t,\varepsilon,h_t}(o) = \big(1 + \varepsilon h_t(o)\big)\, \mu_t(o),$$

for $\varepsilon \geq 0$, with $h_t : \mathcal{O} \to \mathbb{R}$ such that $h_t \in \sigma(L(t), \mathcal{F}_{t-})$. To ensure that $\mu_{t,\varepsilon,h}$ for all $\varepsilon > 0$ actually gives rise to a well-defined probability measure, note that:

$$\int_{\mathcal{O}} \mu_{t,\varepsilon,h_t}\, d\nu^\ell = \underbrace{\int_{\mathcal{O}} \mu_t\, d\nu^\ell}_{=1} + \varepsilon \int_{\mathcal{O}} h_t\, \mu_t\, d\nu^\ell = 1 \quad \text{if and only if}$$

$$\int_{\mathcal{O}} h_t\, \mu_t\, d\nu^\ell = \mathbb{E}[h_t \,|\, \mathcal{F}_{t-}] = 0.$$

The contribution to the log-likelihood is

$$\log dP_{\varepsilon,h_t}(o) = \int_0^\tau \log\Big(\big(1 + \varepsilon h_t(o)\big)\, \mu_t(o)\Big) N^\ell(dt),$$

and we derive the score accordingly

$$\frac{d}{d\varepsilon} \log dP_{\varepsilon,h_t}(o)\bigg|_{\varepsilon=0} = \frac{d}{d\varepsilon}\left(\int_0^\tau \log\Big(\big(1 + \varepsilon h_t(o)\big)\, \mu_t(o)\Big) N^\ell(dt)\right)\bigg|_{\varepsilon=0}$$
$$= \int_0^\tau h_t(o)\, N^\ell(dt).$$

This shows that the tangent space is given by:

$$\mathscr{T}_{\mu}(P) = \left\{ \int_0^{\tau} h_t \, N^{\ell}(dt) \; : \; h_t \in \sigma(L(t), N^{\ell}(t), \mathcal{F}_{t-}) \wedge \right.$$

$$\left. \mathbb{E}_P\left[h_t \mid N^{\ell}(t), \mathcal{F}_{t-}\right] = 0 \right\} \cap L_2(P).$$

$\square$

The following lemma deals with the tangent spaces $\mathscr{T}_{\Lambda^a}$, $\mathscr{T}_{\Lambda^{\ell}}$, $\mathscr{T}_{\Lambda^d}$.

LEMMA 4. *The tangent space $\mathscr{T}_{\Lambda^x}$ associated with the intensity Λ^x of N^x is given by:*

$$\mathscr{T}_{\Lambda^x}(P) = \left\{ \int_0^{\tau} h_t \left(N^x(dt) - \Lambda^x(dt) \right) \; : \; h_t \in \mathcal{F}_{t-} \right\} \cap L_2(P), \quad x = a, \ell, d.$$

PROOF. For $x = a, \ell, d$, let $h_t : \mathcal{O} \to \mathbb{R}$ be such that $h_t \in \mathcal{F}_{t-}$ and consider the class of submodels

$$\lambda^x_{\varepsilon, h_t}(t \mid \mathcal{F}_{t-}) = \exp\left(\varepsilon h_t(o)\right) \lambda^x(t \mid \mathcal{F}_{t-}).$$

These are valid submodels since $\lambda^x_{0, h_t}(t \mid \mathcal{F}_{t-}) = \lambda^x(t \mid \mathcal{F}_{t-})$ and $\lambda^x_{\varepsilon, h_t}(t \mid \mathcal{F}_{t-}) > 0$ for all t. The contribution to the log-likelihood is

$$\log dP_{\varepsilon, h_t}(o) = \int_0^{\tau} \left(\varepsilon h_t(o) + \log \lambda^x(t \mid \mathcal{F}_{t-})\right) N^x(dt) -$$

$$\int_0^{\tau} \exp\left(\varepsilon h_t(o)\right) \lambda^x(t \mid \mathcal{F}_{t-}) dt,$$

and we derive the score

$$\frac{d}{d\varepsilon} \log dP_{\varepsilon, h_t}(o)\Big|_{\varepsilon=0} = \frac{d}{d\varepsilon}\left(\int_0^{\tau} \left(\varepsilon h_t(o) + \log \lambda^x(t \mid \mathcal{F}_{t-}) dt\right) N^x(dt) - \right.$$

$$\left. \int_0^{\tau} \exp\left(\varepsilon h_t(o)\right) \lambda^x(t \mid \mathcal{F}_{t-}) dt \right)\Big|_{\varepsilon=0}$$

$$= \int_0^{\tau} h_t(o) \, N^x(dt) - \int_0^{\tau} h_t(o) \, \lambda^x(t \mid \mathcal{F}_{t-}) dt.$$

Thus, the tangent space is given by:

$$\mathscr{T}_{\Lambda^x}(P) = \left\{ \int_0^{\tau} h_t \left(N^x(dt) - \lambda^x(t \mid \mathcal{F}_{t-}) dt \right) \; : \; h_t \in \mathcal{F}_{t-} \right\},$$

for $x = a, \ell, d$.

$\square$

A.4. Projection onto tangent spaces. We have characterized the tangent space $\mathscr{T}_G$ and provided an initial gradient $D_{\text{IPW}}^{G^*}(P)$. We can now compute the canonical gradient by projecting $D_{\text{IPW}}^{G^*}(P)$ onto $\mathscr{T}_G$. Note that, to simplify notation, we use the shorthand $\mathscr{D} = D_{\text{IPW}}^{G^*}(P)$ for the remainder of this subsection.

We denote the projection onto a tangent space $\mathscr{T}$ by $\Pi(\cdot \,|\, \mathscr{T})$. The orthogonal sum decomposition of $\mathscr{T}_G$ implies that:

(31)
$$\Pi(\mathscr{D} \,|\, \mathscr{T}_G(P)) = \Pi(\mathscr{D} \,|\, \mathscr{T}_{\mu_{L_0}}(P)) + \Pi(\mathscr{D} \,|\, \mathscr{T}_\mu(P)) + \sum_{x=a,\ell,d} \Pi(\mathscr{D} \,|\, \mathscr{T}_{\Lambda^x}(P)).$$

The individual projections are given in the following lemmas.

LEMMA 5. *The projection of $\mathscr{D}$ onto the tangent space $\mathscr{T}_{\mu_{L_0}}(P)$ is given by:*

$$\Pi(\mathscr{D} \,|\, \mathscr{T}_{\mu_{L_0}}(P)) = \mathbb{E}_{P^{G^*}}[Y \,|\, \mathcal{F}_0] - \Psi^{G^*}(P).$$

PROOF. Recall that $\mathscr{T}_{\mu_{L_0}}(P) = \{h \in \mathcal{F}_0 \,:\, \mathbb{E}_P[h] = 0\} \cap L_2(P)$. The projection of $\mathscr{D}$ onto $\mathscr{T}_{\mu_{L_0}}(P)$ is obtained as

$$\Pi(\mathscr{D} \,|\, \mathscr{T}_{\mu_{L_0}}) = \mathbb{E}[\mathscr{D} \,|\, L_0] - \mathbb{E}[\mathscr{D}] = \mathbb{E}_{P^{G^*}}[Y \,|\, L_0] - \Psi^{G^*}(P),$$

noting that $\mathcal{F}_0 = \sigma(L_0)$. Above we used that $\mathbb{E}[\mathscr{D}] = 0$, and further that the projection onto $\mathscr{T}_{\mu_{L_0}}(P)$ can be obtained by first projecting onto $L_2(P)$ and then projecting that projection onto $\mathscr{T}_{\mu_{L_0}}(P) \subset L_2(P)$ combined with Durrett (2019, Theorem 4.1.15). □

LEMMA 6. *The projection of $\mathscr{D}$ onto the tangent space $\mathscr{T}_\mu(P)$ is given by:*

$$\Pi(\mathscr{D} \,|\, \mathscr{T}_\mu(P)) = \int_0^\tau \left(\mathbb{E}[\mathscr{D} \,|\, L(t), N^\ell(t), \mathcal{F}_{t-}] - \mathbb{E}[\mathscr{D} \,|\, N^\ell(t), \mathcal{F}_{t-}] \right) N^\ell(dt).$$

PROOF. We suggest that the projection is given by:

$$\widetilde{\Pi}(\mathscr{D} \,|\, \mathscr{T}_\mu(P)) = \int_0^\tau \left(\mathbb{E}[\mathscr{D} \,|\, L(t), N^\ell(t), \mathcal{F}_{t-}] - \mathbb{E}[\mathscr{D} \,|\, N^\ell(t), \mathcal{F}_{t-}] \right) N^\ell(dt).$$

To verify that $\widetilde{\Pi}(\mathscr{D} \mid \mathscr{T}_\mu(P))$ is in fact the projection, first note that $\widetilde{\Pi}(\mathscr{D} \mid \mathscr{T}_\mu(P)) \in \mathscr{T}_\mu(P)$. What remains to be shown is that:

$$(32) \qquad \mathbb{E}\left[\left(\mathscr{D} - \widetilde{\Pi}(\mathscr{D} \mid \mathscr{T}_\mu(P))\right) S\right] = 0,$$

for any $S \in \mathscr{T}_\mu(P)$. Since $S \in \mathscr{T}_\mu(P)$, we can write

$$S = \int_0^\tau h_t^S \, N^\ell(dt),$$

for some $h_t^S \in \sigma(L(t), N^\ell(t), \mathcal{F}_{t-})$ such that $\mathbb{E}_P\left[h_t^S \mid N^\ell(t), \mathcal{F}_{t-}\right] = 0$. Now, the second term of (32) can be written as follows

$$\mathbb{E}\left[\widetilde{\Pi}(\mathscr{D} \mid \mathscr{T}_\mu(P)) \, S\right]$$
$$= \mathbb{E}\left[\int_0^\tau \mathbb{E}\left[\left(\mathbb{E}[\mathscr{D} \mid L(t), N^\ell(t), \mathcal{F}_{t-}] - \right.\right.\right.$$
$$\left.\left.\left. \mathbb{E}[\mathscr{D} \mid N^\ell(t), \mathcal{F}_{t-}]\right) h_t^S \, \middle| \, N^\ell(t), \mathcal{F}_{t-}\right] N^\ell(dt)\right]$$
$$= \mathbb{E}\left[\int_0^\tau \left(\mathbb{E}\left[\mathbb{E}[h_t^S \mathscr{D} \mid L(t), N^\ell(t), \mathcal{F}_{t-}]\right] - \right.\right.$$
$$\left.\left. \mathbb{E}\left[\mathbb{E}[\mathscr{D} \mid N^\ell(t), \mathcal{F}_{t-}] \underbrace{\mathbb{E}[h_t^S \mid N^\ell(t), \mathcal{F}_{t-}]}_{=0}\right]\right) N^\ell(dt)\right]$$
$$= \mathbb{E}\left[\int_0^\tau h_t^S \mathscr{D} \, N^\ell(dt)\right] = \mathbb{E}\left[\mathscr{D}S\right],$$

where we have used the law of iterated expectations. Hence, we conclude that $\widetilde{\Pi}(\mathscr{D} \mid \mathscr{T}_\mu(P)) = \Pi(\mathscr{D} \mid \mathscr{T}_\mu(P))$. $\square$

LEMMA 7.   *The projection of $\mathscr{D}$ onto the tangent space $\mathscr{T}_{\Lambda^x}(P)$ is given by:*

$$\Pi(\mathscr{D} \mid \mathscr{T}_{\Lambda^x}(P)) = \int_0^\tau \left(\mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 1, \mathcal{F}_{t-}] - \right.$$
$$\left. \mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 0, \mathcal{F}_{t-}]\right)\left(N^x(dt) - \Lambda^x(dt)\right),$$

for $x = a, \ell, d$.

PROOF. Define:

$$(33) \qquad \begin{aligned} \widetilde{\Pi}(\mathscr{D} \mid \mathscr{T}_{\Lambda^x}(P)) = \int_0^\tau \Big(\mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 1, \mathcal{F}_{t-}] - \\ \mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 0, \mathcal{F}_{t-}]\Big)\left(N^x(dt) - \Lambda^x(dt)\right). \end{aligned}$$

To verify that $\widetilde{\Pi}\big(\mathscr{D} \mid \mathscr{T}_{\Lambda^x}(P)\big)$ is in fact the projection, first note that $\widetilde{\Pi}\big(\mathscr{D} \mid \mathscr{T}_{\Lambda^x}(P)\big) \in \mathscr{T}_{\Lambda^x}(P)$. What remains to be shown is that $\mathscr{D} - \widetilde{\Pi}\big(\mathscr{D} \mid \mathscr{T}_{\Lambda^x}(P)\big)$ is orthogonal to all $S \in \mathscr{T}_{\Lambda^x}(P)$, i.e.,

$$(34) \qquad \mathbb{E}\left[\Big(\mathscr{D} - \widetilde{\Pi}\big(\mathscr{D} \mid \mathscr{T}_{\Lambda^x}(P)\big)\Big)S\right] = 0.$$

Since $S \in \mathscr{T}_{\Lambda^x}(P)$, we can write:

$$S = \int_0^\tau h_t^S \, M^x(dt),$$

for some $h_t^S \in \mathcal{F}_{t-}$.

For the proof, we will use that (see, e.g., (Fleming and Harrington, 2011, Theorem 2.6.1) or Andersen et al. (1993, Chapters II.3–II.4)):

$$\mathbb{E}[M^x(dt)^2 \mid \mathcal{F}_{t-}] = \langle M^x, M^x \rangle(dt) = (1 - \Delta\Lambda^x(t))d\Lambda^x(t),$$

where $\Delta\Lambda^x(t) = \Lambda^x(t) - \Lambda^x(t-)$. Furthermore, (see Fleming and Harrington (2011, Theorem 2.4.4) or Andersen et al. (1993, Chapter II.3)),

$$\mathbb{E}\left[\int_0^t H_1(s)M^x(ds) \int_0^t H_2(u)M^x(du)\right] = \mathbb{E}\left[\int_0^t H_1(s)H_2(s)\langle M^x, M^x\rangle(ds)\right],$$

for $H_1(t), H_2(t) \in \mathcal{F}_{t-}$.

Applying this, we see that

$$(35) \qquad \begin{aligned} \mathbb{E}\left[\widetilde{\Pi}\big(\mathscr{D} \mid \mathscr{T}_{\Lambda^x}(P)\big)S\right] = \mathbb{E}\bigg[\int_0^\tau \Big(&\mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 1, \mathcal{F}_{t-}] \\ &- \mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 0, \mathcal{F}_{t-}]\Big)h_t^S\left(1 - \Delta\Lambda^x(t)\right)\Lambda^x(dt)\bigg]. \end{aligned}$$

We want to show that

$$\mathbb{E}\left[\mathscr{D}S\right] = \mathbb{E}\left[\widetilde{\Pi}\big(\mathscr{D} \mid \mathscr{T}_{\Lambda^x}(P)\big)S\right].$$

To begin, we write out the left hand side of the previous display:

$$\mathbb{E}\left[\mathscr{D}S\right] = \mathbb{E}\left[\mathscr{D}\int_0^\tau h_t^S M^x(dt)\right] = \mathbb{E}\left[\sum_{t \leq \tau} \mathscr{D}h_t^S \Delta N^x(t)\right] - \mathbb{E}\left[\int_0^\tau \mathscr{D}h_t^S \Lambda^x(dt)\right].$$

We start by rewriting the first term as follows

$$
\mathbb{E}\left[\sum_{t\leq\tau}\mathscr{D}h_t^S\Delta N^x(t)\right] = \mathbb{E}\left[\sum_{t\leq\tau}\mathbb{E}[\mathscr{D}h_t^S\mid\Delta N^x(t),\mathcal{F}_{t-}]\Delta N^x(t)\right]
$$

$$
= \mathbb{E}\left[\sum_{t\leq\tau}h_t^S\sum_{u=0,1}\mathbb{E}[\mathscr{D}\mid\Delta N^x(t)=u,\mathcal{F}_{t-}] \right.
$$
$$
\left. \left(\Delta N^x(t)\right)^u\left(1-\Delta N^x(t)\right)^{1-u}\Delta N^x(t)\right]
$$

$$
= \mathbb{E}\left[\sum_{t\leq\tau}h_t^S\mathbb{E}[\mathscr{D}\mid\Delta N^x(t)=0,\mathcal{F}_{t-}]\Delta N^x(t)\right]
$$

$$
+ \mathbb{E}\left[\sum_{t\leq\tau}h_t^S\big(\mathbb{E}[\mathscr{D}\mid\Delta N^x(t)=1,\mathcal{F}_{t-}] \right.
$$
$$
\left. - \mathbb{E}[\mathscr{D}\mid\Delta N^x(t)=0,\mathcal{F}_{t-}]\big)\Delta N^x(t)\Delta N^x(t)\right]
$$

$$
= \mathbb{E}\left[\int_0^\tau h_t^S\mathbb{E}[\mathscr{D}\mid\Delta N^x(t)=0,\mathcal{F}_{t-}]N^x(dt)\right]
$$

$$
+ \mathbb{E}\left[\int_0^\tau h_t^S\big(\mathbb{E}[\mathscr{D}\mid\Delta N^x(t)=1,\mathcal{F}_{t-}] - \mathbb{E}[\mathscr{D}\mid\Delta N^x(t)=0,\mathcal{F}_{t-}]\big)N^x(dt)\right],
$$

and then the second term as

$$
\mathbb{E}\left[\int_0^\tau \mathscr{D}h_t^S\Lambda^x(dt)\right]
$$

$$
= \mathbb{E}\left[\int_0^\tau h_t^S\mathbb{E}[\mathscr{D}\mid\Delta N^x(t),\mathcal{F}_{t-}]\Lambda^x(dt)\right]
$$

$$
= \mathbb{E}\left[\int_0^\tau h_t^S\sum_{u=0,1}\mathbb{E}[\mathscr{D}\mid\Delta N^x(t)=u,\mathcal{F}_{t-}] \right.
$$
$$
\left. \left(\Delta N^x(t)\right)^u\left(1-\Delta N^x(t)\right)^{1-u}\Lambda^x(dt)\right]
$$

$$
= \mathbb{E}\left[\int_0^\tau h_t^S\mathbb{E}[\mathscr{D}\mid\Delta N^x(t)=0,\mathcal{F}_{t-}]\Lambda^x(dt)\right]
$$

$$
+ \mathbb{E}\left[\int_0^\tau h_t^S\big(\mathbb{E}[\mathscr{D}\mid\Delta N^x(t)=1,\mathcal{F}_{t-}] \right.
$$
$$
\left. - \mathbb{E}[\mathscr{D}\mid\Delta N^x(t)=0,\mathcal{F}_{t-}]\big)\Delta N^x(t)\Lambda^x(dt)\right].
$$

Collecting the above shows that

$$\mathbb{E}\left[\mathscr{D}S\right] = \mathbb{E}\left[\sum_{t \le \tau} \mathscr{D}h_t^S \Delta N^x(t)\right] - \mathbb{E}\left[\int_0^\tau \mathscr{D}h_t^S \Lambda^x(dt)\right]$$

$$= \mathbb{E}\left[\int_0^\tau h_t^S \mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 0, \mathcal{F}_{t-}]\big(N^x(dt) - \Lambda^x(dt)\big)\right]$$

$$+ \mathbb{E}\left[\int_0^\tau h_t^S \big(\mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 1, \mathcal{F}_{t-}]\right.$$
$$\left. - \mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 0, \mathcal{F}_{t-}]\big)\big(N^x(dt) - \Delta N^x(t)\Lambda^x(dt)\big)\right].$$

The first term on the right hand side of the previous display is zero. For the second term, we have that

$$\mathbb{E}\left[\int_0^\tau h_t^S \big(\mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 1, \mathcal{F}_{t-}]\right.$$
$$\left. - \mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 0, \mathcal{F}_{t-}]\big)\big(N^x(dt) - \Delta N^x(t)\Lambda^x(dt)\big)\right]$$

$$= \mathbb{E}\left[\int_0^\tau h_t^S \big(\mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 1, \mathcal{F}_{t-}]\right.$$
$$\left. - \mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 0, \mathcal{F}_{t-}]\big)\big(\Lambda^x(dt) - \Delta \Lambda^x(t)\Lambda^x(dt)\big)\right]$$

$$= \mathbb{E}\left[\int_0^\tau h_t^S \big(\mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 1, \mathcal{F}_{t-}]\right.$$
$$\left. - \mathbb{E}[\mathscr{D} \mid \Delta N^x(t) = 0, \mathcal{F}_{t-}]\big)\big(1 - \Delta \Lambda^x(t)\big)\Lambda^x(dt)\right].$$

We see now that the right hand side displayed above is exactly equal to the right hand side of (35). Thus, we conclude that

$$\mathbb{E}\left[\widetilde{\Pi}\big(\mathscr{D} \mid \mathscr{T}_{\Lambda^x}(P)\big)S\right] = \mathbb{E}\left[\mathscr{D}S\right],$$

which verifies (34). Hence, $\Pi(\mathscr{D} \mid \mathscr{T}_{\Lambda^x}(P)) = \widetilde{\Pi}(\mathscr{D} \mid \mathscr{T}_{\Lambda^x}(P))$. $\qquad\square$

A.5. Proof of Theorem 1. We are now ready to prove Theorem 1 by applying the results of Section A.4. For this purpose, recall that $dG_t(O)$ and $dQ_t(O)$ denote the conditional measures of the interventional and non-interventional parts of the likelihood at time t given the observed history

$\mathcal{F}_{t-}$. In the proof we will use the following equation repeatedly:

$$\mathbb{E}_{PG^*}\left[Y \mid \mathcal{F}_{t-}\right] = \int y \prod_{s \geq t} dQ_s(o) \, dG_s^*(o)$$

$$= \int y \prod_{s \geq t} dG_s^*(o) \prod_{s \geq t} \frac{dG_s(o)}{dG_s(o)} \prod_{s \geq t} dQ_s(o)$$

$$= \int \left(y \prod_{s \geq t} \frac{dG_s^*(o)}{dG_s(o)} \right) \prod_{s \geq t} dQ_s(o) \, dG_s(o) = \mathbb{E}\left[Y \prod_{s \geq t} \frac{dG_s^*(O)}{dG_s(O)} \,\middle|\, \mathcal{F}_{t-} \right].$$

PROOF. (Theorem 1). Collecting the results of Lemma 5–7, we can now compute the canonical gradient by the decomposition of the projection operator from display (31) as follows:

$$D^*(P) = \Pi(D_{\mathrm{IPW}}^{G^*}(P) \mid \mathscr{T}_G)$$

$$= \mathbb{E}_{PG^*}[Y \mid \mathcal{F}_0] - \Psi^{G^*}(P)$$

$$+ \int_0^\tau \left(\mathbb{E}[D_{\mathrm{IPW}}^{G^*}(P) \mid L(t), N^\ell(t), \mathcal{F}_{t-}] - \mathbb{E}[D_{\mathrm{IPW}}^{G^*}(P) \mid N^\ell(t), \mathcal{F}_{t-}] \right) N^\ell(dt)$$

$$+ \sum_{x \in \{\ell,a,d\}} \int_0^\tau \Big(\mathbb{E}[D_{\mathrm{IPW}}^{G^*}(P) \mid \Delta N^x(t) = 1, \mathcal{F}_{t-}] -$$

$$\mathbb{E}[D_{\mathrm{IPW}}^{G^*}(P) \mid \Delta N^x(t) = 0, \mathcal{F}_{t-}] \Big) \big(N^x(dt) - \Lambda^x(dt) \big).$$

Recall that:

$$D_{\mathrm{IPW}}^{G^*}(P)(O) = \prod_{s \leq \tau} \frac{dG_s^*(O)}{dG_s(O)} Y - \Psi^{G^*}(P).$$

Consider first:

$$\mathbb{E}[D_{\mathrm{IPW}}^{G^*}(P) \mid L(t), N^\ell(t), \mathcal{F}_{t-}] - \mathbb{E}[D_{\mathrm{IPW}}^{G^*}(P) \mid N^\ell(t), \mathcal{F}_{t-}]$$

$$= \mathbb{E}\left[\left(\prod_{s<t} \frac{dG_s^*}{dG_s} \right) \left(\prod_{s \geq t} \frac{dG_s^*}{dG_s} \right) Y \,\middle|\, L(t), N^\ell(t), \mathcal{F}_{t-} \right]$$

$$- \mathbb{E}\left[\left(\prod_{s<t} \frac{dG_s^*}{dG_s} \right) \left(\prod_{s \geq t} \frac{dG_s^*}{dG_s} \right) Y \,\middle|\, N^\ell(t), \mathcal{F}_{t-} \right]$$

$$= \prod_{s<t} \frac{dG_s^*}{dG_s} \left(\mathbb{E}\left[\left(\prod_{s \geq t} \frac{dG_s^*}{dG_s} \right) Y \,\middle|\, L(t), N^\ell(t), \mathcal{F}_{t-} \right] \right.$$

$$\left. - \mathbb{E}\left[\left(\prod_{s \geq t} \frac{dG_s^*}{dG_s} \right) Y \,\middle|\, N^\ell(t), \mathcal{F}_{t-} \right] \right)$$

$$= \prod_{s<t} \frac{dG_s^*}{dG_s} \left(\mathbb{E}_{PG^*}\left[Y \mid L(t), N^\ell(t), \mathcal{F}_{t-} \right] - \mathbb{E}_{PG^*}\left[Y \mid N^\ell(t), \mathcal{F}_{t-} \right] \right),$$

and, by the same line of argument:

$$\mathbb{E}[D_{\mathrm{IPW}}^{G^*}(P) \mid \Delta N^x(t) = 1, \mathcal{F}_{t-}] - \mathbb{E}[D_{\mathrm{IPW}}^{G^*}(P) \mid \Delta N^x(t) = 0, \mathcal{F}_{t-}]$$
$$= \prod_{s<t} \frac{dG_s^*}{dG_s} \Big(\mathbb{E}_{PG^*} \big[Y \mid \Delta N^x(t) = 1, \mathcal{F}_{t-} \big] - \mathbb{E}_{PG^*} \big[Y \mid \Delta N^x(t) = 0, \mathcal{F}_{t-} \big] \Big).$$

Finally, note that:

$$\mathbb{E}_{PG^*} \big[Y \mid \Delta N^d(t) = 1, \mathcal{F}_{t-} \big] = 1.$$

This gives the expression for the canonical gradient displayed in Theorem 1. □

A.6. Corollary 1. The following corollary provides an alternative representation of the canonical gradient, that is utilized to analyze the estimation problem in Section A.7. In the following, we use $\bar{\mathcal{O}}_t$ to denote the space where $\bar{O}(t)$ takes its values and $\mathcal{Q}_t$ the space where $Q(t) = \{O(s) : t \le s \le \tau\}$ takes its values.

COROLLARY 1 (Canonical gradient). *We can rewrite the canonical gradient from Theorem 1 for $\Psi^{G^*} : \mathcal{M} \to \mathbb{R}$ as follows:*

$$D^*(P) = \mathbb{E}_{PG^*}[Y \mid \mathcal{F}_0] - \Psi^{G^*}(P)$$
$$+ \int_0^\tau \prod_{s<t} \frac{dG_s^*}{dG_s} \int_{\mathcal{Q}_t} Y \Big(\prod_{s>t} dQ_s \prod_{s\ge t} dG_s^* - \prod_{s\ge t} dQ_s dG_s^* \Big).$$

PROOF. Defining

$$Z^{G^*}(dt) := \mathbb{E}_{PG^*}[Y \mid L(t), N^\ell(dt), N^a(dt), N^d(dt), \mathcal{F}_{t-}] - \mathbb{E}_{PG^*}[Y \mid \mathcal{F}_{t-}],$$

the last line of the representation for $D^{G^*}(P)$ displayed in the corollary can be written

$$\int_0^\tau \prod_{s<t} \frac{dG_s^*}{dG_s} \int_{\mathcal{Q}_t} Y \Big(\prod_{s>t} dQ_s \prod_{s\ge t} dG_s^* - \prod_{s\ge t} dQ_s dG_s^* \Big) = \int_0^\tau \Big(\prod_{s<t} \frac{dG_s^*}{dG_s} \Big) Z^{G^*}(dt).$$

To prove the corollary, it is sufficient to show that

$$Z^{G^*}(dt) = \Big(\mathbb{E}[Y \mid L(t), \Delta N^\ell(t) = 1, \mathcal{F}_{t-}]$$
$$- \mathbb{E}[Y \mid L(t), \Delta N^\ell(t) = 1, \mathcal{F}_{t-}] \Big) N^\ell(dt)$$
$$+ \sum_{x \in \{\ell, a, d\}} \Big(\mathbb{E}_{PG^*}[Y \mid \Delta N^x(t) = 1, \mathcal{F}_{t-}]$$
$$- \mathbb{E}_{PG^*}[Y \mid \Delta N^x(t) = 0, \mathcal{F}_{t-}] \Big) \big(N^x(dt) - \Lambda^x(dt) \big).$$

We expand $Z^{G^*}(dt)$ as follows

$$
\mathbb{E}_{PG^*}[Y \mid L(t), N^\ell(dt), N^a(dt), N^d(dt), \mathcal{F}_{t-}]
$$

$$
\underbrace{- \mathbb{E}_{PG^*}[Y \mid N^\ell(dt), N^a(dt), N^d(dt), \mathcal{F}_{t-}]}_{=:Z_1^{G^*}(dt)}
$$

$$
+ \underbrace{\mathbb{E}_{PG^*}[Y \mid N^\ell(dt), N^a(dt), N^d(dt), \mathcal{F}_{t-}] - \mathbb{E}_{PG^*}[Y \mid \mathcal{F}_{t-}]}_{=:Z_2^{G^*}(dt)}.
$$

Since $L(t)$ only changes at jumps of $N^\ell(t)$, it follows that

$$
Z_1^{G^*}(dt) = \big(\mathbb{E}[Y \mid L(t), \Delta N^\ell(t) = 1, \mathcal{F}_{t-}] - \mathbb{E}[Y \mid \Delta N^\ell(t) = 1, \mathcal{F}_{t-}]\big) N^\ell(dt).
$$

Next, considering $Z_2^{G^*}(dt)$, we note that

$$
\begin{aligned}
Z_2^{G^*}(dt) = {} & \mathbb{E}_{PG^*}[Y \mid N^\ell(dt), N^a(dt), N^d(dt), \mathcal{F}_{t-}] \\
& - \Lambda^\ell(dt)\, \mathbb{E}_{PG^*}[Y \mid \Delta N^\ell(t) = 1, \mathcal{F}_{t-}] \\
& - \Lambda^a(dt)\, \mathbb{E}_{PG^*}[Y \mid \Delta N^a(t) = 1, \mathcal{F}_{t-}] \\
& - \Lambda^d(dt)\, \mathbb{E}_{PG^*}[Y \mid \Delta N^d(t) = 1, \mathcal{F}_{t-}] \\
& - \big(1 - \Lambda^\ell(dt) - \Lambda^a(dt) - \Lambda^d(dt)\big) \\
& \qquad \mathbb{E}_{PG^*}[Y \mid \Delta N^\ell(t) = 0, \Delta N^a(t) = 0, \Delta N^d(t) = 0, \mathcal{F}_{t-}],
\end{aligned}
$$

assuming for ease of presentation that the processes N^ℓ, N^a and N^d do not jump at the same time. Collecting terms now yields that

$$
\begin{aligned}
Z_2^{G^*}(dt) = \sum_{x \in \{\ell, a, d\}} \Big(& \mathbb{E}_{PG^*}[Y \mid \Delta N^x(t) = 1, \mathcal{F}_{t-}] \\
& - \mathbb{E}_{PG^*}[Y \mid \Delta N^x(t) = 0, \mathcal{F}_{t-}]\Big) \big(N^x(dt) - \Lambda^x(dt)\big),
\end{aligned}
$$

which finishes the proof. $\qquad\qquad\square$

A.7. Representation of the second-order remainder $R_2(P, P_0)$.
As in Section A.6, we use $\bar{\mathcal{O}}_t$ to denote the space where $\bar{O}(t)$ takes its values and $\mathcal{Q}_t$ the space where $Q(t) = \{O(s) : t \le s \le \tau\}$ takes its values. We now express $P_0 D^*(P)$ for any $P \in \mathcal{M}$ using the representation of the canonical

gradient in Corollary 1 as follows:

$$
\begin{aligned}
\int_{\mathcal{O}} & D^*(P)\, dP_0 \\
&= \int_{\bar{\mathcal{O}}_t} \int_0^\tau \prod_{s<t} \frac{dG_s^*}{dG_s} \Bigg(\Bigg(\int_{\mathcal{Q}_t} Y \prod_{s>t} dQ_s \prod_{s\geq t} dG_s^* \Bigg) \prod_{s\leq t} dQ_{0,s} \prod_{s<t} dG_{0,s} \\
&\hspace{5cm} - \Bigg(\int_{\mathcal{Q}_t} Y \prod_{s\geq t} dQ_s dG_s^* \Bigg) \prod_{s<t} dQ_{0,s} dG_{0,s} \Bigg) \\
&= \int_0^\tau \int_{\mathcal{O}} \prod_{s<t} \frac{dG_s^*}{dG_s} \Bigg(Y \prod_{s\geq t} dG_s^* \prod_{s>t} dQ_s \prod_{s<t} dG_{0,s} \prod_{s\leq t} dQ_{0,s} - \\
&\hspace{5cm} Y \prod_{s\geq t} dG_s^* \, dQ_s \prod_{s<t} dG_{0,s}\, dQ_{0,s} \Bigg) \\
&= \int_0^\tau \int_{\mathcal{O}} Y \prod_{s<t} \frac{dG_s^*}{dG_s} \prod_{s<t} dG_{0,s} dQ_{0,s} \left(dQ_{0,t} - dQ_t \right) \prod_{s\geq t} dG_s^* \prod_{s>t} dQ_s \\
&= \int_0^\tau \int_{\mathcal{O}} Y \prod_{s<t} \frac{dG_{0,s}}{dG_s} \prod_{s<t} dG_s^* dQ_{0,s} \left(dQ_{0,t} - dQ_t \right) \prod_{s\geq t} dG_s^* \prod_{s>t} dQ_s \\
(*1)\quad &= \int_0^\tau \int_{\mathcal{O}} Y \left(\prod_{s<t} \frac{dG_{0,s}}{dG_s} - 1 \right) \prod_{s\leq \tau} dG_s^* \prod_{s<t} dQ_{0,s} \left(dQ_{0,t} - dQ_t \right) \prod_{s>t} dQ_s
\end{aligned}
$$

$(*2)$

$$
= \underbrace{R_2(P, P_0)}_{(*1)} + \underbrace{\Psi^{G^*}(P_0) - \Psi^{G^*}(P)}_{(*2)}.
$$

Next we apply the Duhamel equation (Andersen et al., 1993) which in our setting yields that:

$$
\prod_{s\leq \tau} dQ_{0,s} - \prod_{s\leq \tau} dQ_s = \int_{t\leq \tau} \prod_{s<t} dQ_{0,s}(dQ_{0,t} - dQ_t) \prod_{s>t} dQ_s.
$$

This allows us to establish the relation $(*2) = \Psi^{G^*}(P_0) - \Psi^{G^*}(P)$, applying the Duhamel equation at the fourth equality:

$$
\begin{aligned}
\Psi^{G^*}(P_0) - \Psi^{G^*}(P) &= \mathbb{E}_{P_0^{G^*}}\big[Y\big] - \mathbb{E}_{P^{G^*}}\big[Y\big] \\
&= \int_{\mathcal{O}} Y \prod_{s \in [0,\tau]} dG_s^* \, dQ_{0,s} - \int_{\mathcal{O}} Y \prod_{s \in [0,\tau]} dG_s^* \, dQ_s \\
&= \int_{\mathcal{O}} Y \prod_{s \in [0,\tau]} dG_s^* \left(\prod_{s \in [0,\tau]} dQ_{0,s} - \prod_{s \in [0,\tau]} dQ_s \right) \\
&= \int_{\mathcal{O}} Y \prod_{s \in [0,\tau]} dG_s^* \left(\int_0^\tau \prod_{s \in [0,t)} dQ_{0,s} \, (dQ_{0,t} - dQ_t) \prod_{s \in (t,\tau]} dQ_s \right) \\
&= \int_0^\tau \int_{\mathcal{O}} Y \prod_{s \in [0,\tau]} dG_s^* \prod_{s \in [0,t)} dQ_{0,s} \, (dQ_{0,t} - dQ_t) \prod_{s \in (t,\tau]} dQ_s.
\end{aligned}
$$

This again implies that:

(36) $$ \Psi^{G^*}(P) - \Psi^{G^*}(P_0) = -P_0 D^*(P) + R_2(P, P_0), $$

with the second-order remainder $R_2(P, P_0)$ given by $(*1)$ above:

$$
\begin{aligned}
&R_2(P, P_0) \\
&= \int_0^\tau \int_{\mathcal{O}} Y \left(\prod_{s<t} \frac{dG_{0,s}}{dG_s} - 1 \right) \prod_{s \leq \tau} dG_s^* \prod_{s<t} dQ_{0,s} \, (dQ_{0,t} - dQ_t) \prod_{s>t} dQ_s \\
&= \int_0^\tau \int_{\mathcal{O}} Y \frac{1}{\bar{g}_t} (\bar{g}_{0,t} - \bar{g}_t) \prod_{s \leq \tau} dG_s^* \prod_{s<t} dQ_{0,s} \, (dQ_{0,t} - dQ_t) \prod_{s>t} dQ_s.
\end{aligned}
$$

A.8. Proof of Lemma 1. For the proof of Lemma 1 recall that:

$$
Z_t^{G^*} = \int Y \prod_{s \geq t} dG_s^* \prod_{s>t} dQ_s,
$$

$$
Z_{t,L(t)}^{G^*} = \int \left(\int Y \prod_{s \geq t} dG_s^* \prod_{s>t} dQ_s \right) d\mu_{0,t}(L(t) \mid \mathcal{F}_{t-}).
$$

where $dG_t(O)$ and $dQ_t(O)$ denote the conditional measure of the interventional and non-interventional parts of the likelihood at time t given the observed history $\mathcal{F}_{t-}$. Particularly, these are defined as:

(37) $$ dG_t(O) = \big(\pi_t(A(t) \mid \mathcal{F}_{t-})\big)^{N^a(dt)} \big(d\Lambda^c(t \mid \mathcal{F}_{t-})\big)^{N^c(dt)} \\ \big(1 - d\Lambda^c(t \mid \mathcal{F}_{t-})\big)^{1 - N^c(dt)}, $$

and

(38)
$$
dQ_t(O) = \big(d\Lambda_0^a(t \,|\, \mathcal{F}_{t-})\big)^{N^a(dt)} \big(1 - d\Lambda^a(t \,|\, \mathcal{F}_{t-})\big)^{1-N^a(dt)}
$$
$$
\big(d\Lambda^\ell(t \,|\, \mathcal{F}_{t-})\, \mu_{0,t}(L(t) \,|\, \mathcal{F}_{t-})\big)^{N^\ell(dt)} \big(1 - d\Lambda^\ell(t \,|\, \mathcal{F}_{t-})\big)^{1-N^\ell(dt)}
$$
$$
\big(d\Lambda^d(t \,|\, \mathcal{F}_{t-})\big)^{N^d(dt)} \big(1 - d\Lambda^d(t \,|\, \mathcal{F}_{t-})\big)^{1-N^d(dt)}.
$$

Recall also that our statistical model $\mathcal{M}$ is defined by:

$$
\mathcal{M} = \left\{ P \, : \, dP = dP_{Q,G} = \prod_{t \in [0,\tau]} dQ_t dG_t, \; G \in \mathcal{G}, \, Q \in \mathcal{Q} \right\},
$$

so that any $P \in \mathcal{M}$ admits a factorization into a G-part and a Q-part.

The statement of Lemma 1 is that the target parameter $\Psi^{G^*} : \mathcal{M} \to \mathbb{R}$, defined by

(39)
$$
\Psi^{G^*}(P) = \int Y \prod_{t \le \tau} dQ_t \, dG_t^*,
$$

can be represented as a functional of $P \in \mathcal{M}$ only through $\boldsymbol{Z}$

$$
\boldsymbol{Z} = \boldsymbol{Z}(P) := \big(Z_t^{G^*}, Z_{t,L(t)}^{G^*}, \Lambda^\ell(t), \Lambda^a(t), \Lambda^d(t)\big)_{t \in [0,\tau]}.
$$

The basic idea of the proof is to use Fubini's theorem repeatedly to rearrange the order of integration and thereby rewrite the target parameter (39) in terms of iterated integrals.

PROOF. (Lemma 1). Fix $P \in \mathcal{M}$ such that

$$
dP = \prod_{t \le \tau} dQ_t dG_t,
$$

with dQ_t and dG_t as defined by Equations (37)–(38) above. For the sequence of time-points, $0 = t_0 = t_0 < t_1 < \cdots < t_R \le t_{R+1} = \tau$, we can evaluate the distribution of Y to write the target parameter as:

$$
\Psi^{G^*}(P) = \int\limits_{0=t_0<t_1<\cdots<t_R\le\tau} Y \prod_{r=0}^{R} \prod_{t\in(t_{r-1},t_r]} dQ_t \, dG_t^* \prod_{t\in(t_R,\tau]} dQ_t \, dG_t^*.
$$

This can also be written as:

$$
\Psi^{G^*}(P) = \int\limits_{0=t_0<t_1<\cdots<t_R\leq\tau} \underbrace{\left(\int Y \prod_{t\in(t_R,\tau]} dG_t^*\right)}_{E_{P^{G^*}}[Y|L(\tau),N^\ell(\tau),N^a(\tau),N^d(\tau),\mathcal{F}_{t_R}]=Y} \prod_{t\in(t_R,\tau]} dQ_t \prod_{r=0}^{R} \prod_{t\in(t_{r-1},t_r]} dQ_t\, dG_t^*
$$

$$
= \int\limits_{0=t_0<t_1<\cdots<t_R} \underbrace{\left(\int Y \prod_{t\in(t_R,\tau]} \left(d\Lambda^d(t)\right)^{N^d(dt)}\left(1-d\Lambda^d(t)\right)^{1-N^d(dt)}\right)}_{\mathbb{E}_P[Y|\mathcal{F}_{t_R}]} \prod_{r=0}^{R} \prod_{t\in(t_{r-1},t_r]} dQ_t\, dG_t^*
$$

$$
= \int\limits_{0=t_0<t_1<\cdots<t_R} \underbrace{\left(\int \mathbb{E}_P[Y\mid\mathcal{F}_{t_R}] \prod_{t\in(t_{R-1},t_R]} dG_t^*\right)}_{E_{P^{G^*}}[Y|L(t_R),N^\ell(t_R),N^a(t_R),N^d(t_R),\mathcal{F}_{t_{R-1}}]=Z_{t_R}^{G^*}} \prod_{t\in(t_{R-1},t_R]} dQ_t \prod_{r=0}^{R-1} \prod_{t\in(t_{r-1},t_r]} dQ_t\, dG_t^*
$$

$$
= \int\limits_{0=t_0<t_1<\cdots<t_R} Z_{t_R}^{G^*} \prod_{t\in(t_{R-1},t_R]} dQ_t \prod_{r=0}^{R-1} \prod_{t\in(t_{r-1},t_r]} dQ_t\, dG_t^*.
$$

Next, recall that

$$
\prod_{t\in(t_{R-1},t_R]} dQ_t = \prod_{t\in(t_{R-1},t_R]} \left(d\Lambda^a(t)\right)^{N^a(dt)}\left(1-d\Lambda^a(t)\right)^{1-N^a(dt)}
$$
$$
\left(d\Lambda^\ell(t)\,\mu_t(L(t))d\nu_L(L(t))\right)^{N^\ell(dt)}\left(1-d\Lambda^\ell(t)\right)^{1-N^\ell(dt)}
$$
$$
\left(d\Lambda^d(t)\right)^{N^d(dt)}\left(1-d\Lambda^d(t)\right)^{1-N^d(dt)},
$$

where we have suppressed the conditioning on $\mathcal{F}_{t-}$ to simplify the presenta-

tion. We use this to rewrite the following:

$$
\int Z_{t_R}^{G^*} \prod_{t \in (t_{R-1}, t_R]} dQ_t = \int Z_{t_R}^{G^*} \prod_{t \in (t_{R-1}, t_R]} \left(\mu_t(L(t)) d\nu_L(L(t)) \right)^{N^\ell(dt)}
$$
$$
\left(d\Lambda^\ell(t) \right)^{N^\ell(dt)} \left(1 - d\Lambda^\ell(t) \right)^{1 - N^\ell(dt)}
$$
$$
\left(d\Lambda^a(t) \right)^{N^a(dt)} \left(1 - d\Lambda^a(t) \right)^{1 - N^a(dt)}
$$
$$
\left(d\Lambda^d(t) \right)^{N^d(dt)} \left(1 - d\Lambda^d(t) \right)^{1 - N^d(dt)}
$$
$$
= \int \underbrace{ \left(\int Z_{t_R}^{G^*} \prod_{t \in (t_{R-1}, t_R]} \left(\mu_t(L(t)) d\nu_L(L(t)) \right)^{N^\ell(dt)} \right) }_{=Z_{t_R, L(t_R)}}
$$
$$
\prod_{t \in (t_{R-1}, t_R]} \left(d\Lambda^\ell(t) \right)^{N^\ell(dt)} \left(1 - d\Lambda^\ell(t) \right)^{1 - N^\ell(dt)}
$$
$$
\left(d\Lambda^a(t) \right)^{N^a(dt)} \left(1 - d\Lambda^a(t) \right)^{1 - N^a(dt)}
$$
$$
\left(d\Lambda^d(t) \right)^{N^d(dt)} \left(1 - d\Lambda^d(t) \right)^{1 - N^d(dt)}
$$
$$
= \int Z_{t_R, L(t_R)}^{G^*} \prod_{t \in (t_{R-1}, t_R]} \left(d\Lambda^\ell(t) \right)^{N^\ell(dt)} \left(1 - d\Lambda^\ell(t) \right)^{1 - N^\ell(dt)}
$$
$$
\left(d\Lambda^a(t) \right)^{N^a(dt)} \left(1 - d\Lambda^a(t) \right)^{1 - N^a(dt)}
$$
$$
\left(d\Lambda^d(t) \right)^{N^d(dt)} \left(1 - d\Lambda^d(t) \right)^{1 - N^d(dt)}.
$$

Combined with

$$
\int \left(\int Z_{t_R}^{G^*} \prod_{t \in (t_{R-1}, t_R]} dQ_t \right) \prod_{t \in (t_{R-2}, t_{R-1}]} dG_t^*
$$
$$
= E_{PG^*}[Y \mid L(t_{R-1}), N^\ell(t_{R-1}), N^a(t_{R-1}), N^d(t_{R-1}), \mathcal{F}_{t_{R-2}}] = Z_{t_{R-1}}^{G^*}
$$

we have that:

$$
Z_{t_{R-1}}^{G^*} = \int \left(\int Z_{t_R, L(t_R)}^{G^*} \prod_{t \in (t_{R-1}, t_R]} \left(d\Lambda^\ell(t) \right)^{N^\ell(dt)} \left(1 - d\Lambda^\ell(t) \right)^{1 - N^\ell(dt)} \right.
$$
$$
\left(d\Lambda^a(t) \right)^{N^a(dt)} \left(1 - d\Lambda^a(t) \right)^{1 - N^a(dt)}
$$
$$
\left. \left(d\Lambda^d(t) \right)^{N^d(dt)} \left(1 - d\Lambda^d(t) \right)^{1 - N^d(dt)} \right) \prod_{t \in (t_{R-2}, t_{R-1}]} dG_t^*.
$$

Hence, $Z_{t_R, L(t_R)}, \Lambda^\ell, \Lambda^a, \Lambda^d$ together with the specified intervention G^* completely characterizes $Z_{t_{R-1}}^{G^*}$. Further, the target parameter is now reduced

to:

$$\Psi^{G^*}(P) = \int\limits_{0<t_1<\cdots<t_{R-1}} Z_{t_{R-1}}^{G^*} \prod_{t\in(t_{R-2},t_{R-1}]} dQ_t \prod_{r=0}^{R-2} \prod_{t\in(t_{r-1},t_r]} dQ_t \, dG_t^*$$

By backwards induction, applying the same arguments as above, we see that

$$Z_{t_r}^{G^*} = \int \left(\int Z_{t_{r+1},L(t_{r+1})}^{G^*} \prod_{t\in(t_r,t_{r+1}]} \left(d\Lambda^\ell(t)\right)^{N^\ell(dt)} \left(1 - d\Lambda^\ell(t)\right)^{1-N^\ell(dt)} \right.$$
$$\left(d\Lambda^a(t)\right)^{N^a(dt)} \left(1 - d\Lambda^a(t)\right)^{1-N^a(dt)}$$
$$\left. \left(d\Lambda^d(t)\right)^{N^d(dt)} \left(1 - d\Lambda^d(t)\right)^{1-N^d(dt)} \right) \prod_{t\in(t_{r-1},t_r]} dG_t^*,$$

for any $r = R, \ldots, 0$, and further that

$$\Psi^{G^*}(P) = \int\limits_{0=t_0<t_1<\cdots<t_r} Z_{t_r}^{G^*} \prod_{t\in(t_{r-1},t_r]} dQ_t \prod_{l=0}^{r-1} \prod_{t\in(t_{l-1},t_l]} dQ_t \, dG_t^*.$$

We finally note that $Z_{t_0}^{G^*} = \mathbb{E}_{PG^*}[Y \mid L_0]$, and thus:

$$\Psi^{G^*}(P) = \int Z_{t_0}^{G^*} \mu_{L_0}(L_0) d\nu_{L_0}(L_0).$$

In total, this shows that the target parameter defined in (39) can be characterized entirely by the time-sequence of conditional expectations, $Z_t^{G^*}$, $Z_{t,L(t)}^{G^*}$, and the conditional intensities $\Lambda^\ell, \Lambda^a, \Lambda^d$. This was the statement of Lemma 1. $\qquad\square$

APPENDIX B: HIGHLY ADAPTIVE LASSO (HAL)

This appendix is concerned with highly adaptive lasso (HAL) estimation of the nuisance parameters of our estimation problem. The appendix is structured as follows. Section B.1 gives the general integral representation of càdlàg functions with finite sectional variation norm. Section B.2 outlines parametrizations of the nuisance parameters and states the assumptions required to prove the HAL convergence results. Section B.3 defines the HAL estimator. Section B.4 presents the theoretical results for HAL. Section B.5 provides the proofs. We need a fair amount of extra notation that will be introduced when needed throughout the sections of this appendix.

B.1. Càdlàg functions with finite sectional variation norm. Let $\mathbb{D}^k([0, \eta])$ denote the Banach space of k-variate càdlàg functions on $[0, \eta] \subset \mathbb{R}^k$, $\eta \in \mathbb{R}^k_+$. We define the sectional variation norm of $f \in \mathbb{D}^k([0, \eta])$ as the sum of the variation norms of the sections of f (Gill et al., 1995):

$$(40) \qquad \|f\|_{\mathrm{v}} = |f(0)| + \sum_{\mathcal{S} \subset \{1, \ldots, k\}} \int_{(0(\mathcal{S}), \eta(\mathcal{S})]} |f(dx(\mathcal{S}), 0(\mathcal{S}^c))|.$$

Here, $\sum_{\mathcal{S} \subset \{1, \ldots, k\}}$ is the sum over all subsets of $\{1, \ldots, k\}$, $x(\mathcal{S}) = (x_j)_{j \in \mathcal{S}}$ corresponds to the $\mathcal{S}$-specific coordinates of x, $x(\mathcal{S}^c) = (x_j)_{j \notin \mathcal{S}}$ are the coordinates in the complement of the index set $\mathcal{S}$, and $x \to f(x(\mathcal{S}), 0(\mathcal{S}^c))$ is the $\mathcal{S}$-specific section of f that sets the coordinates in the complement of $\mathcal{S}$ equal to zero. Furthermore, let

$$\mathscr{F}_{\mathrm{v}, \mathscr{M}} = \big\{ f \in \mathbb{D}^k([0, \eta]) \,:\, \|f\|_{\mathrm{v}} \leq \mathscr{M} \big\},$$

denote the subset of càdlàg functions with sectional variation norm bounded by a constant $\mathscr{M} < \infty$. Any $f \in \mathscr{F}_{\mathrm{v}, \mathscr{M}}$ admits an integral representation in terms of the measures generated by its $\mathcal{S}$-specific sections (Gill et al., 1995) which is used to define the HAL estimator.

B.1.1. *Representation of càdlàg functions with finite variation norm.* Any $f \in \mathscr{F}_{\mathrm{v}, \mathscr{M}}$ admits an integral representation as follows (Gill et al., 1995):

$$f(x) = f(0) + \sum_{\mathcal{S} \subset \{1, \ldots, k\}} \int_{(0(\mathcal{S}), x(\mathcal{S})]} f(du(\mathcal{S}), 0(\mathcal{S}^c)).$$

Particularly, consider a function $f \in \mathscr{F}_{\mathrm{v}, \mathscr{M}}$ defined on a finite set of support points $\{s_j\}_{j \in \mathcal{I}}$ indexed by $\mathcal{I}$. The above integral representation of $f \in \mathscr{F}_{\mathrm{v}, \mathscr{M}}$

can be written in terms of a finite linear combination of indicator basis functions as follows:

$$(41) \qquad f(x) = f(0) + \sum_{\mathcal{S} \subset \{1,\ldots,k\}} \sum_{j \in \mathcal{I}} \mathbb{1}\{s_j(\mathcal{S}) \le x(\mathcal{S})\} f(ds_j(\mathcal{S}), 0(\mathcal{S}^c)),$$

where $f(ds_j(\mathcal{S}), 0(\mathcal{S}^c))$ is the point-mass that the $\mathcal{S}$th section function assigns to the jth support point $s_j(\mathcal{S})$.

Now, define the indicator basis functions $\phi_{\mathcal{S},j}(x) = \mathbb{1}\{s_j(\mathcal{S}) \le x(\mathcal{S})\}$ and the corresponding coefficients $\beta_{\mathcal{S},j} = f(ds_j(\mathcal{S}), 0(\mathcal{S}^c))$. Then we can write (41) as:

$$(42) \qquad f(x) = \beta_0 + \sum_{\mathcal{S} \subset \{1,\ldots,k\}} \sum_{j \in \mathcal{I}} \phi_{\mathcal{S},j}(x) \beta_{\mathcal{S},j}.$$

We further note that the sectional variation norm (c.f., (40)) of f is the sum of the absolute values of its coefficients:

$$(43) \qquad \|f\|_{\mathrm{v}} = \|\beta\|_1 = |\beta_0| + \sum_{\mathcal{S} \subset \{1,\ldots,k\}} \sum_{j \in \mathcal{I}(\mathcal{S})} |\beta_{\mathcal{S},j}|.$$

Generally, the HAL estimator is defined as the minimizer of the empirical risk over all linear combinations of indicator basis functions under the constraint that the sectional variation norm, i.e., the absolute value of the coefficients, is smaller than or equal to a finite constant. We get back to this in Section B.3.

B.2. Parametrization of nuisance parameters. In this section we detail parametrizations of our nuisance parameters to apply the tools from the previous section to define HAL estimation. To formulate the assumptions we need, recall first that, for any subject, $\bar{O}(t)$ only changes at the observed event times $T_1, \ldots, T_{K(t)}$. It is essential to our analysis that we, at any point in time t, can represent the observed data $\bar{O}(t)$ in terms of a finite-dimensional vector. For this purpose, we define:

$$\bar{O}_k = \left\{ \left(L_0, s, dN^a(s), A(s), dN^\ell(s), L(s), dN^d(s), dN^c(s) \right) : s \in \{T_j\}_{j=0}^k \right\},$$

where $\{T_k\}_{k=1}^{K(\tau)}$ denotes the ordered set of unique event times of one subject. Then $\bar{O}_k \in \mathbb{R}^{kd'+d_0}$ where $d' \in \mathbb{N}$ denotes the dimension of an observation at a monitoring time T_k, i.e.,

$$\left(T_k, dN^a(T_k), A(T_k), dN^\ell(T_k), L(T_k), dN^d(T_k), dN^c(T_k) \right) \in \mathbb{R}^{d'},$$

and $d_0 \in \mathbb{N}$ is the dimension of L_0. Following the notation from Section B.1, where $x(\mathcal{S}) = (x_j)_{j \in \mathcal{S}}$ denotes the $\mathcal{S}$-specific coordinates of x, we use $\bar{O}_k(\mathcal{S})$ to denote the $\mathcal{S}$-specific coordinates of $\bar{O}_k$ for an index set $\mathcal{S} \subset \{1, \ldots, kd' + d_0\}$.

Recall that we need initial estimators for the following time-sequence of conditional densities, conditional expectations, and conditional intensities:

$$G = \big(\pi_t, \Lambda^c(t)\big)_{t \in [0,\tau]}, \qquad \text{and,}$$
$$\boldsymbol{Z} = \big(Z_t^{G^*}, Z_{t,L(t)}^{G^*}, \Lambda^\ell(t), \Lambda^a(t), \Lambda^d(t)\big)_{t \in [0,\tau]}.$$

For estimation of $Z_t^{G^*}$ and $Z_{t,L(t)}^{G^*}$, we will proceed by estimating the conditional density μ_t directly. Then we construct substitution estimators for $Z_t^{G^*}$ and $Z_{t,L(t)}^{G^*}$ based on estimators for $\mu_t, \Lambda^\ell(t), \Lambda^a(t), \Lambda^d(t)$ by evaluating the g-computation formula. Accordingly, we define parametrizations and loss functions for the conditional densities π_t and μ_t, and for the conditional intensities $\Lambda^c, \Lambda^\ell, \Lambda^a, \Lambda^d$.

B.2.1. *Parametrizations and loss functions.* We parametrize the conditional density μ_t of $L(t)$ in terms of a function $f^L(t, \bar{O}(t))$, the conditional distribution π_t of $A(t)$ in terms of $f^A(t, \bar{O}(t))$, and the intensities $\Lambda^x(t)$ in terms of $f^x(t, \bar{O}(t))$, $x = \ell, a, c, d$.

To keep the notation simple, we assume that $A(t)$ and $L(t)$ are binary such that π_t and μ_t can be parametrized as follows:

$$\pi_t(1 \mid \bar{O}(t)) = \text{expit}(f^A(t, \bar{O}(t))),,$$

and

$$\mu_t(1 \mid \bar{O}(t)) = \text{expit}(f^L(t, \bar{O}(t))).$$

Note that, with Assumption 3 stated further below, we assume that the functions f^A, f^L have bounded sectional variation which implies that π_t and μ_t are bounded away from zero and one.

For the intensities, Λ^x, $x = \ell, a, d, c$, we consider the continuous case. We parametrize the intensity process λ^x for which $\Lambda^x(t \mid \mathcal{F}_{t-}) = \int_0^t \lambda^x(s \mid \mathcal{F}_{s-})ds$ as follows:

$$\lambda^x(t \mid \bar{O}(t)) = \exp(f^x(t, \bar{O}(t))), \qquad x = \ell, a, d, c.$$

Now, all required nuisance parameters are represented by a function f^x, $x \in \{L, A, c, a, \ell, d\}$. We further parametrize each f^x in terms of a sequence of

real-valued functions $(t, \bar{O}_k) \mapsto f_k^x(t, \bar{O}_k)$ with a fixed-dimensional support, such that:

$$(44) \qquad f^x(t, \bar{O}(t)) = \sum_{k=0}^{K(\tau)} \mathbb{1}\{K(t) = k\} \, f_k^x(t, \bar{O}_k), \quad x \in \{L, A, c, a, \ell, d\}.$$

The following assumption is central: It will allow us to define HAL estimators and it provides the basis for establishing condition 2 of Theorem 2. Assumption 3 is formulated for f_k^x defined by Display (44), but translates to f^x because the sum in (44) is finite.

ASSUMPTION 3 (Càdlàg and finite variation). *We assume that $f_k^x \in \mathscr{F}_{v, \mathscr{M}^x}$ for all $k \leq K(\tau)$ and all $x = L, A, c, a, \ell, d$, that is, f_k^x is càdlàg and has sectional variation norm bounded by a constant $\mathscr{M}^x < \infty$.*

For $x = L, A, c, a, \ell, d$, let $(O, f^x) \mapsto \mathscr{L}_x(f^x)(O)$ be the log-likelihood loss. For example, for $x = L$, $(O, f^L) \mapsto \mathscr{L}_L(f^L)(O)$ is defined as:

$$\mathscr{L}_L(f^L)(O) = \sum_{k=0}^{K(\tau)} \Delta N^\ell(t_k) \big(L(k) \log \big(1 + \exp(-f_k^L(T_k, \bar{O}_k)) \big)$$
$$+ \big(1 - L(k)\big) \log \big(1 + \exp(f_k^L(T_k, \bar{O}_k)) \big) \big),$$

whereas for $x = \ell$, in the continuous case considered in Section B.2.1, it is:

$$\mathscr{L}_\ell(f^\ell)(O) = \sum_{k=1}^{K(\tau)} \Delta N^\ell(t_k) f_k^\ell(t_k, \bar{O}_k)$$
$$- (t_k - t_{k-1}) \exp(f_{k-1}^\ell(t_{k-1}, \bar{O}_{k-1})).$$

We denote by $f_0^x = \operatorname{argmin}_{f^x} P_0 \mathscr{L}_x(f^x)$, the minimizer of the risk under P_0. Since the log-likelihood is strictly proper (Gneiting and Raftery, 2007), the data-generating f_0^x attains this minimum. We define the sum loss function $(O, f^Q) \mapsto \mathscr{L}_Q(f^Q)(O)$ for the Q-factor of the likelihood, i.e.,

$$\mathscr{L}_Q(f^Q) = \mathscr{L}_L(f^L) + \mathscr{L}_\ell(f^\ell) + \mathscr{L}_a(f^a) + \mathscr{L}_d(f^d),$$

where $f^Q = (f^L, f^\ell, f^a, f^d)$, and, also, the sum loss function $(O, f^G) \mapsto \mathscr{L}_G(f^G)(O)$ for the G-factor of the likelihood, i.e.,

$$\mathscr{L}_G(f^G) = \mathscr{L}_A(f^A) + \mathscr{L}_c(f^c),$$

where $f^G = (f^A, f^c)$. Note that minimizing the sum of a set of loss functions is the same as minimizing each loss function separately with respect to its respective parameter.

Assumption 4 below guarantees the oracle properties of the cross-validation selector (van der Laan and Dudoit, 2003; van der Vaart et al., 2006). We note that (45) holds for most common loss functions.

ASSUMPTION 4 (Bounded loss functions). *We assume that the loss functions are uniformly bounded in the sense that* $\sup_{f^x, O} \mathscr{L}_x(f^x)(O) < \infty$ *a.s. where the supremum is over the support of* P_0, *i.e., all possible realizations of* O *for a single subject, and all* f^x *such that* $f_k^x \in \mathscr{F}_{v, \mathscr{M}^x}$. *In addition, we assume that,*

$$
\begin{aligned}
(45) \qquad & \sup_{f^G} \frac{\|\mathscr{L}_G(f^G) - \mathscr{L}_G(f_0^G)\|_{P_0}^2}{\mathscr{D}_G(f^G, f_0^G)} < \infty, \\
& \sup_{f^Q} \frac{\|\mathscr{L}_Q(f^Q) - \mathscr{L}_Q(f_0^Q)\|_{P_0}^2}{\mathscr{D}_Q(f^Q, f_0^Q)} < \infty,
\end{aligned}
$$

where $\mathscr{D}(f, f_0) := P_0\mathscr{L}(f) - P_0\mathscr{L}(f_0)$ *denotes the loss-based dissimilarity measure.*

As detailed in Appendix B.1.1, the representation of a càdlàg function with finite sectional variation norm becomes a finite sum over indicator basis functions when the function is defined on a discrete support. The HAL estimator for f^x is defined as the minimizer of the empirical risk over all measures with a particular support defined by the actual observations $\{O_i\}_{i=1}^n$.

B.3. The HAL estimator. We apply the representation of Section B.1.1 to $(t, \bar{O}_k) \mapsto f_k^x(t, \bar{O}_k)$, which, again, translates into a representation for f^x by (44). Then we can define the HAL estimator for f^x as the minimizer of the empirical risk over all linear combinations of indicator basis function for a specific set of support points under the constraint that the sectional variation norm is bounded by the constant $\mathscr{M}^x$. By selecting the particular support defined by the n observations $\{O_i\}_{i=1}^n$, the minimizer of the finite-dimensional minimization problem equals the minimizer of the empirical risk over all measures f^x with sectional variation norm smaller than $\mathscr{M}^x$.

Specifically, let $\mathcal{I}_k$ be the index set for the unique observed values of $\bar{O}_k$. Recall that $\bar{O}_k(\mathcal{S})$ denotes the $\mathcal{S}$-specific coordinates $\bar{O}_k$, and that $t_0 < \cdots < t_{\kappa_n}$ is the ordered sequence of unique times of changes. Consider functions $f_{k,\beta}^x$ such that $\bar{O}_k \mapsto f_{k,\beta}^x(t, \bar{O}_k)$ has support $\{s_{k,j}\}_{j \in \mathcal{I}_k}$ and $t \mapsto f_{k,\beta}^x(t, \bar{O}_k)$ has support $\{t_0, \ldots, t_{\kappa_n}\}$. Separating the representation of $f_{k,\beta}^x$ along the

lines of Section B.1.1 into terms involving the time axis and terms involving $\bar{O}_k$ gives:

(46)

$$f_{k,\beta}^x(t, \bar{O}_k) = \sum_{r=0}^{\kappa_n} \mathbb{1}\{t_r \le t\}\left(\beta_{k,r,0}^x + \sum_{\mathcal{S} \subset \{1,\ldots,kd'+d_0\}} \sum_{j \in \mathcal{I}_k} \phi_{k,\mathcal{S},j}^x(\bar{O}_k)\beta_{k,r,\mathcal{S},j}^x\right).$$

Here, $\beta_{k,r,\mathcal{S},j}$ is the measure that the $\mathcal{S}$th section of $f_{k,\beta}^x$ assigns to the jth support point for $t_r \le t$ and $\phi_{k,\mathcal{S},j}(\bar{O}_k) = \mathbb{1}\{s_{k,j}(\mathcal{S}) \le \bar{O}_k(\mathcal{S})\}$ is the indicator that the support point $s_{k,j}(\mathcal{S})$ is smaller than or equal to $\bar{O}_k(\mathcal{S})$.

Corresponding to the representation $f_{k,\beta}^x$ for f_k^x in (46) we have an equivalent representation f_β^x for f^x. Now we can define the HAL estimator as follows:

(47)
$$\hat{f}_n^x = \operatorname*{argmin}_{f_\beta^x \,:\, \|f_\beta^x\|_v \le \mathscr{M}^x} \mathbb{P}_n \mathscr{L}_x(f_\beta^x).$$

Particularly, the sectional variation norm of the finite sum representation (46) equals the sum of the absolute values of the coefficients by (43) so that we can replace the constraint $\|f_\beta^x\|_v \le \mathscr{M}^x$ in (47) by $\|f_\beta^x\|_1 \le \mathscr{M}^x$. Hence, we can compute the HAL estimator for each f^x, $x = L, A, \ell, a, d, c$, by:

(48)
$$\hat{f}_n^x = \operatorname*{argmin}_{f_\beta^x \,:\, \|\beta\|_1 \le \mathscr{M}^x} \mathbb{P}_n \mathscr{L}_x(f_\beta^x),$$

corresponding to L_1-penalized (Lasso) regression (Tibshirani, 1996) with the indicator functions $\phi_{k,\mathcal{S},j}^x(\bar{O}_k)$ as covariates and $\beta_{k,r,\mathcal{S},j}^x$ as corresponding coefficients. For the log-likelihood loss and the squared error loss functions, standard software can be used to find the estimators (48), including selection of $\mathscr{M}^x$ by cross-validation. Table 3 in Appendix C gives a brief overview.

B.4. Theoretical results for HAL. We collect here the theoretical results for HAL estimation. These results rely on Assumptions 3 and 4 of Section B.2.1.

LEMMA 8. *The canonical gradient can be written as $D^*(P) = D^*(f^x :$ $x = L, A, c, a, \ell, d)$. If $\prod_{s<t} dG_t^*/dG_t$ is uniformly bounded for all t, then:*

$$\left\{D^*(f^x : x = L, A, c, a, \ell, d)\right\}$$

is a Donsker class.

PROOF. See Section B.5.1.   □

THEOREM 3. *For the loss functions $O \mapsto \mathscr{L}_x(f^x)(O)$, for $x = Q, G$, we have, under Assumptions 3 and 4, that*

$$\mathscr{D}_G(\hat{f}_n^G, f_0^G) = P_0\mathscr{L}_G(\hat{f}_n^G) - P_0\mathscr{L}_G(f_0^G) = o_P(n^{-1/2}),$$
$$\mathscr{D}_Q(\hat{f}_n^Q, f_0^Q) = P_0\mathscr{L}_Q(\hat{f}_n^Q) - P_0\mathscr{L}_Q(f_0^Q) = o_P(n^{-1/2}),$$

and further that $\|\hat{f}_n^G - f_0^G\|_{P_0} = o_P(n^{-1/4})$ and $\|\hat{f}_n^Q - f_0^Q\|_{P_0} = o_P(n^{-1/4})$.

PROOF. See Section B.5.2. On a final note, we remark that the $n^{-1/4}$ rate can be improved to $n^{-1/3}\log(n)^{d/2}$ as established by Bibaut and van der Laan (2019). □

In summary, Theorem 3 combined with Remark 1 implies that using HAL for initial estimation fulfills condition 1 of Theorem 2. Moreover, under our nonparametric smoothness assumptions (Assumption 3), the first part of condition 2 of Theorem 2 holds by Lemma 8. The second part of condition 2 can be seen to hold by Lemma 8, the functional delta method, and Hadamard differentiability of the product integral (Gill and Johansen, 1990; van der Vaart, 2000).

B.5. Proofs of results. We here prove the HAL results. Particularly, Section B.5.1 establishes Donsker properties of the canonical gradient (Lemma 8) and the loss functions (Lemma 9), and Section B.5.2 presents the final HAL convergence proof.

B.5.1. *Donsker class conditions.* Lemma 8 (see Section B.4) gives the Donsker properties of the efficient influence function. The subsequent Lemma 9 gives Donsker properties of the loss functions as needed for the HAL proof of Theorem 3.

PROOF. (Lemma 8).
Consider the following representation of the efficient influence curve,

$$D^*(P) = \int_0^\tau \left(\prod_{s<t} \frac{dG_s^*}{dG_s}\right)\left(\int Y \prod_{s>t} dQ_s \prod_{s\geq t} dG_s^* - \int Y \prod_{s\geq t} dQ_s dG_s^*\right).$$

First, consider:

$$\prod_{s<t} dG_s(O) = \prod_{k=1}^{K(t)} \left(d\Lambda^c(T_k)\right)^{\Delta N^c(T_k)} \left(\pi_{T_k}(A(T_k))\right)^{\Delta N^a(T_k)} \prod_{s\in(0,t)} \left(1 - d\Lambda^c(s)\right),$$

and, in the same way,

$$\prod_{s \geq t} dG_s(O) = \prod_{k=K(t)+1}^{K(\tau)} \left(d\Lambda^c(T_k)\right)^{\Delta N^c(T_k)} \left(\pi_{T_k}(A(T_k))\right)^{\Delta N^a(T_k)} \prod_{s \in (t,\tau)} \left(1 - d\Lambda^c(s)\right),$$

with corresponding versions of $\prod_{s<t} dG_s^*$ and $\prod_{s \geq t} dG_s^*$. Note that we have suppressed the conditioning on $\mathcal{F}_{t-}$ to simplify the presentation. Similarly:

$$\prod_{s<t} dQ_s(O) = \prod_{k=1}^{K(t)} \left(d\Lambda^\ell(T_k)\right)^{\Delta N^\ell(T_k)} \left(\mu_{T_k}(L(T_k))\right)^{\Delta N^\ell(T_k)} \prod_{s \in (0,t)} \left(1 - d\Lambda^\ell(s)\right)$$

$$\prod_{k=1}^{K(t)} \left(d\Lambda^a(T_k)\right)^{\Delta N^a(T_k)} \prod_{s \in (0,t)} \left(1 - d\Lambda^a(s)\right)$$

$$\prod_{k=1}^{K(t)} \left(d\Lambda^d(T_k)\right)^{\Delta N^d(T_k)} \prod_{s \in (0,t)} \left(1 - d\Lambda^d(s)\right),$$

and

$$\prod_{s \geq t} dQ_s(O) = \prod_{k=K(t)+1}^{K(\tau)} \left(d\Lambda^\ell(T_k)\right)^{\Delta N^\ell(T_k)} \left(\mu_{T_k}(L(T_k))\right)^{\Delta N^\ell(T_k)} \prod_{s \in (t,\tau)} \left(1 - d\Lambda^\ell(s)\right)$$

$$\prod_{k=1}^{K(t)} \left(d\Lambda^a(T_k)\right)^{\Delta N^a(T_k)} \prod_{s \in (t,\tau)} \left(1 - d\Lambda^a(s)\right)$$

$$\prod_{k=1}^{K(t)} \left(d\Lambda^d(T_k)\right)^{\Delta N^d(T_k)} \prod_{s \in (t,\tau)} \left(1 - d\Lambda^d(s)\right).$$

We now plug in our particular parametrizations from Section B.2.1:

$$\pi_{T_k}(A(T_k)) = \mathrm{expit}(f_k^A(T_k, \bar{O}_{k-1}))^{A(T_k)} \left(1 - \mathrm{expit}(f_k^A(T_k, \bar{O}_{k-1})\right),$$

$$\mu_{T_k}(L(T_k)) = \mathrm{expit}(f_k^L(T_k, \bar{O}_{k-1}))^{L(T_k)} \left(1 - \mathrm{expit}(f_k^L(T_k, \bar{O}_{k-1})\right),$$

and

$$d\Lambda^x(T_k) = \exp\big(f_{k-1}^x(T_{k-1}, \bar{O}_{k-1})\big)(T_k - T_{k-1}),$$

$$\prod_{s \in (0,t)} \big(1 - d\Lambda^x(s)\big) = \prod_{r=0}^{\kappa_n} \prod_{s \in (t_r, \min(t, t_{r+1}))} \big(1 - d\Lambda^x(s)\big)$$

$$= \exp\bigg(\sum_{r=0}^{\kappa_n} \mathbb{1}\{t_r < t\}\big(\min(t, t_{r+1}) - t_r\big)\exp(f_{K(t_r)}^x(t_r, \bar{O}_{K(t_r)}))\bigg),$$

$$\prod_{s \in (t,\tau)} \big(1 - d\Lambda^x(s)\big) = \prod_{r=0}^{\kappa_n} \prod_{s \in (\max(t, t_r), t_{r+1})} \big(1 - d\Lambda^x(s)\big)$$

$$= \exp\bigg(\sum_{r=1}^{\kappa_n} \mathbb{1}\{t_{r+1} \ge t\}\big(t_{r+1} - \max(t, t_r)\big)\exp(f_{K(t_r)}^x(t_r, \bar{O}_{K(t_r)}))\bigg),$$

for $x = c, a, \ell, d$. This shows the first statement of Lemma 8. By assumption, f_k^x is uniformly bounded. Furthermore, $\prod_{s<t} dG_s^*/dG_s$ is uniformly bounded away from zero which preserves the Donsker property of the ratio. Since the set of càdlàg functions with finite variation norm is a Donsker class and since the Donsker property is preserved under Lipschitz transformations and also under products and sums (van der Vaart and Wellner, 1996), we conclude that $\big\{D^*(f^x : x = L, A, c, a, \ell, d)\big\}$ is a Donsker class. $\qquad\square$

LEMMA 9. *For a set of constants $\mathcal{M}^x < \infty$, $x = L, A, a, \ell, d, c$, we have that $\{\mathcal{L}_x(f^x)\}$ is a Donsker class.*

PROOF. The log-likelihood loss $\mathcal{L}_A$ for f^A can be written:

$$\mathcal{L}_A(f^A)(O) = \sum_{k=0}^{K(\tau)} -\Delta N^a(T_k)\Big(A(T_k)\log\big(1 + \exp(-f_k^A(T_k, \bar{O}_k)))\big)$$
$$+ \big(1 - A(T_k)\big)\log\big(1 + \exp(f_k^A(T_k, \bar{O}_k)))\big)\Big),$$

and correspondingly for log-likelihood loss $\mathcal{L}_L$ for f^L:

$$\mathcal{L}_L(f^L)(O) = \sum_{k=0}^{K(\tau)} -\Delta N^\ell(T_k)\Big(L(T_k)\log\big(1 + \exp(-f_k^L(T_k, \bar{O}_k)))\big)$$
$$+ \big(1 - L(T_k)\big)\log\big(1 + \exp(f_k^L(T_k, \bar{O}_k)))\big)\Big).$$

For $x = c, a, \ell, d$, we write the loss function as:

$$
\begin{aligned}
\mathscr{L}_x(f^x)(O) = \sum_{k=1}^{K(\tau)} \Delta N^x(t_k) f_k^x(t_k, \bar{O}_k) \\
- \sum_{r=1}^{\kappa_n} (t_r - t_{r-1}) \exp(f_{K(t_r)-1}^x(t_{r-1}, \bar{O}_{K(t_r)-1})).
\end{aligned}
$$

By Assumption 3, f_k^x is uniformly bounded. Further note that $\inf_{f_k^x} (1 + \exp(f_k^x)) \geq 0$. Accordingly, f_k^x only ranges over values on which $z \mapsto \exp(z)$ and $z \mapsto \log z$ are Lipschitz continuous functions. Since the set of càdlàg functions with finite variation norm is a Donsker class and since the Donsker property is preserved under Lipschitz transformations and also under products and sums (van der Vaart and Wellner, 1996) we conclude that $\mathscr{L}_x(f^x)$ for all $x = L, A, c, a, \ell, d$ is a Donsker class. $\qquad \square$

B.5.2. *HAL proof (Theorem 3).* We refer to the general HAL proof (van der Laan, 2017). What we need to show is that:

$$
(49) \qquad \mathscr{D}_x(\hat{f}_n^x, f_0^x) = P_0 \mathscr{L}_x(\hat{f}_n^x) - P_0 \mathscr{L}_x(f_0^x) = o_P(n^{-1/2}),
$$

for $x = Q, G$. By the general HAL proof, we have that $\mathscr{D}_x(\hat{f}_n^x, f_0^x)$ is bounded by:

$$
-(\mathbb{P}_n - P_0)\big(\mathscr{L}_x(\hat{f}_n^x) - \mathscr{L}_x(f_0^x)\big).
$$

Since $\mathscr{L}_x(\hat{f}_n^x) - \mathscr{L}_x(f_0^x)$ falls in a Donsker class (Lemma 9) it follows that $\mathscr{D}_x(\hat{f}_n^x, f_0^x) = O_P(n^{-1/2})$ which, again, implies that $P_0(\mathscr{L}_x(\hat{f}_n^x) - \mathscr{L}_x(f_0^x))^2 = O_P(n^{-1/2})$. The latter implication relies on (45) stated in Assumption 4, and holds for the squared error loss and the log-likelihood loss as long as these are uniformly bounded (c.f., Assumption 4). It then follows by the Donsker theorem that $-(\mathbb{P}_n - P_0)(\mathscr{L}_x(\hat{f}_n^x) - \mathscr{L}_x(f_0^x)) = o_P(n^{-1/2})$ which gives $\mathscr{D}_x(\hat{f}_n^x, f_0^x) = o_P(n^{-1/2})$.

Finally, since the loss-based dissimilarity (i.e., the Kullback-Leibler divergence) behaves as the squared $L_2(P_0)$-norm (see, for example, van der Laan, 2017, Lemma 4), it follows that $\mathscr{D}_x(\hat{f}_n^x, f_0^x) = o_P(n^{-1/2})$ implies $\|\hat{f}_n^x - f_0^x\|_{P_0} = o_P(n^{-1/4})$.

APPENDIX C: OVERVIEW

C.1. Overview of notation.

$L_0 \in \mathbb{R}^{d_0}$	baseline covariate vector	
$A(t) \in \mathcal{A}$	treatment decision at time t	
$L(t) \in \mathbb{R}^d$	covariate vector t	
$N^a(t)$	counting process recording changes in treatment	
$N^\ell(t)$	counting process recording changes in covariates	
$N^c(t)$	counting process recording changes in censoring status	
$N^d(t)$	counting process recording changes in death status	
Λ^x	the cumulative intensity characterizing the compensator of N^x, and	
$M^x = N^x - \Lambda^x$	the corresponding martingale, $x = a, \ell, c, d$	
π_t	the conditional density of $A(t)$; $\pi_{0,t}(a \,|\, \mathcal{F}_{t-}) = P(A(t) = a \,|\, \mathcal{F}_{t-})$	
μ_t	the conditional density of $L(t)$; $\mu_{0,t}(\ell \,|\, \mathcal{F}_{t-})$	
$K(t)$	the subject-specific total number of unique events in $[0,t]$	p. 7
$T_1^a < \cdots < T_{N^a(\tau)}^a$	the subject-specific jump times of N^a	
$T_1^\ell < \cdots < T_{N^\ell(\tau)}^\ell$	the subject-specific jump times of N^ℓ	
$T_1 < \cdots < T_{K(\tau)}$	subject-specific unique event times	
$O = \bar{O}(\tau)$	subject-specific observed data in $[0,\tau]$	p. 7
$P_0 \in \mathcal{M}$	the distribution of O	p. 8
$\mathcal{M}$	the statistical model containing P_0	p. 11
G, g	interventional part of $P \in \mathcal{M}$ and its density	p. 9
Q, q	non-interventional part of $P \in \mathcal{M}$ and its density	
G^*, g^*	intervention and its density	
$P_{Q,G^*} = P^{G^*}$	the post-interventional distribution defined by the g-computation formula	
$\Psi^{G^*} : \mathcal{M} \to \mathbb{R}$	target parameter for fixed intervention G^*	p. 11
$\boldsymbol{Z}$	$\boldsymbol{Z} = (Z_t^{G^*}, Z_{t,L(t)}^{G^*}, \Lambda^\ell(t), \Lambda^a(t), \Lambda^d(t))_{t \in [0,\tau]}$	p. 14
$Z_t^{G^*}$	$Z_t^{G^*} = \mathbb{E}_{P^{G^*}}\left[Y \,\big|\, L(t), N^\ell(t), N^a(t), N^d(t), \mathcal{F}_{t-}\right],\, t \in [0,\tau]$	p. 14
$Z_{t,L(t)}^{G^*}$	$Z_{t,L(t)}^{G^*} = \mathbb{E}_{P^{G^*}}\left[Y \,\big|\, N^\ell(t), N^a(t), N^d(t), \mathcal{F}_{t-}\right],\, t \in [0,\tau]$	p. 14
$h_t^{G^*}$	clever weights, $t \in (0,\tau]$	p. 17
h_t^ℓ, h_t^a, h_t^d	clever covariates, $t \in (0,\tau]$	p. 18
$O_1, \ldots, O_n \sim P_0$	observed data	p. 7
$\mathbb{P}_n$	the empirical distribution of $\{O_i\}_{i=1}^n$	
$t_0 < t_1 < \cdots < t_{\kappa_n}$	the ordered sequence of unique times of changes $\cup_{i=1}^n \{T_{i,k}\}_{k=1}^{K_i(\tau)}$	p. 7
$\kappa_n = \sum_{i=1}^n K_i(\tau)$	the total number of observation times for the data $\{O_i\}_{i=1}^n$	
$\hat{G}_n$	estimator for G_0 on $[0,\tau]$	
$\hat{\boldsymbol{Z}}_n^m$	estimator for $\boldsymbol{Z}$	
$\hat{P}_n^*$	targeted estimator, characterized by $(\hat{\boldsymbol{Z}}_n^*, \hat{G}_n)$, where $\hat{\boldsymbol{Z}}_n^* = \hat{\boldsymbol{Z}}_n^{m=m^*}$	
$\hat{\psi}_n^{G^*} = \Psi^{G^*}(\hat{P}_n^*)$	TMLE estimator for the target parameter	

C.2. Details of targeting algorithm. We here provide a more detailed description of the targeting procedure (Section 7). As in Section 7, we here use the notation:

$$(50) \qquad Z_{t_r}^{G^*} = \mathbb{E}_{P^{G^*}}[Y \mid L(t_r), N^\ell(t_r), N^a(t_r), N^d(t_r), \mathcal{F}_{t_{r-1}}],$$

$$(51) \qquad Z_{t_r, L(t_r)}^{G^*} = \mathbb{E}_{P^{G^*}}[Y \mid N^\ell(t_r), N^a(t_r), N^d(t_r), \mathcal{F}_{t_{r-1}}],$$

for $r = 1, \ldots, \kappa_n$. Further, we now introduce:

$$(52) \qquad Z_{t_r, N^\ell(t_r)}^{G^*} = \mathbb{E}_{P^{G^*}}[Y \mid N^a(t_r), N^d(t_r), \mathcal{F}_{t_{r-1}}],$$

$$(53) \qquad Z_{t_r, N^a(t_r)}^{G^*} = \mathbb{E}_{P^{G^*}}[Y \mid N^d(t_r), \mathcal{F}_{t_{r-1}}]$$

$$(54) \qquad Z_{t_r, N^d(t_r)}^{G^*} = \mathbb{E}_{P^{G^*}}[Y \mid \mathcal{F}_{t_{r-1}}],$$

where the subscript '$N^x(t_r)$', $x = \ell, a, d$, tells us what was last integrated out over the interval $(t_{r-1}, t_r]$. Given current estimators $\hat{\boldsymbol{Z}}_n^m$ for $\boldsymbol{Z}$, we construct estimators,

$$\hat{Z}_{t_r,m}^{G^*}, \hat{Z}_{t_r,L(t_r),m}^{G^*}, \hat{Z}_{t_r,N^\ell(t_r),m}^{G^*}, \hat{Z}_{t_r,N^a(t_r),m}^{G^*}, \hat{Z}_{t_r,N^d(t_r),m}^{G^*},$$

for (50)–(54). Moreover, given estimators for (50)–(54), we construct estimators $\hat{h}_{t_r,m}^\ell, \hat{h}_{t_r,m}^a, \hat{h}_{t_r,m}^d$ for the clever covariates $h_{t_r}^\ell, h_{t_r}^a, h_{t_r}^d$ by:

$$\hat{h}_{t_r,m}^\ell = \sum_{\delta=0,1} (2\delta - 1)\hat{Z}_{t_r,L(t_r),m}^{G^*}(N^\ell(t_r) = N^\ell(t_{r-1}) + \delta),$$

$$\hat{h}_{t_r,m}^a = \sum_{\delta=0,1} (2\delta - 1)\hat{Z}_{t_r,N^\ell(t_r),m}^{G^*}(N^a(t_r) = N^a(t_{r-1}) + \delta),$$

$$\hat{h}_{t_r,m}^d = 1 - \hat{Z}_{t_r,N^a(t_r),m}^{G^*}(N^d(t_r) = 0).$$

Now we can carry out the individual targeting update steps as described in Sections 7.1 and 7.2. This gives:

$$\begin{aligned}
\hat{Z}_{t_r,L(t_r),k}^{G^*} &\mapsto \hat{Z}_{t_r,L(t_r),k+1}^{G^*} \\
\hat{\Lambda}_m^\ell &\mapsto \hat{\Lambda}_{m+1}^\ell \\
\hat{\Lambda}_m^a &\mapsto \hat{\Lambda}_{m+1}^a \\
\hat{\Lambda}_m^d &\mapsto \hat{\Lambda}_{m+1}^d
\end{aligned}$$

Starting with $\hat{Z}_{t_r,L(t_r),m+1}^{G^*}$, we use $\hat{\Lambda}_{m+1}^\ell$ to integrate out $N^\ell(t_r)$ to obtain the updated $\hat{Z}_{t_r,N^\ell(t_r),m+1}^{G^*}$. Similarly, we use $\hat{\Lambda}_{m+1}^a$ to obtain the updated

$\hat{Z}^{G^*}_{t_r, N^a(t_r), m+1}$ based on $\hat{Z}^{G^*}_{t_r, N^\ell(t_r), m+1}$ and lastly $\hat{\Lambda}^d_{m+1}$ to obtain $\hat{Z}^{G^*}_{t_r, N^d(t_r), m+1}$ based on $\hat{Z}^{G^*}_{t_r, N^a(t_r), m+1}$.

To proceed, recall that $\hat{Z}^{G^*}_{t_r, N^d(t_r), m+1}$ estimates $\mathbb{E}_{P^{G^*}}[Y \mid \mathcal{F}_{t_{r-1}}]$, i.e.,

$$\mathbb{E}_{P^{G^*}}[Y \mid N^c(t_{r-1}), A(t_{r-1}), L(t_{r-1}), N^\ell(t_{r-1}), N^a(t_{r-1}), N^d(t_{r-1}), \mathcal{F}_{t_{r-2}}].$$

The distributions of $N^c(t_{r-1}), A(t_{r-1})$ are specified by our intervention G^*, so that we can now further obtain an updated $\hat{Z}^{G^*}_{t_{r-1}, m+1}$ from $\hat{Z}^{G^*}_{t_r, N^d(t_r), m+1}$ by integrating out $N^c(t_{r-1}), A(t_{r-1})$ according to dG^*_t over $(t_{r-2}, t_{r-1}]$. For example, if our intervention imposes no censoring and sets $A(t)$ to a^* throughout (see Equation (6) in Section 2.2), then we have:

$$\hat{Z}^{G^*}_{t_{r-1}, m+1} = \hat{Z}^{G^*}_{t_r, N^d(t_r), m+1}(N^c(t_{r-1}) = 0, A(t_{r-1}) = a^*).$$

This means that we now have updated estimators:

$$\hat{Z}^{G^*}_{t_r, m+1}, \hat{Z}^{G^*}_{t_r, L(t_r), m+1}, \hat{Z}^{G^*}_{t_r, N^\ell(t_r), m+1}, \hat{Z}^{G^*}_{t_r, N^a(t_r), m+1}, \hat{Z}^{G^*}_{t_r, N^d(t_r), m+1},$$

for the entire sequence (50)–(54). We can now proceed with the next update $m+1$ to $m+2$ in the same way as outlined above.

C.3. Overview: Super learning. In this section we briefly describe super learning (van der Laan et al., 2007) adapted to our setting. The super learner is a machine learning method also known as stacked regression (Wolpert, 1992; Breiman, 1996). In the following, let x run through $\{L, A, c, a, \ell, d\}$. In Section B.2.1 we outlined how all the nuisance parameters can be represented by a function f^x. Super learning for f^x involves the following ingredients:

1. A collection of candidate estimators $\{\hat{f}_j^x\}_{1 \le j \le J}$ for f^x.
2. A loss function $(O, f^x) \mapsto \mathscr{L}_x(f^x)(O)$.

In Section B.2.1 we defined log-likelihood loss functions $(O, f^x) \mapsto \mathscr{L}_x(f^x)(O)$. The super learner identifies the best performing of the estimators in the collection $\{\hat{f}_j^x\}_{1 \le j \le J}$ by minimizing the empirical risk obtained via V-fold cross-validation. A V-fold cross-validation scheme defines $v = 1, \ldots, V$ sample splits into a training sample, $\{1, \ldots, n\} \setminus \text{Val}(v)$, used to construct the estimator, and a validation sample, $\text{Val}(v) \subset \{1, \ldots, n\}$, used to evaluate it.

Let $\mathbb{P}_n^v, \mathbb{P}_n^{-v}$ denote the empirical distribution of the validation and the training sample, respectively. Let $\hat{f}_j^x(\mathbb{P}_n^{-v})$ denote the jth estimator obtained on the training sample. We define the loss function based cross-validation selector as follows:

$$\hat{j}_n^x = \underset{j \in \{1, \ldots, J\}}{\operatorname{argmin}} \frac{1}{V} \sum_{v=1}^{V} \mathbb{P}_n^v \mathscr{L}_x(\hat{f}_j^x(\mathbb{P}_n^{-v})),$$

which yields the super learner $\hat{f}_n^J = \hat{f}_{\hat{j}_n^x}^x$.

C.4. Preliminaries on HAL implementation.

HAL estimation using `R` software.

`hal9001::fit_hal(X, Y, family=family)`

    generates a HAL design matrix consisting of basis functions corresponding to covariates and interactions

    makes a call to:
    `glmnet::glmnet(x=X, y=Y, family=family)`

    automatically selects a CV-optimal value of this regularization parameter:
    `glmnet::cv.glmnet(x=X, y=Y, family=family)`

Logistic regression:

`X`	HAL design matrix
`Y`	outcome variable (factor with two levels)
`family`	`'binomial'`

Squared error loss:

`X`	HAL design matrix
`Y`	outcome variable (real-valued)
`family`	`'gaussian'`

Intensity estimation with Poisson likelihood:

`X`	HAL design matrix
`Y`	Number of events observed for each combination of covariates
`R`	The amount of risk time for each combination of covariates
	`log(R)` is included as an offset in the regression formula
`family`	`'poisson'`

Intensity estimation with partial likelihood:

`X`	HAL design matrix
`Y`	outcome variable (two-column matrix with `'time'` and `'status'`)
`family`	`'cox'`

TABLE 3

APPENDIX D: WEBAPPENDIX

We here show the claim from Section 5.1 that:

$$\frac{d}{d\varepsilon} \mathscr{L}_{t,Z_t^{G^*}}\left(Z_{t,L(t)}^{G^*}(\varepsilon)\right)\Big|_{\varepsilon=0} = h_t^{G^*}\left(Z_t^{G^*} - Z_{t,L(t)}^{G^*}\right),$$

when

$$\mathscr{L}_{t,Z_t^{G^*}}\left(Z_{t,L(t)}^{G^*}\right) = Z_t^{G^*}\log Z_{t,L(t)}^{G^*} + \left(1 - Z_t^{G^*}\right)\log\left(1 - Z_{t,L(t)}^{G^*}\right).$$

and

$$\operatorname{logit} Z_{t,L(t)}^{G^*}(\varepsilon) = \operatorname{logit} Z_{t,L(t)}^{G^*} + \varepsilon h_t^{G^*}.$$

Recall that:

$$\operatorname{expit}(x) = \frac{e^x}{1+e^x} = \frac{1}{1+e^{-x}}, \qquad \operatorname{logit}(x) = \log\left(\frac{x}{1-x}\right),$$

such that

$$\operatorname{expit}(\operatorname{logit}(x)) = x,$$

and

$$
\begin{aligned}
\operatorname{expit}(-\operatorname{logit}(x)) &= \operatorname{expit}(-\log(x) + \log(1-x)) \\
&= \operatorname{expit}(\log(1-x) - \log(x)) \\
&= \operatorname{expit}(\operatorname{logit}(1-x)) = 1 - x.
\end{aligned}
$$

Furthermore, it is easily seen that

$$
\begin{aligned}
\log(\operatorname{expit}(x)) &= -\log(1+e^{-x}), \\
\log(1 - \operatorname{expit}(x)) &= -\log(1+e^x),
\end{aligned}
$$

so that

$$
\begin{aligned}
\frac{d}{dx}\log(\operatorname{expit}(x)) &= \frac{e^{-x}}{1+e^{-x}} = \operatorname{expit}(-x), \\
\frac{d}{dx}\log(1 - \operatorname{expit}(x)) &= -\frac{e^x}{1+e^x} = -\operatorname{expit}(x).
\end{aligned}
$$

Now we can differentiate the composite functions

$$\frac{d}{d\varepsilon}\log(\operatorname{expit}(\operatorname{logit}(x) + \varepsilon h)) = h\operatorname{expit}(-(\operatorname{logit}(x) + \varepsilon h)),$$

$$\frac{d}{d\varepsilon}\log(1 - \operatorname{expit}(\operatorname{logit}(x) + \varepsilon h)) = -h\operatorname{expit}(\operatorname{logit}(x) + \varepsilon h),$$

where setting $\varepsilon = 0$ gives

$$\frac{d}{d\varepsilon}\log(\operatorname{expit}(\operatorname{logit}(x) + \varepsilon h))\Big|_{\varepsilon=0} = h\operatorname{expit}(-(\operatorname{logit}(x))) = 1 - x,$$

$$\frac{d}{d\varepsilon}\log(1 - \operatorname{expit}(\operatorname{logit}(x) + \varepsilon h))\Big|_{\varepsilon=0} = -h\operatorname{expit}(\operatorname{logit}(x)) = x.$$

Applying these steps to $\mathscr{L}_{t,Z_t^{G^*}}\big(Z_{t,L(t)}^{G^*}(\varepsilon)\big)$ now gives:

$$\frac{d}{d\varepsilon}\mathscr{L}_{t,Z_t^{G^*}}\big(Z_{t,L(t)}^{G^*}(\varepsilon)\big)\Big|_{\varepsilon=0} = Z_t^{G^*}h_t^{G^*}(1 - Z_{t,L(t)}^{G^*}) - (1 - Z_t^{G^*})h_t^{G^*}Z_{t,L(t)}^{G^*}$$

$$= Z_t^{G^*}h_t^{G^*} - h_t^{G^*}Z_{t,L(t)}^{G^*} = h_t^{G^*}\big(Z_t^{G^*} - Z_{t,L(t)}^{G^*}\big),$$

which completes the proof.

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