Semi-Parametric Sensitivity Analysis for Trials with Irregular and Informative Assessment Times

Bonnie Smith\(^1\)\(^*,\) Shu Yang\(^2\), Andrea J. Apter\(^3\), and Daniel O. Scharfstein\(^4\)

\(^1\) Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
\(^2\) Department of Statistics, North Carolina State University, Raleigh, NC, USA
\(^3\) Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
\(^4\) Department of Population Health Sciences, University of Utah School of Medicine, Salt Lake City, UT, USA

\(^*\) email: bsmit179@jhmi.edu

Abstract

Many trials are designed to collect outcomes at or around pre-specified times after randomization. In practice, there can be substantial variability in the times at which participants are actually assessed. As a result, treatment effects can be driven by the timing of assessments, rather than the effect of treatment on participants' underlying outcome trajectories. One way to deal with this problem is to focus on the treatment effect at each of the (fixed) targeted assessment times. For this, untestable assumptions are needed, and it is therefore important to assess how inferences would change under departures from these assumptions via sensitivity analysis. We develop such a sensitivity analysis methodology here, along with a semi-parametric, influence function-based estimation approach. We apply our method to a study of low-income participants with uncontrolled asthma, and we evaluate the performance of our procedure in a realistic simulation study.

Keywords: Assessment at random; asthma; influence function; inverse intensity weighting; semi-parametric estimation.
1 Introduction

Randomized trials are often designed to collect outcome information at or around certain pre-specified times after randomization. In practice, there can be substantial variability in the times at which participants’ outcomes are actually assessed. In this case, we say that the study has irregular assessment times. For example, in the Asthma Research for the Community (ARC) trial (Apter et al., 2019), a pragmatic randomized trial of 301 low-income participants with uncontrolled asthma, the study protocol called for outcome data to be collected at 3, 6, 9, and 12 months after randomization. However, research coordinators were often unable to schedule data collection appointments until substantially later than these targeted times. Figure 1 shows the distribution of the actual times at which assessments took place.

Figure 1: Assessment times in the ARC study. The four panels show the distributions of the actual times of participants’ first, second, third, and fourth post-baseline assessments. The protocol called for assessments at 3, 6, 9, and 12 months, but there was substantial spread in the actual times of assessment around these targeted times.

When analyzing trials with irregular assessment times, researchers often focus on the outcome at the (random) time of assessment in each treatment arm. However, differences in this endpoint between treatment arms can be driven by the timing of assessments, rather than by an effect of treatment on participants’ underlying outcome trajectories. For this reason, basing inference on the means of the observed outcomes can be problematic (even in trials without missing data). Examples include trials where the treatment effect changes with time, or where the times of assessments are different between treatment arms.

One way to deal with this problem is to target the treatment effect at each of the (fixed) targeted
assessment times stipulated in the protocol. A number of methods for estimating these effects have been developed in the literature. The key caveat is that, as with trials with missing data, untestable assumptions are needed, and assessing how inferences would change under departures from these assumptions is crucial (see, for example, the report *The Prevention and Treatment of Missing Data in Clinical Trials* (National Research Council 2010)).

Here we develop a sensitivity analysis methodology for estimating the treatment-specific mean outcome at fixed times after randomization, together with an influence function-based, semi-parametric estimation approach. Our methodology is anchored around the assumption of *assessment at random* (AAR), which posits that assessment at time $t$ is independent of the outcome at time $t$, conditional on the history of observed data though $t$—(see Section 2.2). However, in some studies, participants’ assessment at a given time could be directly tied with their outcomes at that time. For example, in an asthma trial, a participant may be less likely to attend a data collection appointment at a time when they are having an asthma exacerbation. Our sensitivity analysis takes into account the possibility of such *informative* assessment times, and shows how inference is impacted by departures from AAR. Our estimation approach adapts augmented inverse weighting to the informative assessment time models considered in our sensitivity analysis. We show that our method allows for flexible modeling of the intensity function and outcome regression, while yielding an estimator for the target parameter that converges at $\sqrt{n}$ rates.

The paper is organized as follows. In Section 2, we introduce our setting and notation, define assessment at random, and review previous work on inverse intensity weighting. We present our sensitivity analysis framework and models in Section 3. In Section 4, we develop semi-parametric estimation theory and compute the large-sample distribution of our estimator. In Section 5, we describe our approach for bounding the sensitivity analysis parameters. We analyze the ARC trial in Section 6. In Section 7, we evaluate our method in a realistic simulation study, and Section 8 concludes with a discussion.

## 2 Background

### 2.1 Setting and notation

Consider a randomized trial where each participant has an outcome assessed at baseline and at some number of subsequent times, where the timing and number of post-baseline assessments may vary by participant. Covariate information may also be collected at each assessment time. We suppose that the goal of the trial is to learn about the treatment arm-specific mean outcome at given fixed times after randomization.

Let $X$ be treatment assignment for a random individual, let $Y(t)$ denote their outcome at time $t$, and let $N(t)$ be their number of assessments up through and including time $t$. We treat the assessments as recurrent events occurring in continuous time. We refer to the counting process $\{N(t) : 0 \leq t \leq \tau\}$, where $\tau$ is the end of follow-up, as the *assessment process*, and we refer to $\{Y(t) : 0 \leq t \leq \tau\}$ as the *outcome process*. We also use the shorthand notation $L$ for the outcome process. Additionally, let $\{W(t) : 0 \leq t \leq \tau\}$ be a process of time-varying and/or fixed covariates. Let $A(t)$ be the indicator that the individual has an assessment at time $t$. The observed data for a random individual is $O := \{X\} \cup \{N(t) : 0 \leq t \leq \tau\} \cup \{W(t), Y(t) : A(t) = 1, 0 \leq t \leq \tau\}$. We let $\bar{O}(t)$ denote the participant’s observed data up to, but not including, time $t$; we refer to this as their *observed past*.

Assessment times may be associated with outcomes, for example through baseline variables.
and time-varying factors. We will account for this using the intensity function \cite{Andersen1985, Andersen1993} of the assessment process. Let \( A(t, t + \epsilon) \) be the indicator that the participant has an assessment in the time window \([t, t + \epsilon)\). We denote by \( \lambda(t, \bar{O}(t)) \) the intensity function of the assessment process given a participant’s observed past: 

\[
\lambda(t, \bar{O}(t)) = \lim_{\epsilon \to 0^+} \frac{P(A(t, t + \epsilon) = 1 | \bar{O}(t))}{\epsilon}.
\]

Additionally, we denote by \( \rho(t, \bar{O}(t), L) \) the intensity function of the assessment process given a participant’s observed past and their full outcome process: 

\[
\rho(t, \bar{O}(t), L) = \lim_{\epsilon \to 0^+} \frac{P(A(t, t + \epsilon) = 1 | \bar{O}(t), L)}{\epsilon}.
\]

2.2 The assessment at random assumption

In order to learn about \( E[Y(t)|X] \) at a fixed time \( t \) after randomization from a trial with irregular assessment times, untestable assumptions are needed. While some methods assume that assessment times and outcomes are completely unrelated, this may not be realistic in many studies. Assessment at random (AAR) \cite{Lin2004, Pullenayegum2004} has been proposed as an assumption that allows assessment times to be associated with underlying outcomes, but posits that controlling for the observed past accounts for this association. Specifically, under AAR, for each time \( t \) and within each stratum of the observed past \( \bar{O}(t) \), the distribution of \( Y(t) \) is assumed to be the same among participants who were, and who were not, assessed at that time. That is, 

\[
dF(y(t)|A(t) = 0, \bar{O}(t)) = dF(y(t)|A(t) = 1, \bar{O}(t)).
\]

2.3 Inverse-intensity weighting

To account for association between assessment times and outcomes in trials with irregular assessment times, a method of weighting by the inverse of the intensity function was developed by Lin, Scharfstein, and Rosenheck \cite{Lin2004}. Weighting each observed outcome \( Y(t) \) by \( 1/\lambda(t, \bar{O}(t)) \) gives more (respectively, less) weight to outcomes if they were less (more) likely to have been assessed at that time, based on the participant’s observed past. Under AAR, this creates a pseudo-population in which outcomes and assessment times are unrelated. In Lin et al. \cite{Lin2004}, inverse-intensity weighting was used in an estimating equation approach to inference for the regression parameters of a structural model for \( E[Y(t)|X] \). Bužková and Lumley \cite{Buzkovova2007} adapted this method to allow an intensity function with discontinuities. Pullenayegum and Feldman \cite{Pullenayegum2013} combined inverse-intensity weighting with a model for the increments of the outcome process to form a doubly robust estimator, while Sun et al. \cite{Sun2016} extended inverse-intensity weighting to the setting of quantile regression.

A second approach that has been taken by several authors is based on joint modeling of the assessment and outcome processes; see for example Lin and Ying \cite{Lin2001}, Lipsitz et al. \cite{Lipsitz2002}, Liang et al. \cite{Liang2009}, Cai et al. \cite{Cai2012}, Sun et al. \cite{Sun2012}, Pullenayegum \cite{Pullenayegum2016}. Methods in this category are also based on untestable modeling assumptions, and so do not obviate the need for sensitivity analysis.

Our method uses augmented inverse-intensity weighting, which allows for flexible modeling of the intensity function and makes more complete use of the data compared to inverse-intensity weighting alone (see Section \ref{augment}). Another important difference relative to previous methods is that our weights account for non-AAR assessments—a generalization needed for implementation of our sensitivity analysis.
3 Sensitivity analysis framework and models

Here we present our framework for a sensitivity analysis to the AAR assumption, which uses an approach first developed for trials with non-ignorable missing data. All of our assumptions are treatment arm-specific; for ease of notation, we suppress dependence on treatment group.

3.1 Sensitivity analysis framework

One common approach to sensitivity analysis is to anchor around some benchmark assumption. The sensitivity analysis considers a family of assumptions indexed by sensitivity parameters $\alpha$, which includes the benchmark as a special case. Target parameters are estimated under each assumption in the family, showing how inference changes under departures from the benchmark assumption.

A family of assumptions can be specified using the benchmark assumption and exponential tilting [Barndorff-Nielsen and Cox, 1994], a device for constructing a family of distributions from an initial distribution through multiplication by a tilting term. This approach has been used for trials with missing or censored data by [Rotnitzky, Scharfstein, Su, and Robins, 2001; Birmingham, Rotnitzky, and Fitzmaurice, 2003; Vansteelandt, Rotnitzky, and Robins, 2007; and Scharfstein and McDermott, 2019], among others. It was also used by [Franks, D’Amour, and Feller, 2020] for observational studies with possible unmeasured confounding.

Exponential tilting has also been proposed for sensitivity analysis for trials with irregular and informative assessment times by [Wang, 2020]. They work within a discrete-time framework, and estimation is carried out using g-computation based on fully parametric models. In contrast, our approach treats the outcome and assessment processes as stochastic processes in continuous time. We use semi-parametric estimation based on an influence function which we derive, and we model the intensity of assessment using a semi-parametric model for recurrent events.

Our sensitivity analysis uses AAR as the benchmark and a family of assumptions determined by one or more user-specified tilting functions $q(Y(t), \bar{O}(t); \alpha)$ and range(s) of values for $\alpha$. Our method does not explore the whole space of alternatives to AAR, but rather traces one or more specific paths through this space (determined by the choices of $q( )$). By doing so, it allows the researcher to view how inference changes along the course of these paths. As in settings with missing data or causal inference, one cannot know whether the true relationship between the distributions of unobserved and observed data is exactly captured using a given choice of tilt function (that is, whether it lies along a given path). However, even without this knowledge, sensitivity analysis provides important information that can strengthen the quality of evidence from trials. Namely, if inferences change as one moves away from AAR along the paths investigated by the sensitivity analysis, then researchers should have reservations about conclusions based on AAR. Conversely, if inferences are relatively stable along these paths, this can strengthen conclusions made under AAR (though the possibility of incorrect inference cannot be ruled out absolutely).

To conduct our sensitivity analysis, target parameters are estimated under Assumption 1 below with a fixed value of $\alpha$, and this is repeated for each $\alpha$ in the range chosen by the analyst (see Section 5). For a fixed value of the observed past $\bar{O}(t)$, let Subgroup 1 (respectively, Subgroup 0) be the group with this observed past who were (were not) assessed at time $t$. Assumption 1 posits that the distribution of outcomes for Subgroup 0 is equal to the distribution for Subgroup 1 times a tilting factor which shifts the center of mass while preserving the support of $Y(t)$:
Assumption 1. *(Tilting assumption)* Let $\alpha$ be a $\mathbb{R}^m$-valued parameter for some $m$, and let $q(Y(t), \bar{O}(t); \alpha)$ be a user-specified function which is equal to zero at $\alpha = 0$. For all $t$,

$$dF(Y(t) = y(t) | A(t) = 0, \bar{O}(t)) =$$

$$dF(Y(t) = y(t) | A(t) = 1, \bar{O}(t)) \times \frac{\exp\{q(y(t), \bar{O}(t); \alpha)\}}{c(t, \bar{O}(t); \alpha)},$$

where $c(t, \bar{O}(t); \alpha) = E[\exp\{q(Y(t), \bar{O}(t); \alpha)\} | A(t) = 1, \bar{O}(t)]$ is a normalizing constant.

We illustrate Assumption 1 using the tilting function $q(Y(t), \bar{O}(t); \alpha) = \alpha Y(t)$, with $\alpha \in \mathbb{R}$. Under this choice of $q(\cdot)$, for a negative (respectively, positive) value of $\alpha$, the outcome distribution for Subgroup 0 is tilted to the left (right) relative to the distribution for Subgroup 1, with smaller (larger) values of $Y(t)$ receiving greater weight. Figure 2 shows tilting for values of $\alpha = -0.6, -0.3, 0, 0.3$, and 0.6 in the context of the ARC trial, where the outcome $Y(t)$ is on a scale from 0 to 6.

![Figure 2: Illustration of the tilt assumption in the context of the ARC trial. Here we consider the distribution of the Asthma Control outcome $Y(t)$ at $t = 6$ months among participants with a certain observed past. The distribution of $Y(6)$ among participants who were assessed at 6 months is shown in the left panel. Under the AAR assumption ($\alpha = 0$), the distribution of $Y(6)$ for participants who had the same observed past but were not assessed at 6 months would be the same; under a positive (negative) value of $\alpha$, the distribution for for non-assessed participants would be tilted with more weight on higher (lower) values of $Y(6)$, as shown in the right panel. Shown are smoothed depictions of the probability mass functions.](image)

Under Assumption 1, the conditional mean $E[Y(t)|\bar{O}(t)]$, and therefore the marginal mean $E[Y(t)]$, are identified from the observed data:
**Proposition 1.** Under Assumption 1,

\[
E[Y(t)|\bar{O}(t)] = \frac{E[Y(t)|\exp\{q(Y(t), \bar{O}(t); \alpha)\} \mid A(t) = 1, \bar{O}(t)]}{E[\exp\{q(Y(t), \bar{O}(t); \alpha)\} \mid A(t) = 1, \bar{O}(t)]}.
\]

*Proof.* Using the fact that, in continuous time, \( P(A(t) = 1|\bar{O}(t) = \bar{o}(t)) = 0 \), we have:

\[
E[Y(t)|\bar{O}(t) = \bar{o}(t)] = \int_{\bar{y}(t)} y(t) \left\{ \frac{\exp\{q(y(t), \bar{o}(t); \alpha)\}}{\exp\{q(y(t), \bar{O}(t); \alpha)\}} \mid A(t) = 1, \bar{O}(t) = \bar{o}(t) \right\} dF(y(t)|A(t) = 1, \bar{O}(t) = \bar{o}(t)).
\]

In addition to Assumption 1, we assume that the intensity function \( \rho(t, \bar{O}(t), L) \) is not impacted by unobserved variables other than the current outcome \( Y(t) \), or by any future outcome variables occurring after time \( t \):

**Assumption 2.** (Intensity function assumption) The intensity function given a participant’s observed past \( \bar{O}(t) \) and their full outcome process \( L = \{Y(t) : 0 \leq t \leq \tau\} \) depends only on \( t, Y(t), \) and \( \bar{O}(t) \). That is:

\[
\rho(t, \bar{O}(t), L) := \lim_{\epsilon \to 0^+} \frac{P(A[t, t + \epsilon] = 1, \bar{O}(t), L)}{\epsilon} = \lim_{\epsilon \to 0^+} \frac{P(A[t, t + \epsilon] = 1, \bar{O}(t), Y(t))}{\epsilon}.
\]

In light of Assumption 2, we denote this intensity function now by \( \rho(t, Y(t), \bar{O}(t)) \).

A key advantage of the exponential tilting model of Assumption 1 is that, together with Assumption 2, it provides the following link between the intensity functions \( \rho(t, Y(t), \bar{O}(t)) \) and \( \lambda(t, \bar{O}(t)) \):

**Proposition 2.** Under Assumptions 1 and 2,

\[
\rho(t, Y(t), \bar{O}(t)) = \lambda(t, \bar{O}(t)) \frac{E[\exp\{q(Y(t), \bar{O}(t); \alpha)\} \mid A(t) = 1, \bar{O}(t)]}{\exp\{q(Y(t), \bar{O}(t); \alpha)\}}.
\]

The proof is given in Appendix A. Proposition 2 shows that \( \rho(t, Y(t), \bar{O}(t)) \) is determined by the observed data distribution and the value of \( \alpha \). Importantly, this link allows us to estimate \( \rho(t, Y(t), \bar{O}(t)) \) by modeling observed data in a way that places no restrictions on the sensitivity parameters; we leverage this property throughout Section 4. Additionally, the link also gives an interpretation for \( \alpha \) via selection models in certain cases. If we choose \( q(Y(t), \bar{O}(t); \alpha) \) to be \( aY(t) \), then we have:

\[
\frac{\rho(t, Y(t) + 1, \bar{O}(t))}{\rho(t, Y(t), \bar{O}(t))} = \exp\{-\alpha\}.
\]

That is, with this tilting function, \( \exp\{-\alpha\} \) has an interpretation as the ratio of the intensities for participants with the same observed past whose outcomes \( Y(t) \) differ by one unit.
3.2 Structural assumption and target estimand

Our approach targets the curve of means \( E[Y(t)] \) over some chosen time interval \( a \leq t \leq b \). Here \( a \) should be a time just before any post-baseline assessments, and \( b \) can be any time before the end of follow-up such that the interval \([a, b]\) is well-supported by the data. To facilitate inference at root-\(n\) rates, we assume the following structural form for the curve of means:

\[ \text{Assumption 3. (Structural assumption) Let } B(t) \text{ be a specified spline basis, let } p \text{ be its dimension, and let } s( ) \text{ be a specified invertible link function. We assume that } E[Y(t)] = s(\beta' B(t)), a \leq t \leq b, \text{ for some } \beta \in \mathbb{R}^p. \]

We take \( \beta \) to be our target parameter, as each mean \( E[Y(t)] \) is determined by \( \beta \) under Assumption 3.

Proposition 3. Under Assumptions 1 and 3, \( \beta \) is identified from the observed data as:

\[
\beta = \int_{t=a}^{b} V^{-1}(t)B(t)B'(t)\beta dt = \int_{t=a}^{b} V^{-1}(t)s^{-1}(E[Y(t)])\beta dt,
\]

where \( V := \int_{t=a}^{b} B(t)B(t)'dt \).

Here the second equality is by Assumption 3; and under Assumption 1, \( E[Y(t)] \) is identified for each \( t \) by Proposition 1.

4 Inference

Here we suppose that Assumptions 1-3 hold for a given known value of \( \alpha \), and we develop an inference procedure for \( \beta \) separately by treatment arm; as before we suppress the treatment assignment indicator. We assume that we observe \( n \) independent and identically distributed copies of the observed data \( O \). We use the subscript \( i \) to refer to data for the \( i \)th individual, and we let \( P \) denote the true distribution of the observed data. We derive an influence function for \( \beta \) under a general invertible link function \( s( ) \), then specialize to the identity link to develop our estimation procedure and derive our asymptotic results.

4.1 Influence function

Set \( V(\beta) = \int_{t=a}^{b} \left\{ \frac{\partial}{\partial \beta} s(\beta' B(t)) \right\} \left\{ \frac{\partial}{\partial \beta'} s(\beta' B(t)) \right\} dt \) and \( W(t; \beta) = V(\beta)^{-1} \frac{\partial}{\partial \beta} s(\beta' B(t)) \), where \( s( ), \beta, \) and \([a, b]\) are as in Assumption 3. Our inference procedure is based on the following:

Theorem 1. An influence function for \( \beta \) is given by:

\[
\varphi(O; P) = \int_{t=a}^{b} W(t; \beta) \left\{ \frac{1}{\rho(t, Y(t), \bar{O}(t))} \left( Y(t) - E[Y(t)|\bar{O}(t)] \right) \right\} dN(t) + \int_{a}^{b} W(t; \beta) \left( E[Y(t)|\bar{O}(t)] - s(\beta' B(t)) \right) dt.
\]
Corollary 1. When \( s(\cdot) \) is the identity link, an influence function for \( \beta \) is given by \( \varphi(O; P) = m(O; P) - \beta \), where \( m(O; P) := \int_{t=a}^{b} \left\{ V^{-1}(t) B(t) \frac{Y(t) - E[Y(t)|\bar{O}(t)]}{\rho(t,Y(t),\bar{O}(t))} \right\} dN(t) + \int_{t=a}^{b} \left\{ V^{-1}(t) E[Y(t)|\bar{O}(t)] \right\} dt \) (2)

and \( V := \int_{t=a}^{b} B(t) d(t) \). Here \( \varphi(O; P) \) is a function of the observed data by Propositions 1 and 2. We prove Theorem 1 using the semi-parametric theory for missing data presented in Scharfstein et al. (1999) and Tsiatis (2006), together with tools from stochastic process theory. The proof is given in Appendix B. Throughout the rest of the paper, we take \( s(\cdot) \) to be the identity link. The first term in \( m(O; P) \) uses inverse intensity weighting by \( \rho(t,Y(t),\bar{O}(t)) \); under Assumption 2 this breaks the association between outcomes and times of assessment. The second term is an augmentation term that uses each participant’s predicted mean outcome at each time in the inference period \( a \leq t \leq b \).

4.2 Point estimation

With estimators of \( \rho(t,Y(t),\bar{O}(t)) \) and \( E[Y(t)|\bar{O}(t)] \), the influence function \( \varphi(O; P) \) can be used as an estimating function for \( \beta \). Note that the first integral in \( \varphi(O; P) \) is a sum with jumps at the participant’s assessment times. Thus, when \( s(\cdot) \) is the identity link, the resulting estimator for \( \beta \) will be:

\[
\hat{\beta} = \frac{1}{n} \sum_{i=1}^{n} \sum_{t_k \in S_i} V^{-1}(t_k) \left( Y_i(t_k) - \hat{E}[Y(t_k)|\bar{O}(t_k)] \right) \rho(t_k,Y_i(t_k),\bar{O}(t_k)) + \int_{t=a}^{b} V^{-1}(t_k) \hat{E}[Y(t)|\bar{O}(t)] d(t) \] (3)

where \( S_i \) denotes the set of participant \( i \)'s assessment times that occur in the interval \([a,b] \).

A key consideration in estimating \( \rho(t,Y(t),\bar{O}(t)) \) and \( E[Y(t)|\bar{O}(t)] \) is that models should impose no restrictions on the value of \( \alpha \). For this we leverage Propositions 1 and 2 of Section 3.1, which show that modeling \( \lambda(t,\bar{O}(t)) \) and the conditional distribution of observed outcomes \( dF(y(t)|A(t) = 1,\bar{O}(t)) \) (which does not restrict \( \alpha \)) allows us to obtain estimates for \( \rho(t,Y(t),\bar{O}(t)) \) and \( E[Y(t)|\bar{O}(t)] \). We assume that the models for \( \lambda(t,\bar{O}(t)) \) and \( dF(y(t)|A(t) = 1,\bar{O}(t)) \) are correctly specified and chosen in such a way that the estimators \( \hat{\rho}(t,Y(t),\bar{O}(t)) \) and \( \hat{E}[Y(t)|\bar{O}(t)] \) converge to the true values \( \rho(t,Y(t),\bar{O}(t)) \) and \( E[Y(t)|\bar{O}(t)] \) at fast enough rates, as discussed in Section 4.4. In general, using models that are too flexible can result in an estimator for the target parameter that converges to the truth at slower than root-\( n \) rates and for which valid confidence intervals cannot be readily obtained (Naimi et al., 2021). A key advantage of using an estimator based on \( \varphi(O; P) \) is that \( \hat{\rho}(t,Y(t),\bar{O}(t)) \) and \( \hat{E}[Y(t)|\bar{O}(t)] \) can be estimated flexibly, at slower than \( n^{-1/2} \) rates, while still yielding a root-\( n \)-consistent estimator for \( \beta \), as we show in Section 4.4.

4.3 Large sample distribution and confidence intervals

Here we derive the asymptotic distribution of the estimator \( \hat{\beta} \) in (3). Let \( \hat{P} \) be an estimate of the distribution \( P \) that uses the empirical distribution of \( \bar{O}(t) \), and estimates of \( \rho(t,Y(t),\bar{O}(t)) \) and \( E[Y(t)|\bar{O}(t)] \) based on models for \( \lambda(t,\bar{O}(t)) \) and \( dF(y(t)|A(t) = 1,\bar{O}(t)) \) as described in Section 4.2. Following Kennedy (2016), \( \sqrt{n}(\hat{\beta} - \beta) \) can be expanded as the sum of three terms: a central
limit term \( \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \varphi(O_i; P) \), an empirical process term, and a remainder term \( \sqrt{n} \text{Rem(}\hat{P}, P) \).

We compute the remainder term below:

**Proposition 4.** The remainder term \( \text{Rem(}\hat{P}, P) \) is given by:

\[
E \left[ \int_{t=a}^{b} \left\{ V^{-1} B(t) \left( \frac{\hat{\rho}(t, Y(t), \hat{O}(t))}{\hat{\rho}(t, Y(t), O(t))} - 1 \right) \left( E[Y(t)|\hat{O}(t)] - E[Y(t)|O(t)] \right) \right\} dt \right].
\]

The proof of Proposition 4 is given in Web Appendix C. Suppose \( \hat{\rho}(t, Y(t), \hat{O}(t)) \) and \( \hat{E}[Y(t)|\hat{O}(t)] \) converge to the truth at fast enough rates such that \( \sqrt{n} \text{Rem}(\hat{P}, P) \) is \( o_P(1) \) (see Section 4.4), and suppose also that Donsker conditions hold by which the empirical process term is \( o_P(1) \). Then \( \hat{\beta} \) is asymptotically normal with asymptotic variance equal to the variance of \( \varphi(O; P) \). Then a consistent variance estimator for \( \hat{\beta} \) is given by \( \hat{\text{Var}}(\hat{\beta}) = \frac{1}{n} \sum_{i=1}^{n} \left[ m(O_i; \hat{P}) - \hat{\beta} \right] \left[ m(O_i; \hat{P}) - \hat{\beta} \right]' \), where \( m(O; P) \) is given in Corollary 1. The mean at any fixed time \( t \), \( \mu_t = E[Y(t)] = \beta' B(t) \), can be estimated as \( \hat{\mu}_t = \beta' B(t) \) with influence function-based variance estimator \( \hat{\text{Var}}(\hat{\mu}_t) = B(t)' \hat{\text{Var}}(\hat{\beta}) B(t) \). This variance estimator can be used to construct a Wald confidence interval for \( \mu_t \), or it can be used within a bootstrap procedure to form a bootstrap-\( t \) confidence interval. Bootstrap-\( t \) confidence intervals are second-order accurate [Hall, 1988; DiCiccio and Efron, 1996] and therefore tend to have improved coverage compared to Wald intervals.

### 4.4 Estimation details and rates of convergence

Here we discuss the modeling choices for \( \lambda(t, \hat{O}(t)) \) and \( dF(y(t)|A(t) = 1, \hat{O}(t)) \) that we used in our analysis of the ARC data, and we show sufficient conditions under which the remainder term \( \sqrt{n} \text{Rem}(\hat{P}, P) \) is asymptotically negligible.

We modeled \( \lambda(t, \hat{O}(t)) \) using a stratified Andersen-Gill model [Andersen and Gill, 1982]:

\[
\lambda(t, \hat{O}(t)) = \lambda_{0,k}(t) \exp \{ \gamma Z(t) \} D_k(t)
\]

with stratification variable \( k = N(t-) \), the number of assessments that the participant had prior to time \( t \). Here \( \lambda_{0,k}(t) \) is an unspecified baseline intensity function for the \( k \)th assessment, \( Z(t) \) is a specified function of \( \hat{O}(t) \), \( \gamma \) is a vector of unknown parameters, and \( D_k(t) \) is the indicator that the participant is at risk for having the \( k \)th assessment at time \( t \). We estimated \( \gamma \) and the cumulative baseline intensity functions \( \lambda_{0,k}(t) = \int_{s=0}^{t} \lambda_{0,k}(s) ds \) for \( k = 1, \ldots, J \) (where \( J \) is the maximum possible number of assessments), using the partial likelihood estimator \( \hat{\gamma} \) of Cox [Cox, 1972; 1975] and the Breslow estimator \( \hat{\Lambda}_{0,k}(t) \) [Breslow, 1972]. Andersen and Gill [1982] derived the asymptotic distribution of \( \hat{\gamma} \) and \( \hat{\Lambda}_{0,k}(t) \) in the univariate \( (J = 1) \) setting. Andersen et al. [1985] generalized their results to multivariate counting processes with \( J > 1 \), such as our stratified model. (See also Cook and Lawless [2007] for more discussion of stratified models.) We then used kernel smoothing of \( \hat{\Lambda}_{0,k}(t) \) to estimate the baseline intensity \( \lambda_{0,k}(t) \) as \( \hat{\lambda}_{0,k}(t) = \frac{1}{h} \sum_j K \left( \frac{t - T_j}{h} \right) d\hat{\Lambda}_{0,k}(T_j) \), where \( h \) is a bandwidth, \( K(\ ) \) is a choice of kernel, \( T_j \) is a time at which one or more participants had their \( k \)th assessment, and \( d\hat{\Lambda}_{0,k}(T_j) \) is the size of the jump in \( \hat{\Lambda}_{0,k}(t) \) at \( T_j \). Ramlau-Hansen [1983] proposed this approach for kernel-smoothing the Nelson-Aalen estimator for a univariate counting process, and showed the large-sample distribution of the resulting estimator. [Andersen...
et al. (1985), Andersen et al. (1993), and Wells (1994) extended his results to multivariate versions of the Andersen-Gill model.

Let $\theta$ denote the parameters of the model for $dF(y(t)|A(t) = 1, \bar{O}(t))$. We modeled $dF(y(t)|A(t) = 1, \bar{O}(t); \theta)$ using a fully parametric model. The asymptotic behavior of the remainder term under these models is shown by the following theorem.

**Theorem 2.** Suppose that the following conditions hold:

1. The models for $\lambda(t, \bar{O}(t))$ and $dF(y(t)|A(t) = 1, \bar{O}(t); \theta)$ are correctly specified, and Assumptions 1, 2, and 3 hold.
2. $\lambda(t, \bar{O}(t))$ is modeled as in [3], $\gamma$ and $\lambda_{0,k}(t)$, $k = 1, \ldots, J$, are estimated as described above, and the bandwidth $h = h_n$ used for $\lambda_{0,k}(t)$ is chosen using a procedure such that $\lim_{n \to \infty} nh_n^5 = d$, for some constant $d$ with $0 < d < \infty$.
3. The model for $dF(y(t)|A(t) = 1, \bar{O}(t); \theta)$ and the estimator $\hat{\theta}$ are such that

   $$E \left[ \int_{t=a}^{b} \left\{ dF(y(t)|A(t) = 1, \bar{O}(t), \hat{\theta}) - dF(y(t)|A(t) = 1, \bar{O}(t), \theta) \right\}^2 \right] = o_p(n^{-1/2}).$$

4. There is some value $c > 0$ such that $\rho(t, Y(t), \bar{O}(t)) > c$ for all $t$ and all values of $Y(t)$ and $\bar{O}(t)$.

Then the remainder term $Rem(\hat{P}, P)$ in (4) is $o_p(n^{-1/2})$.

In particular, if a fully parametric model is used for $dF(y(t)|A(t) = 1, \bar{O}(t); \theta)$, then the expectation in (iii) is $O_p(n^{-1})$, and therefore (iii) is satisfied; and this also suggests that replacing a fully parametric model with a more flexible model may also be possible. The proof of Theorem 2 is given in Appendix C.

## 5 Selection of a range of sensitivity parameter values

The analyst must decide on a range of $\alpha$ values to include in the sensitivity analysis. Domain expertise should be used to make this decision; how best to use such expertise is a key question for all sensitivity analyses. Cinelli and Hazlett (2020) have noted that “perhaps [the] most fundamental obstacle to the use of sensitivity analysis is the difficulty in connecting the formal results to the researcher’s substantive understanding about the object under study,” and that the “bounding procedure we should use depends on which . . . quantities the investigator prefers and can most soundly reason about in their own research.”

In the context of sensitivity analysis for unmeasured confounding in observational studies, Cinelli and Hazlett (2020), Franks, D’Amour, and Feller (2020), and Veitch and Zaveri (2020) have proposed ways for using the strength of the impact of a key covariate or group of covariates $X_j$ given the remaining covariates $X_{-j}$ to obtain a posited bound on the strength of unmeasured confounders, and hence obtain bounds for the sensitivity parameters. However, this may not adapt well to our setting: the impact of any group of variables $Z(t)$ in the observed past on assessment at time $t$ may actually be weaker—by an amount that would not be known—than the impact of $Y(t)$ on assessment at time $t$ (after adjusting for the remaining variables in the observed past in each case).
Instead, we query domain experts for extreme values $\mu_{\min}$ and $\mu_{\max}$ such that, in their judgment, a mean outcome $E[Y(t)]$ outside of the bounds $(\mu_{\min}, \mu_{\max})$ at any time $t$ would be implausible. We then treat any $\alpha$ under which $E[Y(t)]$ falls outside of $(\mu_{\min}, \mu_{\max})$ for some $t$ as implausible and exclude such values from our sensitivity analysis. We do this separately for each treatment arm. This approach is aligned with Cinelli and Hazlett’s recommendation, as it is based on the treatment arm-specific mean outcome, a quantity about which subject matter experts can provide direct guidance.

6 Data analysis: ARC trial

In this study, participants in both the control and intervention groups received usual care plus access to and training in a web-based portal designed to improve communication between participants and their healthcare providers. Participants in the intervention group additionally received home visits by community health workers, during which the health workers created plans of action for asthma care and helped participants use the portal to schedule appointments and send messages to their doctors. The primary outcome was Asthma Control score, reflecting symptoms over the week prior to assessment on a scale from 0 (completely controlled) to 6 (extremely uncontrolled).

We used our proposed methodology to estimate the treatment-specific curves for mean Asthma Control score over the period from 60 to 460 days after randomization. The target assessment times of interest are 90, 180, 270, and 360 days. For each treatment, we assumed $E[Y(t)] = \beta' B(t)$, $60 \leq t \leq 460$, where $B(t)$ is a basis of cubic B-splines with one interior knot at $t = 260$ days. We modeled the intensity function $\lambda(t, O(t))$ using a stratified Andersen-Gill model (Andersen and Gill, 1982) as in (5), where the stratification variable was the number of previous assessments, and where the number of strata was $J = 4$. We took the predictor $Z(t)$ to be the outcome at the previous assessment. We then used kernel smoothing with an Epanechnikov kernel and a bandwidth of 30 days to estimate the baseline intensity function. For the outcome regression model, we used negative binomial regression, using current time, time of previous assessment, and outcome at the previous assessment as predictors.

We initially considered a range of $-0.6 \leq \alpha \leq 0.6$ for the sensitivity parameter in each arm. Figure 3 shows estimates of the curves $E[Y(t)], 60 \leq t \leq 460$, for each arm (upper panels), and estimates and 95% confidence intervals for the means at the targeted assessment times (lower panels). Confidence intervals are bootstrap-t confidence intervals based on $B = 500$ bootstrap resamples. Our clinical collaborator considered, for each treatment arm, a mean Asthma Control score of 3.0 or higher at any time, or a mean of 1.2 or lower at any time, as extreme. These bounds are shown in Figures 3. Based on this, $\alpha = 0.6$ is outside the range that should be considered for the intervention arm, while both $\alpha = 0.3$ and $\alpha = 0.6$ are implausible in the control arm. We therefore considered the ranges $-0.6 \leq \alpha \leq 0.55$ and $-0.6 \leq \alpha \leq 0.25$ for the intervention and control arms respectively.

Next we considered the difference of the mean outcome in the intervention arm minus the mean in the control arm at the targeted assessment times. Under the AAR assumption, the estimate and 95% bootstrap-t confidence interval for the treatment effect at 6 months are $-0.39 (-0.91, 0.13)$. The point estimate under the AAR assumption is consistent with the home visits intervention reducing (improving) mean Asthma Control at six months; however, the evidence is not strong enough to conclude that there is a nonzero treatment effect. For the treatment effect at 12 months, the estimate and confidence interval under the AAR assumption are $0.05 (-0.28, 0.38)$. Figure 3 shows the sensitivity analysis for these two treatment effects as we deviate from the AAR assumption.
Figure 3: Mean outcomes in the ARC trial under a range of sensitivity parameter values. Here we show inference for the mean Asthma Control score in the intervention (PT+HV) and control (PT) arm, under values of $\alpha = -0.6, -0.3, 0, 0.3, 0.6$. The upper panels show the estimated curves of mean Asthma Control scores at time $t$, for $t = 60$ to 460 days after randomization. The lower panels show estimates and 95% bootstrap-$t$ confidence intervals for the mean at each of the 4 target times. For each arm, only those values of $\alpha$ under which the mean falls between the dotted lines at $\mu_{\min} = 1.2$ and $\mu_{\max} = 3.0$ at all times are considered plausible based on subject-matter expertise.
Figure 4: Sensitivity analysis for the ARC trial. Here we present inference for the difference of the mean Asthma Control score in the intervention (PT+HV) arm minus the mean in the control (PT) arm at 6 months and at 12 months, under a range of different sensitivity parameter values $\alpha$ for each arm. Panels (a) and (c) show the point estimates for these treatment effects under the varying values of $\alpha$. Panels (b) and (d) give information about the confidence intervals: each white region corresponds to sensitivity parameter values for which the confidence interval contains zero. In the green regions in the lower right of these plots, confidence intervals are entirely negative, and the values shown are the upper bound of the confidence interval. In the orange regions in the upper left of these plots, confidence interval are entirely positive, and the values shown in these regions are the lower bound of the confidence interval.
in each treatment arm, within the range of \( \alpha \) values given above. In panels (b) and (d), the regions in white correspond to sensitivity parameter values under which the confidence interval contains zero. The green regions in the lower right of panels (b) and (d) correspond to values of \( \alpha \) under which the confidence intervals are entirely negative, i.e. for which there would be evidence that the intervention reduces the mean Asthma Control score; while the orange regions in the upper left correspond to values for which there would be evidence that the intervention raises the mean Asthma Control score.

7 Simulations

We assessed the finite-sample performance of our estimators in a realistic simulation study based on the ARC data. Simulations were conducted separately by treatment arm. To generate simulated data for participant \( i \), we drew their baseline outcome \( Y_i(0) \) from the empirical distribution of baseline outcomes in the ARC data, then iterated between generating times of subsequent assessments and outcomes at those assessment times. Given their \( k \)th assessment time \( T_{i,k} \) and outcome \( Y_i(T_{i,k}) \), we generated participant \( i \)'s \((k + 1)\)st assessment time \( T_{i,k+1} \) using Ogata’s Thinning Algorithm [Ogata 1981] as follows:

1. Set \( \lambda^* \) to be a value that is greater than or equal to \( \sup \{ \hat{\lambda}_{0,k}(t) \exp\{\hat{\gamma} Y_i(T_{i,k})\} : t \in [0, \tau]\} \), where \( \hat{\lambda}_{0,k}(t) \) and \( \hat{\gamma} \) are the estimates from the stratified Andersen-Gill model that we fit on the ARC data.
2. Take the start time to be \( T_{ik} \).
3. Draw a potential gap time \( s^* \sim \exp(\lambda^*) \), and set \( t^* := \text{start time} + s^* \). Accept the candidate assessment time \( t^* \) with probability \( \hat{\lambda}_{0,k}(t^*) \exp\{\hat{\gamma} Y_i(T_{i,k})\}/\lambda^* \).
4. If \( t^* \) is accepted, set \( T_{i,k+1} := t^* \). If \( t^* \) is rejected, set the new start time to be \( t^* \) and return to step 3. Iterate until a time \( t^* \) is accepted, or until \( t^* > \tau \), in which case \( T_{ik} \) was participant \( i \)'s final assessment time.

After \( T_{i,k+1} \) was generated, we obtained the predicted distribution \( d\hat{F}(y(T_{i,k+1})|A(T_{i,k+1}) = 1, \bar{O}_i(T_{i,k+1})) \) based on the model for \( dF(y(t)|A(t) = 1, \bar{O}(t)) \) that we fit on the ARC data (Section 6), then drew an outcome \( Y_i(T_{i,k+1}) \) based on this predicted distribution.

We computed the true value of \( \beta \) using the identification formula \( \beta = \int_{t=a}^{b} V^{-1} B(t) E[Y(t)] dt \) (Proposition 3), under values of \( \alpha = -0.6, -0.3, 0, 0.3, 0.6 \). We simulated a large sample of \( N = 2,500,000 \) participants. For each time \( t \), we obtained the predicted value of \( E[Y(t)|\bar{O}_i(t)] \) for each participant, using Proposition 3 the model for \( dF(y(t)|A(t) = 1, \bar{O}(t)) \) that we fit on the ARC data, and the given \( \alpha \) value, then used the approximation \( E[Y(t)|\bar{O}_i(t)] \approx \frac{1}{N} \sum_{i=1}^{N} \hat{E}[Y(t)|\bar{O}_i(t)] \). We approximated the integral using intervals of one day. This value of \( \beta \) corresponds to the projection of the true curve of means onto spline curves of the form \( \beta^*B(t) \).

We simulated data with a sample size of \( n = 200 \) for each treatment arm. We analyzed the simulated data using the true value of \( \alpha \) in each case. For each scenario, we evaluated our estimation approach in terms of empirical bias and confidence interval coverage probabilities across 500 simulations. We considered bootstrap-\( t \) intervals, bootstrap percentile intervals, and Wald intervals, with the bootstrap intervals based on \( B = 500 \) bootstrap replications per simulated dataset. Results are shown in Tables 1 and 2. Bias was close to zero. As expected, better coverage was generally
Table 1: Control arm simulation results. Shown are the true values of the four target parameters under each of five different data-generating mechanisms that mimic the control arm of the ARC data with $\alpha = -0.6, -0.3, 0, 0.3, 0.6$; the empirical mean and absolute value of the empirical bias of the estimators across 500 simulations; and the coverage of bootstrap-$t$, bootstrap percentile, and Wald confidence intervals.
Table 2: Treatment arm simulation results. Shown are the true values of the four target parameters under each of five different data-generating mechanisms that mimic the treatment arm of the ARC data with $\alpha = -0.6, -0.3, 0, 0.3, 0.6$; the empirical mean and absolute value of the empirical bias of the estimators across 500 simulations; and the coverage of bootstrap-$t$, bootstrap percentile, and Wald confidence intervals.
obtained with the bootstrap-t confidence intervals than with the bootstrap percentile intervals or the Wald intervals. While the bootstrap-t coverage was close to the nominal level in many cases, it undercovered in some situations, particularly those with large values of $\alpha$. Bias and coverage under $\alpha = 0.6$ both improved at a larger sample size of $n = 1,000$ (results not shown).

8 Discussion

In this paper, we addressed how to analyze randomized trials in which there is variability in assessment times, which are potentially related to the outcome under investigation. We developed a sensitivity analysis anchored around the assessment at random (AAR) assumption, in which flexible, semi-parametric estimation is used to compare inference across a family of assumptions which includes AAR as a special case. The family of assumptions is specified by the analyst, in consultation with domain experts, through their choice(s) of form for the tilting function and range of sensitivity analysis parameters ($\alpha$). Our approach can be used with any functional form and any dimension for $\alpha$; however, we recommend using a one- or two-dimensional $\alpha$ to facilitate presentation of results. Our method provides researchers with a tool showing how inference is impacted as $\alpha$ varies, providing a more informative picture than a single estimate made under AAR. Our approach does not evaluate all possible alternatives to AAR, and so the true distribution may not lie within the family of assumptions chosen by the analyst; and this is not testable from the observed data. Nevertheless, our sensitivity analysis still provides important information about whether inferences are robust or sensitive to deviations from AAR, which can strengthen evidence from trials.

Our method produces estimates for the curve of means on a chosen time interval $[a, b]$, from which the mean at any time of interest within the interval can be obtained. It can be applied in longitudinal trials as we have done here, and it could also be used with a trial with only one post-baseline assessment. In some longitudinal trials, there may be substantial separation in the distribution of assessment times—for example, if there is an appreciable lapse between the end of the first-assessment times and the beginning of the second-assessment times. In this case it may be best to treat each assessment separately, rather than making inference over a period which includes time intervals where there is no data.

Our methodology relies on pre-specification of a spline basis on the interval $[a, b]$ for the treatment-specific mean outcome as a function of time. Using a pre-specified basis, we obtained $\sqrt{n}$-rates of convergence for our estimator of the spline parameters. An interesting direction for future research is the development of a data-adaptive method for choosing the spline basis, while still yielding $\sqrt{n}$ rates. While we derived the influence function for parameters of the spline basis under a general link function (see Theorem 1), our estimation procedure and associated $\sqrt{n}$-asymptotic results were focused on the identity link. Extension to non-linear link functions should follow using ideas in [van der Vaart] (1998), with appropriate modification to the remainder term.

Acknowledgements

The authors thank Eleanor Pullenayegum for helpful discussions. Daniel Scharfstein’s research was partially supported by NIH R01DA046534. Shu Yang’s research is partially supported by NSF DMS 1811245, and by NIH 1R01AG066883 and 1R01ES031651. The ARC study was funded through a Patient-Centered Outcomes Research Institute (PCORI) award (AS-1307-05218).
References

P. K. Andersen and R. D. Gill. Cox’s regression model for counting processes: A large sample study. *The Annals of Statistics*, 10(4):1100 – 1120, 1982. doi: 10.1214/aos/1176345976. URL https://doi.org/10.1214/aos/1176345976.

Per Kragh Andersen, Ørnulf Borgan, Nils Lid Hjort, Elja Arjas, Jon Stene, and Odd Aalen. Counting process models for life history data: A review [with discussion and reply]. *Scandinavian Journal of Statistics*, 12(2):97–158, 1985. ISSN 03036898, 14679469. URL http://www.jstor.org/stable/4615980.

Per Kragh Andersen, Ørnulf Borgan, Richard D. Gill, and Niels Keiding. *Statistical models based on counting processes*. Springer-Verlag, New York, 1993.

Andrea J. Apter, A. Russell Localio, Knashawn H. Morales, Xiaoyan Han, Luzmercy Perez, Alyssa N. Mullen, Marisa Rogers, Heather Klusaritz, John T. Howell, Maryori N. Canales, and Tyra Bryant-Stephens. Home visits for uncontrolled asthma among low-income adults with patient portal access. *Journal of Allergy and Clinical Immunology*, 144(3):846–853.e11, 2019.

O. E. Barndorff-Nielsen and D. R. Cox. *Inference and Asymptotics*. Chapman and Hall, 1994.

Jolene Birmingham, Andrea Rotnitzky, and Garrett M. Fitzmaurice. Pattern–mixture and selection models for analysing longitudinal data with monotone missing patterns. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 65(1):275–297, 2003. doi: https://doi.org/10.1111/1467-9868.00386. URL https://rss.onlinelibrary.wiley.com/doi/abs/10.1111/1467-9868.00386.

Norman E. Breslow. Discussion on Professor Cox’s paper. *Journal of the Royal Statistical Society: Series B (Methodological)*, 34(2):216–217, 1972.

Petra Bůžková and Thomas Lumley. Longitudinal data analysis for generalized linear models with follow-up dependent on outcome-related variables. *The Canadian Journal of Statistics / La Revue Canadienne de Statistique*, 35(4):485–500, 2007. ISSN 03195724. URL http://www.jstor.org/stable/20445273.

Na Cai, Wenbin Lu, and Hao Helen Zhang. Time-varying latent effect model for longitudinal data with informative observation times. *Biometrics*, 68(4):1093–1102, 2012. doi: https://doi.org/10.1111/j.1541-0420.2012.01794.x. URL https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1541-0420.2012.01794.x.

Carlos Cinelli and Chad Hazlett. Making sense of sensitivity: extending omitted variable bias. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 82(1):39–67, 2020. doi: https://doi.org/10.1111/rssb.12348. URL https://rss.onlinelibrary.wiley.com/doi/abs/10.1111/rssb.12348.

Richard J. Cook and Jerald Lawless. *The statistical analysis of recurrent events*. Springer, New York, 2007.

D. R. Cox. Regression models and life-tables. *Journal of the Royal Statistical Society: Series B (Methodological)*, 34(2):187–202, 1972. doi: https://doi.org/10.1111/j.2517-6161.1972.
D.R. Cox. Partial likelihood. *Biometrika*, 62(2):269–276, 1975.

Iván Díaz Muñoz and Mark J. van der Laan. Super learner based conditional density estimation with application to marginal structural models. *The International Journal of Biostatistics*, 7(1), 2011. doi: 10.2202/1557-4679.1356.

Thomas J. DiCiccio and Bradley Efron. Bootstrap confidence intervals. *Statistical Science*, 11(3):189 – 228, 1996. doi: 10.1214/ss/1032280214.

Alexander M. Franks, Alexander D’Amour, and Avi Feller. Flexible sensitivity analysis for observational studies without observable implications. *Journal of the American Statistical Association*, 115(532):1730–1746, 2020. doi: 10.1080/01621459.2019.1604369.

Peter Hall. Theoretical comparison of bootstrap confidence intervals. *The Annals of Statistics*, 16(3):927 – 953, 1988. doi: 10.1214/aos/1176350933.

Edward H. Kennedy. Semiparametric theory and empirical processes in causal inference. In Hua He, Pan Wu, and Ding-Geng (Din) Chen, editors, *Statistical Causal Inferences and Their Applications in Public Health Research*, ICSA Book Series in Statistics, pages 141–167. Springer International Publishing, Cham, 2016. ISBN 978-3-319-41259-7.

Yu Liang, Wenbin Lu, and Zhiliang Ying. Joint modeling and analysis of longitudinal data with informative observation times. *Biometrics*, 65(2):377–384, 2009. doi: 10.1111/j.1541-0420.2008.01104.x.

D. Y Lin and Z Ying. Semiparametric and nonparametric regression analysis of longitudinal data. *Journal of the American Statistical Association*, 96(453):103–126, 2001. doi: 10.1198/016214501750333018.

Haiqun Lin, Daniel O. Scharfstein, and Robert A. Rosenheck. Analysis of longitudinal data with irregular, outcome-dependent follow-up. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 66(3):791–813, 2004. doi: 10.1111/j.1467-9868.2004.b5543.x.

Stuart R. Lipsitz, Garrett M. Fitzmaurice, Joseph G. Ibrahim, Richard Gelber, and Steven Lipschultz. Parameter estimation in longitudinal studies with outcome-dependent follow-up. *Biometrics*, 58(3):621–630, 2002. doi: 10.1111/j.0006-341X.2002.00621.x.

Ashley I Naimi, Alan E Mishler, and Edward H Kennedy. Challenges in obtaining valid causal effect estimates with machine learning algorithms. *American Journal of Epidemiology*, 07 2021. ISSN 0002-9262. doi: 10.1093/aje/kwab201.
National Research Council. *The Prevention and Treatment of Missing Data in Clinical Trials*. The National Academies Press, Washington, DC, 2010. ISBN 978-0-309-15814-5. doi: 10.17226/12955. URL [https://www.nap.edu/catalog/12955/the-prevention-and-treatment-of-missing-data-in-clinical-trials](https://www.nap.edu/catalog/12955/the-prevention-and-treatment-of-missing-data-in-clinical-trials).

Y. Ogata. On Lewis’ simulation method for point processes. *IEEE Transactions on Information Theory*, 27(1):23–31, 1981. doi: 10.1109/TIT.1981.1056305.

Eleanor M. Pullenayegum. Multiple outputation for the analysis of longitudinal data subject to irregular observation. *Statistics in Medicine*, 35(11):1800–1818, 2016. doi: https://doi.org/10.1002/sim.6829. URL [https://onlinelibrary.wiley.com/doi/abs/10.1002/sim.6829](https://onlinelibrary.wiley.com/doi/abs/10.1002/sim.6829).

Eleanor M. Pullenayegum and Brian M. Feldman. Doubly robust estimation, optimally truncated inverse-intensity weighting and increment-based methods for the analysis of irregularly observed longitudinal data. *Statistics in Medicine*, 32(6):1054–1072, 2013. doi: 10.1002/sim.5640. URL [https://onlinelibrary.wiley.com/doi/abs/10.1002/sim.5640](https://onlinelibrary.wiley.com/doi/abs/10.1002/sim.5640).

Eleanor M. Pullenayegum and Daniel O. Scharfstein. Randomized trials with repeatedly measured outcomes: handling irregular and potentially informative assessment times. (In press).

Henrik Ramlau-Hansen. Smoothing counting process intensities by means of kernel functions. *The Annals of Statistics*, 11(2):453–466, 1983. ISSN 0090-5364. URL [http://www.jstor.org/stable/2240560](http://www.jstor.org/stable/2240560).

Andrea Rotnitzky, Daniel Scharfstein, Ting-Li Su, and James Robins. Methods for conducting sensitivity analysis of trials with potentially nonignorable competing causes of censoring. *Biometrics*, 57(1):103–113, 2001. doi: https://doi.org/10.1111/j.0006-341X.2001.00103.x. URL [https://onlinelibrary.wiley.com/doi/abs/10.1111/j.0006-341X.2001.00103.x](https://onlinelibrary.wiley.com/doi/abs/10.1111/j.0006-341X.2001.00103.x).

Daniel O. Scharfstein and Aidan McDermott. Global sensitivity analysis of clinical trials with missing patient-reported outcomes. *Statistical Methods in Medical Research*, 28(5):1439–1456, 2019. doi: 10.1177/0962280218759565. PMID: 29557705. URL [https://doi.org/10.1177/0962280218759565](https://doi.org/10.1177/0962280218759565).

Daniel O. Scharfstein, Andrea Rotnitzky, and James M. Robins. Adjusting for nonignorable dropout using semiparametric nonresponse models. *Journal of the American Statistical Association*, 94(448):1096–1120, 1999. doi: 10.1080/01621459.1999.10473862. URL [https://www.tandfonline.com/doi/abs/10.1080/01621459.1999.10473862](https://www.tandfonline.com/doi/abs/10.1080/01621459.1999.10473862).

Liuquan Sun, Xinyuan Song, Jie Zhou, and Lei Liu. Joint analysis of longitudinal data with informative observation times and a dependent terminal event. *Journal of the American Statistical Association*, 107(498):688–700, 2012. doi: 10.1080/01621459.2012.682528. URL [https://doi.org/10.1080/01621459.2012.682528](https://doi.org/10.1080/01621459.2012.682528).

Xiaoyan Sun, Limin Peng, Amita Manatunga, and Michele Marcus. Quantile regression analysis of censored longitudinal data with irregular outcome-dependent follow-up. *Biometrics*, 72(1):64–73, 2016. doi: https://doi.org/10.1111/biom.12367. URL [https://onlinelibrary.wiley.com/doi/abs/10.1111/biom.12367](https://onlinelibrary.wiley.com/doi/abs/10.1111/biom.12367).

Anastasios A. Tsiatis. *Semiparametric Theory and Missing Data*. Springer, New York, 2006.
A. W. van der Vaart. *Asymptotic Statistics*. Cambridge Series in Statistical and Probabilistic Mathematics. Cambridge University Press, 1998. doi: 10.1017/CBO9780511802256.

Stijn Vansteelandt, Andrea Rotnitzky, and James Robins. Estimation of regression models for the mean of repeated outcomes under nonignorable nonmonotone nonresponse. *Biometrika*, 94(4):841–860, 11 2007. ISSN 0006-3444. doi: 10.1093/biomet/asm070. URL https://doi.org/10.1093/biomet/asm070

Victor Veitch and Anisha Zaveri. Sense and sensitivity analysis: Simple post-hoc analysis of bias due to unobserved confounding. In H. Larochelle, M. Ranzato, R. Hadsell, M. F. Balcan, and H. Lin, editors, *Advances in Neural Information Processing Systems*, volume 33, pages 10999–11009. Curran Associates, Inc., 2020. URL https://proceedings.neurips.cc/paper/2020/file/7d265aa7147bd3913fb84c7963a209d1-Paper.pdf

Zebin Wang. Global sensitivity analysis for randomized trials with informative assessment times: A fully parametric approach. Master’s thesis, Johns Hopkins University, 2020.

Martin T. Wells. Nonparametric kernel estimation in counting processes with explanatory variables. *Biometrika*, 81(4):795–801, 12 1994. ISSN 0006-3444. doi: 10.1093/biomet/81.4.795. URL https://doi.org/10.1093/biomet/81.4.795

**Appendix A: Intensity functions**

Let \( \{F_t\}_{t=0}^\tau \) be the filtration defined by \( F_t = (Y(0), \{Y(u) : A(u) = 1, a \leq u \leq t\}, \{N(u) : a \leq u \leq t\}) \). Here \( F_t \) is the observed past up through time \( t \), and \( F_t = \bar{O}(t) \) is the observed past prior to, but not including, time \( t \). The intensity function \( \lambda(t, \bar{O}(t)) \) is the intensity for the counting process \( \{N(t)\}_{t=0}^\tau \) with respect to the filtration \( \{F_t\}_{t=0}^\tau \). Additionally, let \( L = \{Y(t) : 0 \leq t \leq \tau\} \) and \( \{G_t\}_{t=0}^\tau \) be the filtration defined by \( G_t = (L, \{N(u) : a \leq u \leq t\}) = (L, F_t) \). Under Assumption 2, \( \rho(t, Y(t), \bar{O}(t)) \) is the intensity function for \( \{N(t)\}_{t=0}^\tau \) with respect to the filtration \( \{G_t\}_{t=0}^\tau \).

**Proof of Proposition 2:**

Proof. Fix a time \( t \) and a value \( y(t) \), and for each \( \epsilon > 0 \) let:

\[
A_\epsilon := dF(y(t)|A[t, t+\epsilon] = 0, \bar{O}(t))
\]

\[
B_\epsilon := dF(y(t)|A[t, t+\epsilon] = 1, \bar{O}(t)) \frac{\exp\{q(y(t), \bar{O}(t); \alpha)\}}{E[\exp\{q(Y(t), \bar{O}(t); \alpha)\}|A[t, t+\epsilon] = 1, \bar{O}(t)]}.
\]

For each \( \epsilon > 0 \), by Bayes rule we have:

\[
P(A[t, t+\epsilon] = 1|Y(t) = y(t), \bar{O}(t)) = \frac{P(A[t, t+\epsilon] = 1|\bar{O}(t))dF(y(t)|A[t, t+\epsilon] = 1, \bar{O}(t))}{P(A[t, t+\epsilon] = 1|\bar{O}(t))dF(y(t)|A[t, t+\epsilon] = 1, \bar{O}(t)) + P(A[t, t+\epsilon] = 0|\bar{O}(t))A_\epsilon}
\]

\[
= \frac{P(A[t, t+\epsilon] = 1|\bar{O}(t))}{P(A[t, t+\epsilon] = 1|O(t)) + P(A[t, t+\epsilon] = 0|O(t))D_\epsilon},
\]

(6)
for $D_\epsilon := A_\epsilon/dF(y(t)|A[t, t+\epsilon] = 1, \tilde{O}(t))$. Dividing each side of (6) by $\epsilon$ and taking the limit as $\epsilon \to 0^+$ gives:

$$
\lim_{\epsilon \to 0^+} \frac{P(A[t, t+\epsilon] = 1|Y(t) = y(t), \tilde{O}(t))}{\epsilon} = \left( \lim_{\epsilon \to 0^+} \frac{P(A[t, t+\epsilon] = 1|\tilde{O}(t))}{\epsilon} \right) / \left( \lim_{\epsilon \to 0^+} P(A[t, t+\epsilon] = 0|\tilde{O}(t)) \right) D_\epsilon.
$$

The left hand side of (7) equals $\rho(t, Y(t), \tilde{O}(t))$, while the numerator of the right hand side equals $\lambda(t, \tilde{O}(t))$. In the denominator, write:

$$
D_\epsilon = \frac{B_\epsilon}{dF(y(t)|A[t, t+\epsilon] = 0, \tilde{O}(t))} + \frac{A_\epsilon - B_\epsilon}{dF(y(t)|A[t, t+\epsilon] = 1, \tilde{O}(t))} = \frac{\exp\{q(y(t), \tilde{O}(t); \alpha)\}}{E[\exp\{q(Y(t), \tilde{O}(t); \alpha)\}; A(t) = 1, \tilde{O}(t)]} + \frac{A_\epsilon - B_\epsilon}{dF(y(t)|A[t, t+\epsilon] = 1, \tilde{O}(t))},
$$

and note that:

$$
\lim_{\epsilon \to 0^+} (A_\epsilon - B_\epsilon) = \frac{dF(y(t)|A(t) = 0, \tilde{O}(t))}{dF(y(t)|A(t) = 1, \tilde{O}(t))} \exp\{q(y(t), \tilde{O}(t); \alpha)\} E[\exp\{q(Y(t), \tilde{O}(t); \alpha)\}; A(t) = 1, \tilde{O}(t)] = 0
$$

by Assumption 1. Therefore, the denominator in (7) is equal to:

$$
0 + 1 \times \left( \frac{\exp\{q(y(t), \tilde{O}(t); \alpha)\}}{E[\exp\{q(Y(t), \tilde{O}(t); \alpha)\}; A(t) = 1, \tilde{O}(t)]} + 0 \right),
$$

which gives the result.

\[\square\]

### Appendix B: Influence function derivation

In this appendix we prove Theorem 1 using the semi-parametric theory presented in [Scharfstein et al. (1999)](https://example.com) and [Tsiatis (2006)](https://example.com). We first briefly review elements of this theory applied to our context.

We will refer here to $L = \{Y(t) : 0 \leq t \leq \tau\}$ as the full data. We write $R = \{N(t) : a \leq t \leq \tau\}$, and we refer to $Z = (L, R)$ as the total data. Let $H^L$, $H^O$, and $H^Z$ be the Hilbert spaces of mean-zero, finite-variance, $p$-dimensional functions of the full, observed, and total data respectively, with the covariance inner product. Full-data influence functions are normalized elements of the orthogonal complement of the full-data nuisance tangent space $\Lambda(F_L)$. Observed data influence functions are normalized elements of $\Lambda^O \perp = \Lambda^O_1 \cap \Lambda^O_2 \perp$, where $\Lambda^O_1$ is the image of $\Lambda(F_L)$, and $\Lambda^O_2$ is the image of the coarsening nuisance tangent space $\Lambda(F_{R(L)})$, under the map $A : H^Z \to H^O$.
given by \( A(\cdot) = E[\cdot | \mathcal{O}] \). Therefore, the orthogonal complement \( \Lambda^O_1 \) is equal to the null space of the adjoint of the map \( A_1 : \Lambda(F_L) \rightarrow \mathcal{H}^O \) given by \( A_1(\cdot) = E[\cdot | \mathcal{O}] \), and similarly \( \Lambda_2 \) is the null space of the adjoint of the map \( A_2 : \Lambda(F_{RL}) \rightarrow \mathcal{H}^O \) given by \( A_2(\cdot) = E[\cdot | \mathcal{O}] \). The adjoint of \( A_1 \) is the map \( A_1^* : \mathcal{H}^O \rightarrow \Lambda(F_L) \) given by \( A_1^*(\cdot) = \Pi( E[\cdot | \Lambda(L)] \cdot \Lambda(L) ) \). Therefore, \( \Lambda^O_2 = \{ h(O) \in \mathcal{H}^O : K(g(O)) \in \Lambda(F_L)^\perp \} \), where \( K : \mathcal{H}^O \rightarrow \mathcal{H}^L \) is the map defined by \( K(g(O)) = E[g(O)]|L[\cdot] \).

Again using adjoints, \( \Lambda_2^O = \{ g(O) \in \mathcal{H}^O : g(O) \in \Lambda(F_{RL})^\perp \} = \mathcal{H}^O \cap \Lambda(F_{RL})^\perp \), and therefore, \( \Lambda^O = \Lambda_1^O \cap \Lambda(F_{RL})^\perp \).

Based on this theory, we use the following procedure to derive an observed-data influence function: We first derive a full-data influence function \( \varphi(L) \). We then obtain elements of \( \Lambda^O_1 \) by inverse-weighting \( \varphi(L) \) and adding elements of the augmentation space (defined below). We then identify an element \( h(O) \) of this form which is also orthogonal to \( \Lambda(F_{RL}) \). By the above theory, \( h(O) \) is in the space \( \Lambda^O \). Furthermore, \( h(O) \) inherits the property of being correctly normalized from \( \varphi(L) \), and therefore \( h(O) \) is an observed data influence function.

**Proof of Theorem 1.**

**i. A full-data influence function.** We obtain a full-data influence function for \( \beta \) following the approach of Díaz Muñoz and van der Laan (2011). We begin by considering the nonparametric model on \( L \) that does not make Assumption 3. We consider a squared-error loss function for the loss incurred from approximating the curve \( \ell(Y(t)) \), \( a \leq t \leq b \), using a smooth function of the form \( s(aB(t)) \), for specified \( s(\cdot) \) and \( B(t) \), for some parameter \( \gamma \in \mathbb{R}^p \). We define the parameter \( \gamma_0 \) to be the minimizer of this squared-error loss function:

\[
\gamma_0 := \arg\min_{\gamma} \left\{ \int_{t=a}^b \left( E[Y(t)] - s(\gamma'B(t)) \right)^2 dt \right\},
\]

or equivalently, as the solution of the following system of equations:

\[
\int_{t=a}^b \left\{ \left( E[Y(t)] - s(\gamma'B(t)) \right) \frac{\partial}{\partial \gamma} s(\gamma'B(t)) \right\} dt = 0. \tag{8}
\]

Below we compute the influence function for \( \gamma_0 \) in the nonparametric model, which we denote by \( \varphi^{NP}(L; \gamma_0) \). Since the nonparametric model is a supermodel of our model, \( \varphi^{NP}(L; \gamma_0) \) is also a full-data influence function for \( \gamma_0 \) in our model. If Assumption 3 does hold, then the minimizer of the squared-error loss function is the value for which the loss is zero, i.e. in this case \( \gamma_0 = \beta \). Therefore, \( \varphi^{NP}(L; \gamma_0) \) is also a valid full-data influence function for \( \beta \) in our model.

Let \( \mathcal{P} \) be any parametric submodel (parametrized by \( \epsilon \) such that \( \epsilon = 0 \) corresponds to the true distribution of \( L \)) and let \( a(L) \) denote the score vector for \( \mathcal{P} \). The influence function for \( \gamma_0 \) is the mean-zero, \( p \)-dimensional function of \( L \) satisfying:

\[
\frac{\partial}{\partial \epsilon} \bigg|_{\epsilon=0} E[\varphi^{NP}(L; \gamma_0) a(L)] = E[\varphi^{NP}(L; \gamma_0) a(L)].
\]

For a fixed \( a(L) \), we consider the parametric submodel \( \mathcal{P}_a = \{ P_a(\epsilon) : \epsilon \in D \subset \mathbb{R} \} \), where \( P_a(\epsilon) = dF_0(L)(1 + \epsilon a(L)) \), and where the score of \( P_a(\epsilon) \) evaluated at \( \epsilon = 0 \) is \( a(L) \). In \( \mathcal{P}_a \), equation (8) becomes:

\[
\int_{t=a}^b \left\{ \left( \int_{\ell} y(t) dF_0(\ell)(1 + \epsilon a(\ell)) - s(\gamma(\epsilon)B(t)) \right) \frac{\partial}{\partial \gamma} s(\gamma(\epsilon)B(t)) \right\} dt = 0.
\]

24
Taking the derivative with respect to $\epsilon$ gives:

\[
\int_{t=a}^{b} \left\{ \left( \int_{t} y(t) \, dF_0(t)a(t) - \frac{\partial}{\partial \gamma} s(\gamma(t)B(t)) \frac{\partial \gamma}{\partial \epsilon} \right) \left( \frac{\partial}{\partial \gamma} s(\gamma(t)B(t)) \right) + \left( \int_{t} y(t) \, dF_0(t)(1 + \epsilon \, a(t) - s(\gamma(t)B(t))) \right) \left( \frac{\partial^2}{\partial \gamma \partial \gamma'} s(\gamma(t)B(t)) \frac{\partial \gamma}{\partial \epsilon} \right) \right\} \, dt = 0.
\]

Setting $\epsilon = 0$ gives:

\[
\int_{t=a}^{b} \left\{ E[Y(t)a(L)] \frac{\partial}{\partial \gamma} s(\gamma_0 B(t)) \right\} \, dt = \left( \int_{t=a}^{b} \left\{ \frac{\partial}{\partial \gamma} s(\gamma_0 B(t)) \frac{\partial \gamma}{\partial \epsilon} \right\} \left( E[Y(t)] - s(\gamma_0 B(t)) \right) \right) \, dt \times \left. \frac{\partial \gamma}{\partial \epsilon} \right|_{\epsilon=0}
\]

Solving for $\frac{\partial \gamma}{\partial \epsilon} \big|_{\epsilon=0}$ and writing: $V(\gamma_0) =$

\[
\int_{t=a}^{b} \left\{ \frac{\partial}{\partial \gamma} s(\gamma_0 B(t)) \frac{\partial}{\partial \gamma'} s(\gamma_0 B(t)) - \frac{\partial^2}{\partial \gamma \partial \gamma'} s(\gamma_0 B(t)) \left( E[Y(t)] - s(\gamma_0 B(t)) \right) \right\} \, dt,
\]

we have:

\[
\frac{\partial \gamma}{\partial \epsilon} \big|_{\epsilon=0} = V(\gamma_0)^{-1} \int_{t=a}^{b} \left\{ E[Y(t)a(L)] \frac{\partial}{\partial \gamma} s(\gamma_0 B(t)) \right\} \, dt
\]

\[
= E \left[ \left( \int_{t=a}^{b} \left\{ V(\gamma_0)^{-1} \left( Y(t) - E[Y(t)] \right) \frac{\partial}{\partial \gamma} s(\gamma_0 B(t)) \right\} \, dt \right) a(L) \right]
\]

Therefore:

\[
\varphi^{NP}(L; \gamma_0) = \int_{t=a}^{b} \left\{ V(\gamma_0)^{-1} \left( Y(t) - E[Y(t)] \right) \frac{\partial}{\partial \gamma} s(\gamma_0 B(t)) \right\} \, dt.
\]

Now making Assumption 3, $\varphi^{NP}(L; \gamma_0)$ simplifies as:

\[
\varphi(L) = \int_{t=a}^{b} \left\{ V(\beta)^{-1} \left( Y(t) - s(\beta B(t)) \right) \frac{\partial}{\partial \beta} s(\beta B(t)) \right\} \, dt
\]

where

\[
V(\beta) = \int_{t=a}^{b} \left\{ \frac{\partial}{\partial \beta} s(\beta B(t)) \frac{\partial}{\partial \beta} s(\beta B(t)) \right\} \, dt.
\] (9)

ii. An inverse-weighted element and the augmentation space. Next we find an element $g^*(O) \in \mathcal{H}^D$ which maps to $\varphi(L)$ under the map $K$. One such element is the following inverse-weighted element:

\[
g^*(O) := \int_{t=a}^{b} \left\{ \frac{dN(t)}{p(t, Y(t), O(t))} V(\beta)^{-1} \left( Y(t) - s(\beta B(t)) \right) \frac{\partial}{\partial \beta} s(\beta B(t)) \right\}, \quad (10)
\]

25
as we verify below. To show this, we will make use of a counting process martingale whose properties we will exploit throughout this appendix. Define $M(t) := N(t) - \int_a^b \rho(u, Y(u), \bar{O}(t)) du$. Then \( \{M(t)\}_{t=0}^T \) is a martingale adapted to the filtration \( \{G_t\}_{t=0}^T \) defined in Web Appendix A. Now let $H(t)$ be any predictable process; a sufficient condition for this is that $H(t)$ is left continuous in $t$, and that for each $t$, $H(t)$ is $G_t$-measurable. In particular, $H(t)$ could be any function of random variables in $\bar{O}(t)$ and of $Y(t)$, since we assume that $Y(t)$ is left continuous. Then $U(t) := \int_a^b H(u) dM(u)$ is also a martingale adapted to \( \{G_t\}_{t=0}^T \), and therefore $E[U(t) \mid G_a] = U(s)$ for all $s < t$. In particular, $U(t)$ has mean zero and, since $G_a = L$:

$$E \left[ \int_a^t H(u)dM(u) \mid L \right] = E[U(t) \mid G_a] = U(a) = 0. \tag{11}$$

Therefore, by (11)

$$E[g^*(O) \mid L] = E \left[ \int_a^b \frac{V(\beta)^{-1}(Y(t) - s(\beta'B(t)))}{\rho(t, Y(t), \bar{O}(t))} \frac{\partial}{\partial \beta} s(\beta'B(t)) \left( dN(t) - \rho(t, Y(t), \bar{O}(t)) dt \right) \right] L$$

$$+ E \left[ \int_a^b \left\{ V(\beta)^{-1}(Y(t) - s(\beta'B(t))) \frac{\partial}{\partial \beta} s(\beta'B(t)) \right\} dt \right] L$$

$$= 0 + \int_a^b \left\{ V(\beta)^{-1}(Y(t) - s(\beta'B(t))) \frac{\partial}{\partial \beta} s(\beta'B(t)) \right\} dt = \varphi(L)$$

as claimed. The inverse-weighted element $g^*(O)$ and the augmentation space $Aug := \{ g(O) \in \mathcal{H}^O : E[g(O) \mid L] = 0 \}$ determine the space $\Lambda_1^{0,+}$, and $\Lambda_1^{0,+} = \{ g^*(O) + h^*(O) : h^*(O) \in Aug \}$. By (11), a subset of $Aug$ is given by:

$$\tilde{Aug} := \left\{ \left( \int_a^b h(t, Y(t), \bar{O}(t)) \left[ dN(t) - \rho(t, Y(t), \bar{O}(t)) dt \right] \right) : \text{any } h(t, Y(t), \bar{O}(t)) \right\}.$$

### iii. The coarsening tangent space.

The coarsening tangent space $\Lambda(F_{R/L})$ is the set of all elements of $\mathcal{H}^Z$ that are linear combinations of scores of $R/L$ in a parametric submodel of our model. Following Cook and Lawless (2007), we can compute the likelihood for $R/L$ by first partitioning the interval $[a, b]$ into a finite number of subintervals $[t_k, t_k + \epsilon)$, $k = 0, \ldots, K$, each of length $\epsilon$, and then taking the limit as $K \to \infty$. Let $\Delta(t_k)$ denote the number of visits during the interval $[t_k, t_k + \epsilon)$; for small $\epsilon$, this number of visits is assumed to be 0 or 1. For fixed $K$, the conditional (on $L$) likelihood of $R = (N(t_0), \ldots, N(t_K))$ is the same as the conditional (on $L$) likelihood of $(\Delta(t_0), \ldots, \Delta(t_K))$, which can be written as:

$$P(\Delta(t_0) \mid L) \prod_{k=1}^K P(\Delta(t_k) \mid \Delta(t_0), \ldots, \Delta(t_{k-1}), L).$$

For each $k = 1, \ldots, K$, $P(\Delta(t_k) \mid \Delta(t_0), \ldots, \Delta(t_{k-1}), L) = \rho(t_k, L, \bar{O}(t_k)) + o(\epsilon) = P(\Delta(t_k) \mid \bar{O}(t_k), L) = \rho(t_k, Y(t_k), \bar{O}(t_k)) + o(\epsilon), \quad 26$
where the last equality holds by Assumption 2. Similarly \( P(\Delta(t_0)|L) = \rho(t_0, L, \bar{O}(t_0))\epsilon + o(\epsilon) = \rho(t_0, Y(t_0), \bar{O}(t_0))\epsilon + o(\epsilon) \). Therefore, for fixed \( K \), the conditional (on \( L \)) likelihood of \((\Delta(t_0), \ldots, \Delta(t_K))\) is:

\[
\prod_{k=0}^{K} \left( \rho(t_k, Y(t_k), \bar{O}(t_k))\epsilon + o(\epsilon) \right)^{\Delta(t_k)} \left( 1 - \rho(t_k, Y(t_k), \bar{O}(t_k))\epsilon + o(\epsilon) \right)^{1-\Delta(t_k)}.
\]

After dividing by the constant \( \prod_{k=0}^{K} \epsilon^{\Delta(t_k)} \), the conditional likelihood is proportional to:

\[
\prod_{k=0}^{K} \left( \rho(t_k, Y(t_k), \bar{O}(t_k)) + o(\epsilon)/\epsilon \right)^{\Delta(t_k)} \left( 1 - \rho(t_k, Y(t_k), \bar{O}(t_k))\epsilon + o(\epsilon) \right)^{1-\Delta(t_k)}.
\]

(12)

The continuous-time conditional (on \( L \)) likelihood is the limit of (12) as \( K \to \infty \). We compute this by viewing (12) as a product of three factors and noting that:

\[
\lim_{K \to \infty} \prod_{k=0}^{K} \left( 1 - \rho(t_k, Y(t_k), \bar{O}(t_k))\epsilon + o(\epsilon) \right)^{\Delta(t_k)} = \prod_{t=a}^{b} (\rho(t, Y(t), \bar{O}(t)))^{A(t)} .
\]

By a result on product integrals (Cook and Lawless 2007),

\[
\lim_{K \to \infty} \prod_{k=0}^{K} \left( 1 - \rho(t_k, Y(t_k), \bar{O}(t_k))\epsilon + o(\epsilon) \right) = \exp \left\{ - \int_{t=a}^{b} \rho(t, Y(t), \bar{O}(t))dt \right\} .
\]

Finally, since \( \Delta(t_k) = 1 \) at only a fixed number of values \( t_k \) as \( K \) varies, and since \( \lim_{\epsilon \to 0^+} \{1 - \rho(t_k, Y(t_k), \bar{O}(t_k))\epsilon + o(\epsilon)\} = 1 \) for each \( t_k \), we have:

\[
\lim_{K \to \infty} \prod_{k=0}^{K} (1 - \rho(t_k, Y(t_k), \bar{O}(t_k))\epsilon + o(\epsilon))^{\Delta(t_k)} = 1,
\]

Therefore, the continuous-time conditional (on \( L \)) likelihood \( \mathcal{L} \) is:

\[
\mathcal{L} = \prod_{t=a}^{b} \rho(t, Y(t), \bar{O}(t))^{A(t)} \exp \left\{ - \int_{t=a}^{b} \rho(t, Y(t), \bar{O}(t))dt \right\} .
\]

To compute \( \Lambda(F_{R|L}) \), we now consider the conditional likelihood in a parametric submodel of our model for \( dF(R|L) \). Any such parametric submodel is induced by a model for the intensity function \( \rho(t, Y(t), \bar{O}(t)) \), say \( \{\rho(t, Y(t), \bar{O}(t); \gamma) : \gamma \in \Gamma\} \) with \( \gamma \) a finite-dimensional parameter and \( \gamma = 0 \) corresponding to the truth. In order to satisfy the relation in Proposition 2, we must have \( \rho(t, Y(t), \bar{O}(t); \gamma) = r(t, \bar{O}(t); \gamma) \exp\{-q(Y(t), \bar{O}(t); \alpha)\} \) for some function \( r(t, \bar{O}(t); \gamma) \). The conditional likelihood in this parametric submodel is:

\[
\mathcal{L}(\gamma) = \left\{ \prod_{t=a}^{b} \rho(t, Y(t), \bar{O}(t); \gamma)^{A(t)} \right\} \exp \left\{ - \int_{t=a}^{b} \rho(t, Y(t), \bar{O}(t); \gamma) dt \right\} .
\]

The log-conditional likelihood is:

\[
\ell(\gamma) = \int_{t=a}^{b} dN(t) \log(\rho(t, Y(t), \bar{O}(t); \gamma)) - \int_{t=a}^{b} \rho(t, Y(t), \bar{O}(t); \gamma) dt,
\]
and the score is:

\[
S_{\gamma}(O) = \int_{t=a}^{b} dN(t) \left[ \frac{\partial}{\partial \gamma} \rho(t, Y(t), O(t); \gamma) \right] - \int_{t=a}^{b} \frac{\partial}{\partial \gamma} \rho(t, Y(t), O(t); \gamma) dt
\]

\[
= \int_{t=a}^{b} \left[ \frac{\partial}{\partial \gamma} \rho(t, Y(t), O(t); \gamma) \right] \left[ dN(t) - \rho(t, Y(t), O(t); \gamma) dt \right].
\]

Since \( \frac{\partial}{\partial \gamma} \rho(t, Y(t), O(t); \gamma) = \frac{\partial}{\partial \gamma} r(t, \bar{O}(t); \gamma) \) is a function of \( t, \bar{O}(t) \) only, evaluating the score at the truth \( \gamma = 0 \) shows that:

\[
\Lambda(F_{R|L}) \subseteq \left\{ \left( \int_{t=a}^{b} h(t, \bar{O}(t)) \left[ dN(t) - \rho(t, Y(t), \bar{O}(t)) dt \right] \right) \in \mathcal{H}^Z : \text{any} \ h(t, \bar{O}(t)) \right\}.
\]

iv. An observed-data influence function. We are now ready to identify an element of \( \Lambda^{O, \perp} \). Write \( W(t; \beta) := V(\beta)^{-1} \frac{\partial}{\partial \beta} s(\beta^t B(t)) \) where \( V(\beta) \) as in [9], such that the inverse-weighted element \( g^*(O) \) can be written as:

\[
g^*(O) = \int_{t=a}^{b} W(t; \beta) \left\{ \frac{dN(t)}{\rho(t, Y(t), O(t))} \left[ Y(t) - s(\beta^t B(t)) \right] \right\}.
\]

Consider the function:

\[
h^*(O) = \int_{t=a}^{b} W(t; \beta) \left( E[Y(t)|\bar{O}(t)] - s(\beta^t B) \right) \left[ dN(t) - \rho(t, Y(t), \bar{O}(t)) dt \right].
\]

Here \( h^*(O) \in \widetilde{\Lambda}_ug \), and therefore \( g^*(O) - h^*(O) \in \Lambda^{O, \perp}_1 \). We claim that \( g^*(O) - h^*(O) \) is also orthogonal to \( \Lambda(F_{R|L}) \). To show this, we use the martingale covariance property [Andersen et al., 1993], which says that, for predictable processes \( H_1(t) \) and \( H_2(t) \),

\[
E \left[ \left( \int_{t=a}^{b} H_1(t) \left( dN(t) - \rho(t, Y(t), \bar{O}(t)) dt \right) \right) \left( \int_{t=a}^{b} H_2(t) \left( dN(t) - \rho(t, Y(t), \bar{O}(t)) dt \right) \right) \right]
\]

\[
= E \left[ \int_{t=a}^{b} H_1(t) H_2(t) \rho(t, Y(t), \bar{O}(t)) dt \right]. \quad (13)
\]

To show that \( g^*(O) - h^*(O) \in \Lambda(F_{R|L}) \), let \( w(Z) \) be any element of \( \Lambda(F_{R|L}) \). Then \( w(Z) = \int_{t=a}^{b} h(t, \bar{O}(t)) \left[ dN(t) - \rho(t, Y(t), \bar{O}(t)) dt \right] \) for some \( h(t, \bar{O}(t)) \). Then by (13):

\[
E[w(Z)h^*(O)] = E \left[ \int_{t=a}^{b} h(t, \bar{O}(t)) \frac{W(t; \beta) \left( E[Y(t)|\bar{O}(t)] - s(\beta^t B) \right)}{\rho(t, Y(t), O(t))} \rho(t, Y(t), \bar{O}(t)) dt \right]
\]

\[
= E \left[ \int_{t=a}^{b} h(t, \bar{O}(t)) W(t; \beta) \left( E[Y(t)|\bar{O}(t)] - s(\beta^t B) \right) dt \right].
\]
Next, adding and subtracting to write \( g^*(O) \) as the sum of a martingale plus another term, we have:

\[
E[g^*(O)w(Z)] = E \left[ \left( \int_{t=a}^b \frac{W(t; \beta)(Y(t) - s(\beta^tB(t)))}{\rho(t, Y(t), \bar{O}(t))} \left( dN(t) - \rho(t, Y(t), \bar{O}(t))dt \right) \right) w(Z) \right] + E \left[ \left( \int_{t=a}^b W(t; \beta)(Y(t) - s(\beta^tB(t))) dt \right) w(Z) \right].
\]

(14)

Using iterated expectation conditioning on \( L \), the second term in (14) equals:

\[
E \left[ \left( \int_{t=a}^b W(t; \beta)(Y(t) - s(\beta^tB(t))) dt \right) \times \right.
\]

\[
E \left[ \left( \int_{t=a}^b h(t, \bar{O}(t)) \left[ dN(t) - \rho(t, Y(t), \bar{O}(t))dt \right] \right) |L \right] \bigg] = 0.
\]

By (13), the first term in (14) is equal to:

\[
E \left[ \int_{t=a}^b h(t, \bar{O}(t))W(t; \beta)(Y(t) - s(\beta^tB(t))) dt \right]
\]

\[
= E \left[ \int_{t=a}^b h(t, \bar{O}(t))W(t; \beta) \left( E[Y(t)|\bar{O}(t)] - s(\beta^tB(t)) \right) dt \right].
\]

Therefore \( E \left[ (g^*(O) - h^*(O))w(Z) \right] = 0 \). This shows that \( g^*(O) - h^*(O) \in \Lambda_{O,\perp}^{1,1} \cap \Lambda(F_{R|L})^{\perp} \), and therefore \( g^*(O) - h^*(O) \) is an influence function if it also satisfies the equation \( E \left[ (g^*(O) - h^*(O))S_\beta(O) \right] = 1_{p \times p} \), where \( S_\beta(O) \) is the observed-data score for \( \beta \) and \( 1_{p \times p} \) is the \( p \times p \) identity matrix. Following Tsiatis (2006) Theorem 8.3, we rewrite the left side using iterated expectations and the fact that \( S_\beta(O) = E[S_\beta(L)|O] \), where \( S_\beta(L) \) is the full-data score for \( \beta \):

\[
E \left[ (g^*(O) - h^*(O))S_\beta(O) \right]
\]

\[
= E \left[ (g^*(O) - h^*(O))E[S_\beta(L)|O] \right]
\]

\[
= E \left[ (g^*(O) - h^*(O))S_\beta(L) \right]
\]

\[
= E \left[ \left( E[g^*(O)|L]S_\beta(L) \right) - E \left[ E[h^*(O)|L]S_\beta(L) \right] \right]
\]

\[
= E \left[ \varphi(L)S_\beta(L) \right] = 1_{p \times p}
\]

where the last equality holds since \( \varphi(L) \) is a full-data influence function. Denoting \( g^*(O) - h^*(O) \) now by \( \varphi(O; P) \), we have thus shown that one of the observed-data influence functions for \( \beta \) in our
model is:
\[
\varphi(O; P) = \int_{t=a}^{b} W(t; \beta) \left\{ \frac{1}{\rho(t, Y(t), \bar{O}(t))} (Y(t) - E[Y(t)|\bar{O}(t)]) \right\} dN(t) + \\
\int_{a}^{b} W(t; \beta) \left( E[Y(t)|\bar{O}(t)] - s(\beta^t B(t)) \right) dt.
\]

\[\square\]

Appendix C: Remainder Term

For ease of notation, throughout this appendix we take the tilting function \(q(Y(t), \bar{O}(t); \alpha)\) to be \(\alpha Y(t)\); however all computations are the same for a general \(q(\ )\).

Proof of Proposition 4.

Proof. Let \(\mathcal{M}\) be our model for the observed data \(O\). In what follows, we will use a \(\tilde{P}\) subscript to denote expectations or intensities under a distribution \(\tilde{P} \in \mathcal{M}\). Expectations and intensities with no subscript are taken under the true distribution \(P\). Let \(\psi: \mathcal{M} \to \mathbb{R}^p\) be the parameter mapping, and for each \(\tilde{P} \in \mathcal{M}\), write \(\psi(\tilde{P}) = \beta_{\tilde{P}}\). By Assumption 3, \(E_{\tilde{P}}[Y(t)] = B(t) \beta_{\tilde{P}}\), so that \(\psi(\tilde{P}) = \int_{t=a}^{b} V^{-1} B(t) E_{\tilde{P}}[Y(t)] dt\). Now \(\psi(\tilde{P})\) has a von Mises expansion \(\text{van der Vaart} 1998\) as:

\[\psi(\tilde{P}) = \psi(P) - E[\varphi(O; \tilde{P}) + Rem(\tilde{P}, P),
\]

which we use to compute \(Rem(\tilde{P}, P)\). We have:

\[
E[\varphi(O; \tilde{P})] = E \left[ \int_{t=a}^{b} \left\{ V^{-1} B(t) \frac{(Y(t) - E_{\tilde{P}}[Y(t)|\bar{O}(t)])}{\rho_{\tilde{P}}(t, Y(t), \bar{O}(t))} \right\} \left( dN(t) - \rho(t, Y(t), \bar{O}(t)) \right) \right] = 0
\]

\[= E \left[ \int_{t=a}^{b} \frac{V^{-1} B(t)(Y(t) - E_{\tilde{P}}[Y(t)|\bar{O}(t)])}{\rho_{\tilde{P}}(t, Y(t), \bar{O}(t))} \rho(t, Y(t), \bar{O}(t)) dt \right] - E \left[ \int_{t=a}^{b} \left\{ V^{-1} B(t) E_{\tilde{P}}[Y(t)|\bar{O}(t)] \right\} dt \right] - \beta_{\tilde{P}}
\]

\[= E \left[ \int_{t=a}^{b} E \left[ V^{-1} B(t) \rho(t, Y(t), \bar{O}(t)) \rho_{\tilde{P}}(t, Y(t), \bar{O}(t)) (Y(t) - E_{\tilde{P}}[Y(t)|\bar{O}(t)]) \right] dt \right] - E \left[ \int_{t=a}^{b} V^{-1} B(t) E_{\tilde{P}}[Y(t)|\bar{O}(t)] dt \right] - \beta_{\tilde{P}}
\]

\[= E \left[ \int_{t=a}^{b} \left\{ V^{-1} B(t) \rho(t, Y(t), \bar{O}(t)) \left( E[Y(t)|\bar{O}(t)] - E_{\tilde{P}}[Y(t)|\bar{O}(t)] \right) \right\} dt \right] + E \left[ \int_{t=a}^{b} \left\{ V^{-1} B(t) E_{\tilde{P}}[Y(t)|\bar{O}(t)] \right\} dt \right] - \beta_{\tilde{P}}.
\]
where in the last equality we used the fact that, by Proposition 2:

\[
\frac{\rho(t, Y(t), \hat{O}(t))}{\rho_P(t, Y(t), \hat{O}(t))} = \frac{\lambda(t, \hat{O}(t))}{\lambda_P(t, \hat{O}(t))} \exp\{\alpha Y(t)A(t) = 1, \hat{O}(t)\} \frac{\exp\{\alpha Y(t)A(t) = 1, \hat{O}(t)\}}{\exp\{\alpha Y(t)A(t) = 1, \hat{O}(t)\}}
\]

is a function of \( t \) and \( \hat{O}(t) \) only. Therefore:

\[
\text{Rem}(\hat{P}, P) = \int_a^b \left\{ V^{-1} B(t) \frac{\rho(t, Y(t), \hat{O}(t))}{\rho_P(t, Y(t), \hat{O}(t))} \left( E[Y(t)|\hat{O}(t)] - E_P[Y(t)|\hat{O}(t)] \right) \right\} dt
\]

\[
+ E \left[ \int_a^b \left\{ V^{-1} B(t) E_P[Y(t)|\hat{O}(t)] \right\} dt \right] - \beta P + \psi(\hat{P}) - \psi(P)\quad_{0}
\]

\[
\text{Rem}(\hat{P}, P) = \int_a^b \left\{ V^{-1} B(t) \frac{\rho(t, Y(t), \hat{O}(t))}{\rho_P(t, Y(t), \hat{O}(t))} \left( E[Y(t)|\hat{O}(t)] - E_P[Y(t)|\hat{O}(t)] \right) \right\} dt
\]

\[
+ E \left[ \int_a^b \left\{ V^{-1} B(t) E_P[Y(t)|\hat{O}(t)] \right\} dt \right] - \beta P + \psi(\hat{P}) - \psi(P)\quad_{0}
\]

\[
= \int_a^b \left\{ V^{-1} B(t) \left( \frac{\rho(t, Y(t), \hat{O}(t))}{\rho_P(t, Y(t), \hat{O}(t))} - 1 \right) \left( E[Y(t)|\hat{O}(t)] - E_P[Y(t)|\hat{O}(t)] \right) \right\} dt.
\]

\[
\text{Proof of Theorem 2.}
\]

\[
\text{Proof. Let } \eta = \left( \{ \lambda_0(t) : a \leq t \leq b \}, \gamma, \theta \right), \text{ and let } \hat{\eta} = \left( \{ \hat{\lambda}_0(t) : a \leq t \leq b \}, \hat{\gamma}, \hat{\theta} \right) \text{ be the estimates in the distribution } \hat{P}. \text{ By the Cauchy-Schwarz inequality,}
\]

\[
\left( \text{Rem}(\hat{P}, P) \right)^2 = E \left[ \int_a^b \left\{ V^{-1} B(t) \left( \frac{\rho(t, Y(t), \hat{O}(t); \eta)}{\rho(t, Y(t), \hat{O}(t); \hat{\eta})} - 1 \right) \times \left( E[Y(t)|\hat{O}(t); \hat{\theta}] - E[Y(t)|\hat{O}(t); \theta] \right) \right\} dt \right]^2
\]

\[
\leq E \left[ \int_a^b \left\{ \left( \frac{V^{-1} B(t)}{\rho(t, Y(t), \hat{O}(t); \hat{\eta})} \right)^2 \left( \rho(t, Y(t), \hat{O}(t); \eta) - \rho(t, Y(t), \hat{O}(t); \hat{\eta}) \right)^2 \right\} dt \right] (15)
\]

\[
\times E \left[ \int_a^b \left\{ E[Y(t)|\hat{O}(t); \theta] - E[Y(t)|\hat{O}(t); \hat{\theta}] \right\}^2 dt \right]. (16)
\]

31
In the factor \([15]\), we expand \(\rho(t, Y(t), \bar{O}(t); \eta) - \rho(t, Y(t), \bar{O}(t); \bar{\eta})\) as the sum of three terms, as:

\[
\rho(t, Y(t), \bar{O}(t); \bar{\eta}) - \rho(t, Y(t), \bar{O}(t); \eta) = \bar{\lambda}_0(t) \exp\{\gamma Z(t)\} \exp\{-\alpha Y(t)\} E[\exp\{\alpha Y(t)\}|A(t) = 1, \bar{O}(t); \hat{\theta}] - \
\lambda_0(t) \exp\{\gamma Z(t)\} \exp\{-\alpha Y(t)\} E[\exp\{\alpha Y(t)\}|A(t) = 1, \bar{O}(t); \theta]
\]

\[
= \left(\bar{\lambda}_0(t) - \lambda_0(t)\right) \exp\{\gamma Z(t)\} \exp\{-\alpha Y(t)\} E[\exp\{\alpha Y(t)\}|A(t) = 1, \bar{O}(t); \hat{\theta}] + \
\lambda_0(t) \left( \exp\{\gamma Z(t)\} - \exp\{\gamma Z(t)\} \right) \exp\{-\alpha Y(t)\} E[\exp\{\alpha Y(t)\}|A(t) = 1, \bar{O}(t); \hat{\theta}] + \
\lambda_0(t) \exp\{\gamma Z(t)\} \exp\{-\alpha Y(t)\} \left\{ E[\exp\{\alpha Y(t)\}|A(t) = 1, \bar{O}(t); \hat{\theta}] - \
E[\exp\{\alpha Y(t)\}|A(t) = 1, \bar{O}(t); \theta] \right\}.
\]

Using this expansion and the inequality \(rs \leq \frac{1}{2}(r^2 + s^2)\), the rate for \([15]\) will be determined by the rates of three terms, namely the squares of each of the terms in the expansion above.

For the factor \([16]\), using Proposition 1, we write:

\[
E[Y(t)|\bar{O}(t); \theta] - E[Y(t)|\bar{O}(t); \hat{\theta}] = \
\frac{E[Y(t)|\bar{O}(t); \theta] - E[Y(t)|\bar{O}(t); \hat{\theta}]}{E[\exp\{\alpha Y(t)\}|A(t) = 1, \bar{O}(t); \theta]} \times \
\left( E[\exp\{\alpha Y(t)\}|A(t) = 1, \bar{O}(t); \theta] - E[\exp\{\alpha Y(t)\}|A(t) = 1, \bar{O}(t); \hat{\theta}] \right)
\]

\[
- \frac{E[\exp\{\alpha Y(t)\}|A(t) = 1, \bar{O}(t); \hat{\theta}]}{E[\exp\{\alpha Y(t)\}|A(t) = 1, \bar{O}(t); \theta]} \times \
\left( E[Y(t)|\exp\{\alpha Y(t)\}|A(t) = 1, \bar{O}(t); \bar{\eta}] - E[Y(t)|\exp\{\alpha Y(t)\}|A(t) = 1, \bar{O}(t); \eta] \right)
\]

The rates for \([16]\) will similarly be determined by the rates for the squares of the two terms in this
expansion. Combining these results, we therefore have:

\[
\left| \text{Rem}(\hat{P}, P) \right|^2 \leq \\
\left( C_1(\hat{\eta}) \ E \left[ \int_{t=a}^{b} \left( \hat{\lambda}_n(t) - \lambda_0(t) \right)^2 dt \right] + \\
C_2(\hat{\eta}) \ E \left[ \int_{t=a}^{b} \left( \exp\{\gamma Z(t)\} - \exp\{\hat{\gamma} Z(t)\} \right)^2 dt \right] + \\
C_3(\hat{\eta}) \ E \left[ \int_{t=a}^{b} \left\{ E\left[ \exp\{\alpha Y(t)\} : A(t) = 1, \hat{O}(t); \hat{\theta} \right] - \\
E\left[ \exp\{\alpha Y(t)\} : A(t) = 1, \bar{O}(t); \bar{\theta} \right] \right\}^2 dt \right] \right) \times \\
\left( C_4(\hat{\eta}) \ E \left[ \int_{t=a}^{b} \left\{ E\left[ Y(t) \exp\{\alpha Y(t)\} : A(t) = 1, \hat{O}(t); \hat{\theta} \right] - \\
E\left[ Y(t) \exp\{\alpha Y(t)\} : A(t) = 1, \bar{O}(t); \bar{\theta} \right] \right\}^2 dt \right] + \\
C_5(\hat{\eta}) \ E \left[ \int_{t=a}^{b} \left\{ E\left[ \exp\{\alpha Y(t)\} : A(t) = 1, \hat{O}(t); \hat{\theta} \right] - \\
E\left[ \exp\{\alpha Y(t)\} : A(t) = 1, \bar{O}(t); \bar{\theta} \right] \right\}^2 dt \right] \right)
\]

where \( C_1(\hat{\eta}), \ldots, C_5(\hat{\eta}) \) are terms that are each \( O_P(1) \) under conditions (i) and (iv) of Theorem 2.

We first consider term (17). Let \( X_n(t) = (nb_n)^{1/2} \left( \hat{\lambda}_n(t) - \lambda_0(t) \right) \). Wells (1994) has shown that, under condition (ii) of Theorem 2, the stochastic processes \( \{X_n(t) : a \leq t \leq b\}_{n=1}^{\infty} \) converges weakly to a process \( \{X(t) : a \leq t \leq b\} \) where \( \{X(t) : a \leq t \leq b\} \) is a Wiener process plus a term depending on \( \lambda_0(t) \). Therefore it follows by the Continuous Mapping Theorem that \( \{X_n^2(t) : a \leq t \leq b\}_{n=1}^{\infty} \) converges weakly to \( \{X^2(t) : a \leq t \leq b\} \). Again by the Continuous Mapping Theorem, \( \int_{t=a}^{b} X_n^2(t) dt = nh_n \left( \int_{t=a}^{b} \left( \hat{\lambda}_n(t) - \lambda_0(t) \right)^2 dt \right) \) is \( O_P(1) \). Therefore, the term in (17) is \( O_P((nh_n)^{-1}) \).

By assumption (ii), for large \( n \), \( nh_n \) is approximately \( n^{4/5} \), so in particular the convergence rate for (17) is faster than \( n^{1/2} \).

Since \( \hat{\gamma} \) converges to \( \gamma \) at root-\( n \) rates, the term in (18) is \( O_P(n^{-1}) \).

Next we consider terms (19) and (21). By the Cauchy-Schwarz inequality, for each \( t \), we can
bound the integrand in (19) and (21) as:

\[
\left( E\left[ \exp(\alpha Y(t)) : A(t) = 1, \hat{O}(t); \hat{\theta} \right] - E\left[ \exp(\alpha Y(t))|A(t) = 1, \hat{O}(t); \theta \right] \right)^2
\]

\[
= \left( \int_{y(t)} e^{\alpha y(t)} \left( f(y(t)|A(t) = 1, \hat{O}(t); \hat{\theta}) - f(y(t)|A(t) = 1, \hat{O}(t); \theta) \right) d\nu(y(t)) \right)^2
\]

\[
\leq \left( \int_{y(t)} e^{2\alpha y(t)} d\nu(y(t)) \right) \times
\left( \int_{y(t)} \left( f(y(t)|A(t) = 1, \hat{O}(t); \hat{\theta}) - f(y(t)|A(t) = 1, \hat{O}(t); \theta) \right)^2 d\nu(y(t)) \right),
\]

where \( \nu(\cdot) \) is an appropriate dominating measure. Therefore, since \( \int_{y(t)} e^{2\alpha y(t)} d\nu(y(t)) \) is uniformly bounded, it follows from assumption (iii) of Theorem 2 that (19) and (21) are \( o_P(n^{-1/2}) \).

Therefore, the sum of terms (17), (18), and (19) is \( o_P(n^{-1/2}) \), since each of these terms converges at faster than root-\( n \) rates.

Finally we consider term (20). Since \( \int_{y(t)} y(t)^2 e^{2\alpha y(t)} d\nu(y(t)) \) is also uniformly bounded, (20) is also \( o_P(n^{-1/2}) \) by the same argument as for terms (19) and (21). Therefore, the sum of terms (20) and (21) is \( o_P(n^{-1/2}) \). Hence the product that bounds \( |Rem(\hat{P}, P)|^2 \) is \( o_P(n^{-1}) \), so that \( Rem(\hat{P}, P) \) is \( o_P(n^{-1/2}) \) as claimed.