Long-term effect estimation when combining clinical trial and observational follow-up datasets

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Abstract
Combining experimental and observational follow-up datasets has received a lot of attention lately. In a time-to-event setting, recent work has used medicare claims to extend the follow-up period for participants in a prostate cancer clinical trial. This allows the estimation of the long-term effect that cannot be estimated by clinical trial data alone. In this paper, we study the estimation of long-term effect when participants in a clinical trial are linked to an observational follow-up dataset with incomplete data. Such data linkages are often incomplete for various reasons. We formulate incomplete linkages as a missing data problem with careful considerations of the relationship between the linkage status and the missing data mechanism. We use the popular Cox proportional hazard model as a working model to define the long-term effect. We propose a conditional linking at random (CLAR) assumption and an inverse probability of linkage weighting (IPLW) partial likelihood estimator. We show that our IPLW partial likelihood estimator is consistent and asymptotically normal. We further extend our approach to incorporate time-dependent covariates.
Simulations results confirm the validity of our method, and we further apply our methods to the SWOG study.

*Keywords:* Cox model, Incomplete linkage, Inverse probability weighting, Weighted empirical process, Time-dependent covariate
1 Introduction

With the increasing availability of electronic health data, combining experimental and observational datasets has been widely applied in public health research (Warren et al., 2002; Gilbert et al., 2018). In a time-to-event setting, we consider the setup when data from a clinical trial is combined with an observational follow-up dataset, such as electronic health records or administrative claims. Clinical trials often study the effect of a particular treatment for a fixed period of time and it might not be long enough to determine the maximum benefit of the treatment. In contrast, an observational dataset such as medicare claims naturally extends the follow-up period for clinical trial participants at minimal cost. This enables the estimation of the long-term effect for the treatment after the clinical trial. To combine the observational follow-up dataset with the clinical trial data, records belonging to the same individual can be linked with unique identifiers from both datasets. In this paper, we use Cox model (Cox, 1972) to define the long-term effect as the parameter for treatment when participants from the clinical trial are linked to an observational follow-up dataset.

For a real data example, the Prostate Cancer Prevention Trial (PCPT) was previously launched to examine whether finasteride\footnote{a treatment that inhibits the development potent androgen that fuels the malignancy of prostate cancer} could prevent the development of prostate cancer (PC). PCPT showed that seven years of finasteride reduced PC risk by 25% (Thompson et al., 2003). However, it was unclear if seven years’ of trial follow-up sufficed to determine the maximum benefit of the treatment. Further, the reduced risk of prostate cancer for subjects receiving finasteride might not be maintained after finasteride discontinuation (Unger et al., 2018). A later study linked medicare claims to the clinical records for participants in PCPT with their social security numbers (SSN) (Unger et al., 2018) to estimate the long-
term effect of finasteride on prostate cancer (PC) development. In this example, PCPT is the clinical trial and medicare claim is the observational follow-up dataset. Medicare claims extend the follow-up periods up to a maximum of 20 years compared to 7 years by the PCPT. Thus, we can observe more diagnosis times of PC within the medicare claims dataset.

However, not every participant in the clinical trial can be linked to the observational dataset. For the PCPT-medicare example, some participants might not be willing to share their SSNs or they may be enrolled in health maintenance organization (HMO) and medicare claims are not applicable to HMO individuals (Unger et al., 2018). With incomplete linkages, survival outcomes in the observational dataset might be missing for some participants. For a participant censored in the PCPT, meaning he was not diagnosed with PC within the clinical trial, his survival outcome in the observational dataset would be missing if he is unlinked. On the other hand, if a participant was diagnosed with PC within the clinical trial, his survival outcome has been already observed within the clinical trial and the linkage to the observational follow-up dataset is in fact not necessary. This suggests that the missingness of survival outcome depends both on the linkage status and whether a participant was censored in the clinical trial or not.

To deal with the missing survival outcomes, a complete-case analysis that only includes linked participants will ignore all the unlinked participants with observed survival outcomes within the clinical trial. However, simply adding those unlinked participants to the complete-case analysis will also cause biased estimate. Essentially this would lead to the missingness of the survival outcomes to depend on itself and the missingness is then missing not at random (MNAR). To properly incorporate those unlinked participants with observed survival outcomes, we choose to model the linkage probability directly. As we
discussed above, participants who miss the survival outcomes in the observational dataset are those who are censored in the clinical trial and unlinked. Hence we take a missing data perspective and propose a novel conditional linking at random (CLAR) assumption for the linkage mechanism. More specifically, we assume that for participants who are censored in the clinical trial, linkages are independent of the survival outcomes after conditioning on their covariates vectors, such as social economic status or other clinical factors. No linkage assumptions are made for those participants uncensored in the clinical trial. Under the CLAR assumption, we can then weight each participant appropriately and obtain unbiased estimates for the long-term effect.

As we use Cox model to define the long-term effect, we develop an inverse probability of linkage weighting (IPLW) partial likelihood estimator. We prove the asymptotic normality and consistency of our IPLW partial likelihood estimator. Our approach allows inclusion of time-dependent covariates for more flexibility. While there has been plenty work (Binder, 1992; Robins, 1993; Lin, 2000; Qi et al., 2005) on proving the asymptotic convergence for an inverse probability weighting (IPW) type partial likelihood estimator when there are only time-independent covariates, their proof cannot be easily generalized to the case when there are time-dependent covariates (Breslow and Wellner, 2007). To this end, we establish an IPLW empirical process weak convergence results that builds on the work in Saegusa and Wellner (2013) and borrow the techniques from Lin and Wei (1989) to extend the theoretical results to include time-dependent covariates.

Related work. There has been an increasing amount of work on combining different datasets and studying the treatment effect on long-term outcome in causal inference (Rosenman et al., 2018, 2020; Kallus and Mao, 2020; Athey et al., 2020). All these work focuses on using experimental and observational datasets that contain different set of in-
individuals, which is different from our setup. IPW has also been widely applied in the survival analysis setting (Binder, 1992; Robins et al., 1994; Robins and Finkelstein, 2000; Hernán et al., 2000; Lin, 2000; Qi et al., 2005; Tsiatis, 2007; Breslow and Wellner, 2007; Saegusa and Wellner, 2013). Robins and Finkelstein (2000) applied inverse probability of censoring weights to estimate Cox model that adjusts for dependent censoring by utilizing data collected on time-dependent prognostic factors. IPW has also been applied for Cox models with two-phase stratified sampling under right censoring (Binder, 1992; Lin, 2000; Breslow and Wellner, 2007), while Saegusa and Wellner (2013) further studied the problem of two-phase sampling for Cox model under interval censoring with IPW. Our approach is different from all previous works as we also allow for time-dependent covariates.

Outline. In Section 2, we provide background and notations required for our methodological developments. We also introduce several alternative approaches. We introduce our main IPLW estimator in Section 3 and provide theoretical justifications. We conduct simulation studies in Section 4 to illustrate the validity of the proposed method. We apply our approach to the SWOG prevention trial in Section 5. We further compared our IPLW estimator to an alternative approach in Section 6. In Section 7, we conclude this paper and point out some possible future directions.

2 Background and Notations

We first consider the oracle setting that all participants from the clinical trial are linked. We make a “no gap” assumption such that there is no gap between a participant’s last recorded date within the clinical trial and the start date of the observational follow-up dataset. This “no gap” assumption eliminates the possibility of interval censoring in which a participant is diagnosed with the event of interest while not under observation. For
simplicity, we make this “no gap” assumption to focus on the right censoring problem and we discuss how to relax this no gap assumption in Appendix F (supplementary material).

Time is measured since enrollment in the clinical trial. We define $T$ as the failure time, $C_1$ as the censoring time within the clinical trial and $Q = \mathbb{I}(T \leq C_1)$ as the censoring indicator for the clinical trial. We use $\tau_1$ to denote the end time of clinical trial. Possible reasons for censoring in the clinical trial include loss to follow-up and administrative censoring. In contrast, the length of observational follow-up dataset is often determined by the data availability and also vary from person to person. We set $\tau_2$ with $\tau_2 > \tau_1$ as the common end time for observational follow-up dataset and assume that there are a significant proportion of participants at risk after $\tau_2$. Thus, we are interested in estimating the long-term treatment effect on survival up to time $\tau_2$ using data from clinical trial records and observational follow-up. Similarly, we define $C_2$ as the censoring time in the observational follow-up dataset. Possible reasons for censoring in the observational follow-up include short coverages such that a participant is not covered long enough by the observational dataset, administrative censoring where a participant is event-free and covered by observational follow-up until $\tau_2$.

We use $C = \max(C_1, C_2)$ to denote the actual censoring time and let $\tilde{T} = \min\{T, C\}$ denote the actual observed time and $\Delta = \mathbb{I}(T \leq C)$ be the censoring indicator throughout the entire follow-up period. Let $X \in \mathbb{R}^p$ denote baseline characteristics, clinical factors and treatment assignment. We also use $A$ to denote the treatment assignment when necessary. We make the independent censoring assumption that $T$ and $(C_1, C_2)$ are conditionally independent given $X$. Thus, $T$ is conditionally independent of $\max(C_1, C_2)$ given $X$. 




2.1 Cox model and Long-term effect

We use Cox model to define the long-term effect and we allow for the possibility of model-misspecification. We now discuss the parameter for the long-term effect. Assuming that there are \( n \) participants in the clinical trial and they are all linked to the observational follow-up dataset. \((X_i, Q_i, \bar{T}_i, \Delta_i)\) for \( i = 1, \ldots, n \) are all observed. Cox model assumes that the hazard function has the following form:

\[
\lambda(t|X, \beta_0) = \lambda_0(t) \exp(\beta_1 A + \beta_0^T X_{-A})
\]

(1)

with \( \beta_0 \in \mathbb{R}^{p-1} \) and \( X_{-A} \) is the covariate vector excluding treatment \( A \). \( \lambda_0(t) \) is the baseline hazard function and \( \beta_1 \) represents the long-term treatment effect. To account for potential different treatment effects between clinical trial and the observational follow-up period, we also consider the following model with a change point at time \( \tau_1 \) (Liang et al., 1990; Pons et al., 2003)

\[
\lambda(t|X; \beta_0, \beta_1, \theta) = \lambda_0(t) \exp[(\beta_1 + \theta I_{t>\tau_1})A + \beta_0^T X_{-A}].
\]

(2)

\( \beta_1 \) now represents the effect of treatment in the clinical trial, while \( \theta \) represents the difference of the treatment effect between observational follow-ups and clinical trial. \( \beta_1 + \theta \) now represents the long-term treatment effect. When \( \theta = 0 \), model (2) reduces to (1). Without loss of generality, we will use the parameter notation from model (1) in the following.

Following the notation in Lin and Wei (1989), for the \( i \)-th individual, let \( \lambda_i(t) = \lambda(t|X_i) \) be the true hazard function, \( N_i(t) = I(\bar{T}_i \leq t, \Delta_i = 1) \) and \( Y_i(t) = I(\bar{T}_i \geq t) \). For \( k = 0, 1, 2 \), define

\[
S_n^{(k)}(t) = \frac{1}{n} \sum_{i=1}^{n} Y_i(t)\lambda_i(t)X_i^{(k)}, \quad s^{(k)}(t) = \mathbb{E}[S_n^{(k)}(t)]
\]

\[
S_n^{(k)}(\beta, t) = \frac{1}{n} \sum_{i=1}^{n} Y_i(t)\exp(\beta^T X_i)X_i^{(k)}, \quad s^{(k)}(\beta, t) = \mathbb{E}[S_n^{(k)}(\beta, t)]
\]
where for a column vector $\mathbf{a}$, denote $\mathbf{a}^{\otimes 2} = \mathbf{a} \mathbf{a}^T$, $\mathbf{a}^{\otimes 1} = \mathbf{a}$ and $\mathbf{a}^{\otimes 0}$ refers to the scalar 1. With Cox model as a working model, the parameter of interest is $\beta_0^*$ that solves the following equations (Andersen and Gill, 1982; Lin and Wei, 1989)

$$
U_0(\beta) = \mathbb{E} \left[ \Delta \left( \mathbf{X} - \frac{s^{(1)}(\beta, \tilde{T})}{s^{(0)}(\beta, \tilde{T})} \right) \right] = \int_0^{\tau_2} s^{(1)}(t) dt - \int_0^{\tau_2} \frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)} s^{(0)}(t) dt.
$$

(3)

When Cox model is correctly specified with true parameter $\beta_0$, we have $\beta_0^* = \beta_0$. When Cox model is misspecified, parameter $\beta_0^*$ that solves equation (3) is still well-defined. For the model without change points (1), the long-term effect $\beta_1$ can be interpreted as the averaging effect over the entire follow-up period. For the model with change points (2), the long-term effect $\beta_1 + \theta$ can be interpreted as the effect after the change point.

### 2.2 The linkage problem and assumption

Now we consider the more realistic setup that not every participant is linked to the observational follow-up dataset. We use $L$ to denote the linkage status. $L = 1$ means that the participant is linked to the observational follow-up dataset and $L = 0$ means unlinked. As $C_2$ is unobserved when $L = 0$, $C$ is missing in this case. We classify participants into three classes based on their linkage status $L$ and in-trial censoring indicator $Q$.

**Class 1:** $L = 1$. This class contains all participants linked to the observational follow-up dataset, where we have full observations: $(L, \tilde{T}, \Delta, Q, X)$.

**Class 2:** $L = 0, Q = 1$. This class represents participants diagnosed with the event of interest within the clinical trial but unlinked to observational follow-up. Thus, we still have complete information $(L, \tilde{T}, \Delta, Q, X)$.

**Class 3:** $L = 0, Q = 0$. This class includes participants who did not experience the event of interest during the clinical trial, and were not linked to observational follow-up dataset. Both $\tilde{T}$ and $\Delta$ are missing and we only observe $(L, Q, X)$. 

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Figure 1: A diagram illustrating the three classes of participants and how it is defined via the linkage indicator $L$ and in-trial censoring indicator $Q$.

Figure 1 provides a summary of the three classes defined above. We have completely observed data $(L, \tilde{T}, \Delta, Q, X)$ in class 1 and 2, while two important variables $\tilde{T}, \Delta$ are missing in class 3. To deal with the missing $\tilde{T}$ and $\Delta$, we propose the following conditional linking at random assumption (CLAR):

\[(A1) \quad P(L = 1|\tilde{T}, \Delta, Q = 0, X) = P(L = 1|Q = 0, X).\]

More specifically, (A1) states that for a participant that is censored in the clinical trial, his/her linkage status is independent of the survival outcomes given his baseline covariates, clinical factors and treatment assignment. For example, clinical trial participants with higher social economic status might be more sensitive to personal privacy and not willing to share personal information that are important for data linkage.

We compare our CLAR assumption (A1) with the classical MAR type assumption (Rubin, 1976; Little and Rubin, 2019), which can be written as follows

\[P(L = 1|\tilde{T}, \Delta, Q, X) = P(L = 1|Q, X).\]  

(CLAR is actually implied by MAR (4). However, CLAR is restricting the conditional independence to the subpopulation with $Q = 0$, while MAR (4) is assuming the conditional independence for the entire population.)

| Class 1                  | Class 2                  | Class 3                  |
|--------------------------|--------------------------|--------------------------|
| $L = 1, Q = 1$           | $L = 0, Q = 1$           | $L = 0, Q = 0$           |
| $(L, \tilde{T}, \Delta, Q, X)$ | $(L, \tilde{T}, \Delta, Q, X)$ | $(L, Q, X)$ |

$Q = I(T \leq \Delta)$. 

\[\]
independence for the whole population. To see why this is important, note that MAR (4) implies that

\[ P(L = 1 | T, \Delta, Q = 1, X) = P(L = 1 | Q = 1, X) \]  \hspace{1cm} (5)

and when \( Q = 1 \), both \( T \) and \( \Delta \) are always observed, meaning that (5) might in fact contradict the data. In contrast, with no assumptions for participants with \( Q = 1 \), CLAR is non-parametrically identifiable, i.e., they will never contradict the data (Robins et al., 2000). Further discussions on potential linkage assumptions are given in Appendix E (supplementary material).

### 2.3 Alternative approaches and a motivating example

We now consider three alternative approaches that practitioners may use. We show that they all give inconsistent estimates for \( \beta_0^* \) with a simulated example when Cox model is misspecified and CLAR assumption (A1) holds. These three approaches are

- **Complete-case (CC) analysis** that only includes participants that are linked. These corresponds to participants in Class 1 with \( L = 1 \).

- **Complete-case analysis plus (CC+)** that includes not only participants that are linked, but also participants with \( Q = 1 \). This corresponds to participants in Class 1 and 2 in Figure 1. These are the participants with \( L + Q > 0 \).

- **Non-linked-as-censored (NLAC)** that treats participants from Class 3 \((L = 0, Q = 0)\) as censored and sets their censoring time as \( C = C_1 \). These are the participants that are unlinked and censored in the clinical trial. Then we can fit the Cox regression with all participants from clinical trial.

We simulate data according to a Cox model with hazard function specified by covariates
\(X_1, X_2, X_3^2\) and a Cox model with covariates \(X_1, X_2, X_3\) is fitted. More details are given in Appendix H (supplementary material). Figure 2 presents the 95% confidence intervals for one of the parameters. Oracle method refers to the approach that all participants in the clinical trial are linked. Among all four approaches, CC+ gives the most biased estimates. CC gives less biased estimates than CC+. NLAC also gives biased estimates compared to the oracle method. Although not shown here, the coverage of 95% confidence intervals for CC, CC+, NLAC all decrease as \(n\) increases.

We now discuss these three alternative approaches. One sufficient condition for CC to be consistent is linking completely at random (LCAR), i.e., \(L \perp (\hat{T}, \Delta)\). This is similar to the missing completely at random (MCAR) (Little and Rubin, 2019) condition. The LCAR condition is a strong condition and may contradict the data\(^2\) whereas the CLAR condition will not. Thus the CLAR condition (A1) is a preferred condition in a context similar to our setting. For CC+, the missingness of survival outcomes now also depends on survival outcomes itself as a participant would be included if \(L + Q > 0\). Thus, the missingness can be viewed as MNAR and CC+ will always lead to biased estimates. Finally, for participants from Class 3, NLAC seems like a natural idea that simply uses their censoring time in clinical trial \(C_1\) as the censoring time for the entire follow-up period. However, when Cox model is misspecified, NLAC in fact always give biased estimates of \(\beta_0^*\). More discussions of NLAC are deferred to section 6. As these three approaches are inconsistent, we have to propose a new approach to consistently estimate \(\beta_0^*\). Our proposed approach are different from NLAC as for participants in Class 3, we treat their survival outcomes as missing.

\(^2\)we can easily test this condition
3 Methods

3.1 IPLW Partial likelihood estimator

Due to the missingness of $\tilde{T}$ and $\Delta$, we can not use the classical partial likelihood for Cox model to estimate the parameters. We first illustrate our approach with time-independent covariates only. We start by writing the regular log-likelihood for Cox model as follows:

$$l_n(\beta, \lambda_0) = \frac{1}{n} \sum_{i=1}^{n} l(\tilde{T}_i, \Delta_i, X_i; \beta, \lambda_0) = \frac{1}{n} \sum_{i=1}^{n} \log \left( \lambda(\tilde{T}_i|X_i)^{\Delta_i}S(\tilde{T}_i|X_i) \right)$$

where $S(t|X)$ is the conditional survival function for the failure time $T$. However, $l_n(\beta, \lambda_0)$ is unidentifiable since we do not observe $(\tilde{T}_i, \Delta_i)$ for participants in Class 3 of Figure 1. To resolve the identifiability issue, consider the expected log-likelihood

$$\mathbb{E}(l(\beta, \lambda_0)) = \mathbb{E} \left[ \log \left( \lambda(\tilde{T}|X)^{\Delta}S(\tilde{T}|X) \right) \right]$$

where $\mathbb{E}$ is the expectation with respect to random variable $(\tilde{T}, \Delta, X)$ and $l(\beta, \lambda_0) = l(\tilde{T}, \Delta, X; \beta, \lambda_0)$. By the law of large number, we have $l_n(\beta, \lambda_0) \rightarrow_p \mathbb{E}(l(\beta, \lambda_0))$. 
Proposition 3.1. Under assumption (A1), we have

\[
\mathbb{E}(l(\beta, \lambda_0)) = \mathbb{E} \left[ \frac{I(L + Q > 0)l(\beta, \lambda_0)}{Q + (1 - Q)P(L = 1|X, Q = 0)} \right]
\] (6)

Proposition 3.1 shows that \(\mathbb{E}(l(\beta, \lambda_0))\) can be expressed in the IPLW form and the proof can be found in Appendix C (supplementary material). We assume a logistic regression model for the linkage probability \(P(L = 1|X, Q = 0)\) for simplicity such that

\[
P(L = 1|X, Q = 0; \gamma_0) = \frac{\exp(\gamma_0^T \bar{X})}{1 + \exp(\gamma_0^T \bar{X})} = \pi_{\gamma_0}(X)
\]

with \(\gamma_0 \in \mathbb{R}^{p+1}\) and \(\bar{X} = (1, X^T)^T\). In particular, \(\gamma_0\) can be estimated by the maximum likelihood estimator \(\hat{\gamma}_n\). Using result (6), an IPLW estimator of \(\mathbb{E}(l(\beta, \lambda_0))\) is

\[
l_n(\beta, \lambda_0) = \frac{1}{n} \sum_{i=1}^{n} \frac{I(L_i + Q_i > 0)}{Q_i + (1 - Q_i)\pi_{\hat{\gamma}_n}(X_i)} \left[ \Delta_i \log \lambda(\tilde{T}_i|X_i) + \log S(\tilde{T}_i|X_i) \right]
\]

with the log-likelihood being weighted by \(\hat{w}_i = I(L_i + Q_i > 0)/[Q_i + (1 - Q_i)\pi_{\hat{\gamma}_n}(X_i)]\).

IPLW partial score can then be derived as

\[
\hat{U}_n(\beta) = \frac{1}{n} \sum_{i=1}^{n} \Delta_i \hat{w}_i \left( X_i - \frac{\sum_{j=1}^{n} \hat{w}_j I(\tilde{T}_j \geq \tilde{T}_i) \exp(X_j^T \beta)}{\sum_{j=1}^{n} \hat{w}_j I(\tilde{T}_j \geq \tilde{T}_i) \exp(X_j^T \beta)} \right),
\] (7)

which is a sample analog of equation (3) and \(\hat{\beta}_n\) can be obtained by solving equation (7) using standard statistical software. Detailed derivations of (7) can be found in Appendix A (supplementary material). In summary, our method for estimating the regression parameters of Cox model consists of two steps:

- **Step 1.** We estimate the linkage probability \(P(L = 1|Q = 0, X; \gamma_0) = \pi_{\gamma_0}(X)\) with logistic regression. \(\hat{\gamma}_n\) can be obtained by the maximum likelihood estimation.

- **Step 2.** An individual with \(\Delta_i = 1\) is weighted with weight \(\hat{w}_i\) using the estimated linkage probability \(\pi_{\hat{\gamma}_n}(X_i)\). More specifically, for participants with \(Q_i = 1\), the weight is 1; for participants with \(Q_i = 0\) and \(L_i = 1\), the weight is \(1/\pi_{\hat{\gamma}_n}(X_i)\). \(\hat{\beta}_n\) is then obtained by solving (7).
3.2 Time-dependent covariates

In practice, it is common for Cox regression to include time-dependent covariates and we now extend our IPLW method to incorporate the time-dependent covariates. We builds on the work in Lin and Wei (1989) to extend our theoretical results to include time-dependent covariates with the IPLW partial likelihood estimator. Let $X_i(t) = (Z_{1i}^T, Z_{2i}(t)^T)^T \in \mathbb{R}^p$ denotes the covariates vector, where $Z_{1i} \in \mathbb{R}^{d_1}$ corresponds to the baseline (time-independent) covariates and $Z_{2i}(t) \in \mathbb{R}^{d_2}$ corresponds to the time-dependent covariates for $i = 1, \ldots, n$ at time $t$. We have $d_1 + d_2 = p$. $Z_{2i}(t)$ can represent covariates that are continuously monitored during the clinical trial and observational follow-up datasets. For Cox model with a change point (2), $Z_{2i}(t) = I(t > \tau_1)A$. Let $\bar{X}(t) = \{X(s) : s \in [0, t]\}$ denotes the history of covariates vector $X(s)$, up to time $t$. To incorporate time-dependent covariates into the IPLW partial likelihood, we modify the CLAR assumption (A1) as following:

Assumptions.

(D1) The linkage status satisfies that

$$P(L = 1|\hat{T}, \Delta, Q = 0, \bar{X}(\tau_M)) = P(L = 1|Q = 0, Z_1).$$

The distribution of $Z_1$ is not concentrated on a $(d_1 - 1)$ dimensional affine subspace of $\mathbb{R}^{d_1}$.

(D1) assumes that linkage only depends on time-independent covariates $Z_1$ and also ensures the identifiability of $\gamma_0$ (see, e.g., Example 5.40 of Van der Vaart (2000)). We can further relax this assumption such that linkage also depends on $Z_2(C_1)$, the value of time-dependent covariates at the censoring time in clinical trial. For simplicity, we assume that linkage only depends on the baseline (time-independent) covariates. Based on assumption (D1),
we modify the weights as follows:

\[ w_i = \frac{I(L_i + Q_i > 0)}{Q_i + (1 - Q_i)\pi_{\gamma_0}(Z_{1i})} \]

\[ \hat{w}_i = \frac{I(L_i + Q_i > 0)}{Q_i + (1 - Q_i)\pi_{\gamma_0}(Z_{1i})} \]

with \( \gamma_0 \in \mathbb{R}^{d+1} \). The IPLW partial score incorporating time-dependent covariates is now as follows:

\[ \hat{U}_n(\beta) = \frac{1}{n} \sum_{i=1}^{n} \Delta_i \hat{w}_i \left\{ X_i(\hat{T}_i) - \frac{S_{n,w}^{(1)}(\beta, \hat{T}_i)}{S_{n,w}^{(0)}(\beta, \hat{T}_i)} \right\} = \frac{1}{n} \sum_{i=1}^{n} \hat{w}_i \int_{0}^{\tau_2} X_i(t) dN_i(t) - \int_{0}^{\tau_2} \frac{S_{n,w}^{(1)}(\beta, t)}{S_{n,w}^{(0)}(\beta, t)} d\bar{N}(t) \]

(8)

with \( S_{n,w}^{(k)}(\beta, t) = \frac{1}{n} \sum_{i=1}^{n} \hat{w}_i Y_i(t) \exp(\beta^T X_i(t)) X_i(t)^{\otimes k} \).

We redefine \( s^{(k)}(\beta, t) = \mathbb{E}[Y(t) \exp(\beta^T X(t)) X(t)^{\otimes k}] \) and \( s^{(k)}(t) = \mathbb{E}[Y(t) \lambda(t)|\bar{X}(t)] X(t)^{\otimes k} \)

where \( \lambda(t)|\bar{X}(t) \) is the true hazard function for participants with covariates history \( \bar{X}(t) \).

The estimated parameter \( \hat{\beta}_n \) solves \( \hat{U}_n(\beta) = 0 \) and its population version \( \beta^*_0 \) solves \( U_0(\beta) = 0 \) with

\[ U_0(\beta) = \mathbb{E} \left[ \Delta \left( X(\bar{T}) - \frac{s^{(1)}(\beta, \bar{T})}{s^{(0)}(\beta, \bar{T})} \right) \right] = \int_{0}^{\tau_2} s^{(1)}(t) dt - \int_{0}^{\tau_2} \frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)} s^{(0)}(t) dt \]

In addition to (D1), we consider the following technical assumptions.

**Assumptions.**

(D2) The time-dependent covariates \( X_i(t) \) have bounded total variation such that \( \|X_i(0)\|_1 + \int_{0}^{\tau_2} \|dX_i(t)\|_1 \leq B \) for a fixed constant \( B > 0 \).

(D3) \( P(L = 1|Q = 0, Z_1) = \pi_{\gamma_0}(Z_1) \geq \delta > 0 \) for all possible values of \( Z_1 \).

(D4) The failure time and censoring time satisfy

\[ P(T \geq s|C_1, C_2, \bar{X}(s)) = P(T \geq s|\bar{X}(s)) \]

for \( s \in [0, \tau_2] \) and \( P(\bar{T} \geq \tau_2) > 0 \).

(D5) \( \Sigma_0 = \int_{0}^{\tau_2} \left\{ \frac{s^{(2)}(\beta^*_0, t)}{s^{(0)}(\beta^*_0, t)} - \left( \frac{s^{(1)}(\beta^*_0, t)}{s^{(0)}(\beta^*_0, t)} \right)^{\otimes 2} \right\} s^{(0)}(t) dt \) is positive definite.
(D2) assumes that time-dependent covariates have bounded variation (Bilias et al., 1997). (D3) is a standard positivity assumption for IPW type approach. (D4) is an independent censoring assumption (Bilias et al., 1997) and basically requires that a positive fraction of participants are still at-risk after the end of the observational dataset. (D5) is a standard assumption for Cox models (Andersen and Gill, 1982; Lin and Wei, 1989) that ensures the uniqueness of $\beta_0^*$. Now we present the consistency and asymptotic normality of $\hat{\beta}_n$.

**Theorem 3.2** (Asymptotic results of $\hat{\beta}_n$). Let $\hat{\beta}_n$ be the solution to the equation $\hat{U}_n(\beta) = 0$. Under assumptions (D1) - (D5), we have $\hat{\beta}_n \rightarrow_p \beta_0^*$ and $\sqrt{n}(\hat{\beta}_n - \beta_0^*) \rightarrow_d N(0, \Sigma_0^{-1}\Sigma_U\Sigma_0^{-1})$ and the form of $\Sigma_U$ can be found in Theorem A.1 (supplementary material).

Our proof builds on the convergence results for the underlying IPLW empirical process and we give the relevant results for the IPLW process in Appendix B (supplementary material). In particular, we proved the Glivenko-Cantelli property of the IPLW empirical process and adopt the strategy in (Andersen and Gill, 1982) for the consistency proof. Next we follow Lin and Wei (1989) to derive the asymptotic linear form for our IPLW partial likelihood estimator and we further establish the weak convergence results of the IPLW empiricall process to prove the asymptotic normality.

**Remark 3.3.** We further consider the augmented inverse probability of linkage weighting (AIPLW) estimator in Appendix D (supplementary material). We give the augmented estimating equation and prove that AIPLW estimator is “doubly”-robust when either the linkage probability is consistently estimated or three regression functions are consistently estimated. The limitation of the AIPLW estimator is that we need to consistently estimate three regression functions. These three regression functions are themselves variational dependent and congenial parametric modeling can be difficult for all three functions. On the other hand, nonparametric estimation technique does not have the model congeniality problem,
Figure 3: Revisiting the motivating example in section 2.3. Our approach and the oracle approach are the only methods leading to a valid confidence interval.

but suffers from the curse of dimensionality when there are a large number of covariates. For these reasons, we decide to not implement this “doubly”-robust estimator.

4 Simulation

We now compare the performances of our proposed IPLW method with several other methods, including complete-case analysis (CC), complete-case analysis plus (CC+), Non-linked as censored (NLAC) and the oracle method. The oracle method assumes that all participants in the clinical trial are linked to the observational follow-up dataset. We first revisit the motivating example in section 2.3. Figure 3 shows that our proposed IPLW method gives both consistent estimates and correct coverages for the 95% confidence intervals. On the other hand, CC+, CC and NLAC all give below nominal coverages and inconsistent estimates.

We next perform a more comprehensive set of simulations. We consider the following data generation settings. The hazard function is $\lambda(t|X(t)) = \lambda_0(t) \exp(\beta_1 X_1 + \beta_2 X_2 +$
\( \beta_3 X_3(t) \times X_1 \) and \( \beta_0 = (\beta_1, \beta_2, \beta_3) = (-\ln(4), \ln(1.5), 0.5) \). \( X_1 \) follows a Bernoulli distribution with probability 0.5, \( X_2 \) follows a normal distribution with mean and variance both being 1 and \( X_3 = I(t \geq \tau_1) \) where \( \tau_1 \) is the end time of clinical trial. If we treat \( X_1 \) as the variable for treatment assignment, \( \beta_3 \) now represents the difference between the treatment effect after and before \( \tau_1 \). This is the Cox model with a change point at \( \tau_1 \) (2).

The baseline hazard function is \( \lambda_0(t) = 0.06 \). \( C_1 \) is exponentially distributed with rate 0.01\( X_1 + 0.03 \) and the censoring time \( C_2 \) is set as \( C_1 \) plus an exponential random variable with rate 0.05\( X_1 + 0.03 \). Further, we set \( \tau_1 = 5 \) and \( \tau_2 = 16 \). Three linkage mechanisms are considered as follows:

1. \( P(L = 1) = 0.5 \) and \( L \) is independent of all other variables. This is the linking completely at random (LCAR) case.

2. \( \log \{ P(L = 1|X, Q = 0)/P(L = 0|X, Q = 0) \} = -0.25 + 0.5X_1 + 0.5X_2 \) and \( P(L = 1|Q = 1) = 0.5 \). Thus the linkage satisfies CLAR assumption.

3. \( \log \{ P(L = 1|X, Q = 0, \tilde{T}, \Delta)/P(L = 0|X, Q = 0, \tilde{T}, \Delta) \} = -0.25 + 0.5X_1 + 0.5X_2 - 0.01\tilde{T} - 0.01\Delta \) and \( P(L = 1|Q = 1) = 0.5 \). This is the linking not at random (LNAR(\( \tilde{T} \))) case.

Both mechanisms (1) and (2) satisfy our CLAR assumption. Mechanism (2) shows that under the CLAR assumption, data linkage can still depend on the survival outcomes through the in-trial censoring indicator \( Q \). Mechanism (3) slightly violates the CLAR assumption and serves as a case for sensitivity analysis.
Table 1: Simulation results when Cox model is correctly specified when $n = 2000$.

| Mechanism | Method  | $\beta_1$ (Mean SE) | $\beta_2$ (Mean SE) | $\beta_3$ (Mean SE) | Coverage of 95% CI |
|-----------|---------|---------------------|---------------------|---------------------|--------------------|
| LCAR      | Oracle  | -0.00 (0.108)       | 0.00 (0.033)        | -0.00 (0.140)       | 0.94 0.95 0.96     |
| CC        | -0.00 (0.153) | 0.00 (0.046)        | -0.01 (0.199)       | 0.95 0.96 0.96      |
| CC+       | 0.13 (0.110)    | -0.03 (0.038)       | -0.13 (0.168)       | 0.77† 0.86† 0.89†   |
| NLAC      | -0.00 (0.110)   | 0.00 (0.038)        | -0.01 (0.168)       | 0.94 0.95 0.95      |
| IPLW      | -0.00 (0.114)   | 0.00 (0.041)        | -0.01 (0.170)       | 0.94 0.95 0.95      |
| CLAR      | Oracle  | -0.00 (0.108)       | 0.00 (0.033)        | -0.00 (0.140)       | 0.94 0.95 0.96     |
| CC        | -0.18 (0.151)   | -0.06 (0.045)       | 0.19 (0.188)        | 0.79† 0.75† 0.83†   |
| CC+       | -0.07 (0.109)   | -0.10 (0.038)       | 0.09 (0.157)        | 0.91 0.23† 0.91     |
| NLAC      | -0.00 (0.109)   | 0.00 (0.037)        | -0.00 (0.157)       | 0.94 0.95 0.95      |
| IPLW      | -0.00 (0.110)   | 0.00 (0.040)        | -0.00 (0.159)       | 0.94 0.95 0.96      |
| LNAR ($\tilde{T}$) | Oracle  | -0.00 (0.108)       | 0.00 (0.033)        | -0.00 (0.140)       | 0.94 0.95 0.96     |
| CC        | -0.19 (0.151)   | -0.07 (0.045)       | 0.20 (0.189)        | 0.79† 0.69† 0.84†   |
| CC+       | 0.07 (0.109)    | -0.11 (0.038)       | 0.09 (0.158)        | 0.92 0.16† 0.92     |
| NLAC      | -0.00 (0.109)   | 0.00 (0.037)        | -0.01 (0.158)       | 0.94 0.95 0.95      |
| IPLW      | -0.00 (0.111)   | -0.00 (0.041)       | -0.01 (0.160)       | 0.94 0.95 0.95      |
| LNAR ($C_2$) | Oracle  | -0.00 (0.108)       | 0.00 (0.033)        | -0.00 (0.140)       | 0.94 0.95 0.96     |
| CC        | -0.31 (0.154)   | -0.16 (0.055)       | 0.33 (0.229)        | 0.47† 0.16† 0.70†   |
| CC+       | -0.12 (0.111)   | -0.22 (0.043)       | 0.14 (0.202)        | 0.83† 0.00† 0.88†   |
| NLAC      | -0.00 (0.110)   | 0.00 (0.042)        | -0.02 (0.202)       | 0.93 0.95 0.95      |
| IPLW      | -0.00 (0.117)   | 0.01 (0.057)        | -0.02 (0.211)       | 0.93 0.94 0.94      |

We use † to highlight settings with coverage below 90%.
Table 2: Simulation results for when Cox model is misspecified and $n = 2000$. 

| Mechanism | Method | $\beta_1$ | $\beta_2$ | $\beta_1$ | $\beta_2$ |
|-----------|--------|-----------|-----------|-----------|-----------|
| LCAR      | Oracle | -0.00 (0.068) | 0.00 (0.033) | 0.93 | 0.94 |
|           | CC     | -0.00 (0.096) | 0.00 (0.046) | 0.93 | 0.96 |
|           | CC+    | -0.00 (0.081) | -0.03 (0.038) | 0.93 | 0.84† |
|           | NLAC   | -0.08 (0.081) | 0.00 (0.038) | 0.82† | 0.95 |
|           | IPLW   | -0.00 (0.087) | 0.00 (0.042) | 0.94 | 0.95 |
| CLAR      | Oracle | -0.00 (0.068) | 0.00 (0.033) | 0.93 | 0.94 |
|           | CC     | -0.04 (0.087) | -0.06 (0.045) | 0.92 | 0.76† |
|           | CC+    | -0.08 (0.075) | -0.10 (0.038) | 0.81† | 0.25† |
|           | NLAC   | -0.05 (0.076) | 0.00 (0.037) | 0.89† | 0.95 |
|           | IPLW   | -0.00 (0.079) | 0.00 (0.040) | 0.93 | 0.95 |
| LNAR($\bar{T}$) | Oracle | -0.00 (0.068) | 0.00 (0.033) | 0.93 | 0.94 |
|           | CC     | -0.05 (0.088) | -0.07 (0.046) | 0.91 | 0.70† |
|           | CC+    | -0.09 (0.076) | -0.11 (0.038) | 0.78† | 0.17† |
|           | NLAC   | -0.06 (0.077) | -0.00 (0.038) | 0.88† | 0.94 |
|           | IPLW   | -0.00 (0.080) | -0.00 (0.041) | 0.93 | 0.95 |

We use † to highlight settings with coverage below 90%.

We consider sample sizes $n = 500, 1,000, \ldots, 10,000$ and we generate 1,000 samples for each simulation setting. We fit two Cox regressions. The first Cox regression is fitted with covariates $X_1, X_2, X_3(t) \times X_1$ and the second Cox regression is fitted with $X_1$ and $X_2$. 

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only. Thus, Cox regression is correctly specified for the first regression and mis-specified for the second regression. This suggests that $\beta^*_0 = \beta_0$ for the first Cox regression. For the misspecified case, $\beta^*_0$ is estimated with the oracle method by computing the averages of 1,000 parameter estimates with sample size $n = 10,000$. The mis-specified regression omits the time-dependent covariate $X_3(t) \times X_1$ and thus ignores the change-point at $\tau_1$ for the treatment effect. The corresponding parameter $\beta^*_1$ for $X_1$ can be interpreted as an averaging effect for the entire follow-up period and is equal to $-1.10$, between the clinical trial treatment effect $-\ln(4) \approx -1.39$ and the observational follow-up treatment effect $-\ln(4) + 0.5 \approx -0.89$.

We use the robust variance estimate (Lin and Wei, 1989) when Cox model is misspecified for all methods other than the IPLW method. For the IPLW method, the variance estimate is automatically robust when Cox model is misspecified. When Cox model is correctly specified, one additional mechanism for linkage is considered as

$$\log \{ P(L = 1|X, Q = 0, C_2, \Delta)/P(L = 0|X, Q = 0, C_2, \Delta) \} = -0.25 + 0.5X_1 + 0.5X_2 - 0.1C_2 - 0.1\Delta$$

and $P(L = 1|Q = 1) = 0.5$. We call this linkage mechanism LNAR($C_2$).

Mechanism (4) is a more serious violation of the CLAR assumption and linkage now depends on the unobserved censoring time $C_2$. As discussed in section 6, NLAC should still work under this linkage mechanism. The percentages of samples that are not linked and censored in the clinical trial are approximately 39%, 30%, 32%, 51% for these four mechanisms.

Simulation results are reported in Tables 1 - 2. In the table, bias is the difference of the average of 1,000 parameter estimates and the true parameter value. Mean standard error (SE) is the average of 1,000 SE estimates. CI stands for confidence interval. We first discuss the results when Cox model is correctly specified. When linkage satisfies LCAR, all methods give consistent estimates and correct coverages for the 95% confidence intervals.
except CC+. Oracle method gives the smallest variance estimates as each participant is linked. NLAC gives the second smallest variance estimates. CC can be viewed as an IPW method with known probability as the weights and it has the largest variance estimates among all methods. Our proposed IPLW method gives smaller variance estimates than CC for two reasons. First, IPLW method uses more data than CC; second, IPLW method uses estimated weights, which is known to be more efficient than IPW method with known probability as weights.

When linkage satisfies CLAR but not LCAR, only oracle method, NLAC and our proposed IPLW method give consistent estimate. When CLAR is slightly violated, CC, CC+ all obtain severely biased estimates and confidence intervals with less than nominal coverages. NLAC and our proposed IPLW method still perform relatively well in this case. When linkage depends on the censoring time in observational follow-up $C_2$, NLAC gives consistent estimates and correct coverage as expected. For this particular simulation setting, our proposed IPLW method also works pretty well.

Next, we discuss the simulation results when Cox model is misspecified. When linkage satisfies LCAR, CC+ and NLAC give inconsistent estimates of the parameters and do not achieve nominal coverage for 95% confidence intervals. It is expected that CC would perform well in this case as discussed in section 2.3. Further, NLAC always obtains severely negatively biased estimate of $\beta_1^*$, the averaging treatment effect. Our proposed IPLW method again obtains smaller variance estimates than CC as more data are fitted and estimated weights improve efficiency. When the linkage satisfies CLAR but not LCAR, only oracle method and IPLW method give consistent estimates and correct coverages. When CLAR is slightly violated, IPLW approach performs best among all methods other than the oracle method.
5 SWOG study

We apply the proposed IPLW method to the SWOG study that links medicare claims data to the PCPT data (Unger et al., 2018). The PCPT randomly assigned 18,880 eligible men from 1993 to 1997 to finasteride or placebo daily for seven years. PCPT clinical records are linked to participants’ medicare claims data according to common social security number, sex and date of birth. Medicare claims are available from 1999 to 2011. The linkage enables PC to be identified by both clinical records and medicare claims. 14,176 (75.1\%) participants were linked to medicare claims (finasteride = 7069; placebo = 7107)\textsuperscript{3}. The median time from treatment random assignment to the end of the linked trial medicare dataset was 16 years. We are interested in studying the effect of treatment finasteride on the time to diagnosis of PC. Death is treated as censoring.

Of the 14,176 participants with a link to the medicare, 2,037 have a gap between the end of SWOG trial and the start of medicare claims. The median length of the gap was 1.6 years. We exclude those participants with a gap. We fit Cox regression with covariates including the prostate-specific antigen (PSA) level at study entry, race, body mass index at study entry, first degree family history of prostate cancer, age at baseline. Additional covariates were included for logistic regression modeling linkage: participants’ education level, marital status, employment status, type of jobs. We further remove participants with any missing covariates and we have 16,518 participants left in the study.

Following the studies in Unger et al. (2018), Cox regressions with two change points at 6.5 and 7.5 years are fitted to account for potential differing treatment effects within critical periods of follow-up. We compared the results of CC, CC+, NLAC and our proposed IPLW method in table 3. Table 3 contains the parameter estimates and 95\% confidence

\textsuperscript{3}See Unger et al. (2018) for details on linkage criteria
intervals for treatment Finasteride in different time periods\textsuperscript{4}. Overall, the results does not differ much between all four methods based on the 95% confidence intervals. A key reason might be that the linkage rate was high for the original study (Unger et al., 2018) as 75% of the participants were linked. Further, they examined potential health care utilization differences by arm and other potential biases in Unger et al. (2018) and found no evidence of strong differences. This suggests that linkages might be following a LCAR mechanism. We also obtained robust variance estimates (Lin and Wei, 1989) and the corresponding confidence intervals. The results are very similar to the nonrobust ones. In summary, finasteride arm participants had a 30% decrease in the hazard ratio of prostate cancer (hazard ratio (HR) = 0.70, 95% confidence intervals (CI) = 0.61 - 0.80) during the first 6.5 years. The effect of finasteride is strongest between 6.5 - 7.5 years (HR = 0.67, 95% CI = 0.60 - 0.75). The long-term effect of finasteride after the 7.5 years does not seem to increase the risk of PC (HR = 1.11, 95% CI = 0.95 - 1.30). It is worth noting that CC, CC+ and NLAC obtain more similar long-term effects estimates compared to our proposed IPLW methods. We further fit a Cox regression without any change points and the results are in table 4. The results again does not differ too much between all four methods, despite the fact that CC, CC+ and NLAC share more similar results compared to our IPLW method. In summary, the long-term effect of finasteride, now estimating the averaging effect over the entire follow-up period, is still beneficial (HR = 0.79, 95% CI = 0.73 - 0.85).

\textsuperscript{4}on the exponential level
Table 3: SWOG study long-term effect estimation with two change points

| Methods | Finasteride (0 - 6.5 years) | Finasteride (6.5 - 7.5 years) | Finasteride (7.5 years + ) |
|---------|-----------------------------|------------------------------|-----------------------------|
| IPLW    | 0.696 (0.607 - 0.797)       | 0.670 (0.599 - 0.749)        | 1.113 (0.951 - 1.303)       |
| CC      | 0.683 (0.587 - 0.795)       | 0.662 (0.586 - 0.747)        | 1.087 (0.933 - 1.265)       |
| CC+     | 0.699 (0.610 - 0.801)       | 0.663 (0.594 - 0.740)        | 1.086 (0.933 - 1.265)       |
| NLAC    | 0.697 (0.608 - 0.798)       | 0.668 (0.600 - 0.744)        | 1.079 (0.927 - 1.257)       |

Table 4: SWOG study long-term effect estimation with no change points

| Methods | Finasteride     |
|---------|-----------------|
| IPLW    | 0.790 (0.732 - 0.853) |
| CC      | 0.767 (0.708 - 0.831) |
| CC+     | 0.758 (0.704 - 0.816) |
| NLAC    | 0.757 (0.703 - 0.814) |

6 Comparison of NLAC and IPLW

Now we give a detailed comparison between NLAC and IPLW method. For notational simplicity, we only present the results with time-independent covariates. When Cox model is correctly specified, NLAC gives consistent estimates as long as censoring time $C$ is independent of $T$ given $X$. Recall the censoring time is modified as

$$C_{NLAC} = L \max(C_1, C_2) + (1 - L)C_1 = L[\max(C_1, C_2) - C_1] + C_1$$
with NLAC. The independent censoring assumption holds if

\[ (N1) \quad L \perp T|X, C_1, C_2 \]

holds since

\[ (N1) + (C_1, C_2) \perp T|X \Rightarrow (L, C_1, C_2) \perp T|X \]

and \((L, C_1, C_2) \perp T|X\) implies that \(C_{NLAC} \perp T|X\). Further, we study how NLAC works under the CLAR assumption. First, we can modify the CLAR assumption as

\[ (N2) \quad L \perp (\tilde{T}, \Delta)|X, Q = 0, C_1 \]

as \(C_1\) is always observed when \(Q = 0\) and one sufficient assumption for \((N2)\) is

\[ (N3) \quad L \perp (T, C_2)|(X, Q = 0, C_1). \]

With a bit abuse of notation, we also call assumption \((N3)\) the CLAR assumption. Next, we have the following proposition.

**Proposition 6.1.** When Cox model is correctly specified and \((C_1, C_2) \perp T|X\), if the following assumption

\[ (N4) \quad L \perp (X, Q = 0, C_1, C_2) \]

holds, NLAC provides consistent estimates for \(\beta_0\).

The proof is given in Appendix E (supplementary material). By the weak union property of conditional independence, we have that

\[ (N3) \Rightarrow (N4) \]

On the other hand, using the contraction property of conditional independence, we further have

\[ (N4) + L \perp C_2|X, Q = 0, C_1 \Rightarrow (N3) \]
Thus, to conclude, NLAC works under a slightly weaker assumption than CLAR (N3) in that the linkage can further depends on the potentially missing $C_2$. On the other hand, when Cox model is mis-specified, the parameter of interest $\beta_0^*$ now depends on the actual distribution of the censoring time $C = \max(C_1, C_2)$ and NLAC always gives inconsistent parameter estimates of $\beta_0^*$ since the distribution of the censoring time is modified. In contrast, our proposed IPLW method still gives consistent estimates under the CLAR assumption (A1).

7 Discussion

In this paper, we consider the problem of long-term effect estimation by fitting a Cox model to a partially linked dataset. We propose a novel CLAR assumption that allows us to construct an elegant IPLW estimator that consistently estimates the underlying parameters as if all participants are linked.

There have been a limited number of studies on incomplete linkages, other than Kim and Chambers (2012), but their focus is on linear regression with probabilistic record linkage. While Baldi et al. (2010) have discussed potential biases caused by incomplete linkages for Cox regression with simulation studies, no theoretical analysis has been conducted. In contrast, we consider the problem when data is linked by unique identifiers and thus we do not need account for incorrect linkages. This allows us to develop rigorous asymptotic theories for our proposed estimators and also compare with some other alternative methods. Here we point out some possible future directions.

- **Interval Censoring.** We have made the “no gap” assumption in the current paper to focus on the right censoring problem for simplicity. However, in practice, it is possible that there might be gaps between the clinical trial and observational follow-
up dataset. Thus, to fully deal with the problem, we need to extend our current procedure to the interval censoring case as mentioned in Appendix F (supplementary material). Saegusa and Wellner (2013) has studied the problem of two-phase sampling for Cox models under interval censoring. Generalizing their techniques to the current linkage problem remains an open question.

• Beyond CLAR and sensitivity analysis. CLAR may not hold in certain situations. For instance, if the data being linked is from another study, in which the time to event variable \( T \) may influence the chance that someone participates, then (A1) will no longer be true. In this case, we may need to model the linkage probability that depends on \( T \), which could be seen as a sensitivity analysis (Little et al., 2012; Little and Rubin, 2019) on perturbing assumption (A1). How to analyze the data in this case is left as a future work.

• Missing covariates. Another direction that we will be exploring is the case of missing covariates (Tsiatis, 2007). Missing covariates is a common issue in medical research. When part of \( X \) is missing, CLAR will no longer be enough to identify the underlying parameter since the linkage probability cannot be computed for every individual. In this case, we have to impose additional assumptions on the missingness of \( X \). However, such assumption has to be carefully chosen so that it will not conflict with the assumption on the linkage.

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SUPPLEMENTARY MATERIAL
The supplementary material contains the following appendices. Appendix A contains the derivation of IPLW partial score. Appendix B and C contains the results for IPLW empirical process theory and the proof for technical results. Appendix D discusses the doubly robust estimator. Appendix E contains more discussions of linkage assumptions and NLAC method. Appendix F discusses the relaxation of the “no gap” assumption. Appendix G and H contain more simulation results.

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### A Derivation of IPLW partial score

Assume that there are \( n_{00} \) observations with \( L = 0 \) and \( Q = 0 \) (Class 3 of Figure 1) and define weight \( \hat{w}_i = \frac{I(L_i + Q_i > 0)}{Q_i + (1 - Q_i)\pi_{\gamma_0}(X_i)} \). Now we are ready to derive the IPLW partial likelihood for estimating \( \beta_0^* \). Assume that \( \tilde{T}_{(1)} < \tilde{T}_{(2)} < \cdots < \tilde{T}_{(n-n_{00})} \) are the ordered \( \tilde{T}_i \)'s, and \( X_i, L_i, Q_i, \Delta_i \) are the corresponding covariates, linkage indicator, in-trial censoring
Thus, maximizing this with respect to $l$ and thus we only need to consider the case where $l_n(\beta, \lambda_0) = l_n(\beta, h)$. As a result, the IPLW log-likelihood can be rewritten as:

$$l_n(\beta, \lambda_0) = l_n(\beta, h) = \frac{1}{n} \sum_{i=1}^{n} \left[ \Delta_{(i)} \log h_i + \Delta_{(i)} X_{(i)}^T \beta - \exp(X_{(i)}^T \beta) \sum_{j \leq i} h_j \right].$$

Thus, maximizing this with respect to $h = (h_1, \ldots, h_{n-n_0})$ leads to

$$\hat{h}_i = \frac{\Delta_{(i)} \hat{w}_{(i)}}{\sum_{j \geq i} \hat{w}_{(j)} \exp(X_{(j)}^T \beta)}$$

Take $\hat{h} = (\hat{h}_1, \ldots, \hat{h}_{n-n_0})$ back to the empirical log-likelihood, we obtain the IPLW partial log-likelihood

$$\mathcal{L}_n(\beta) = l_n(\beta, \hat{h}) = \frac{1}{n} \sum_{i=1}^{n} \Delta_{(i)} \hat{w}_{(i)} \left( X_{(i)}^T \beta - \log \left( \sum_{j \geq i} \hat{w}_{(j)} \exp(X_{(j)}^T \beta) \right) \right)$$

which can be further simplified as

$$\mathcal{L}_n(\beta) = \frac{1}{n} \sum_{i=1}^{n} \Delta_{(i)} \hat{w}_{(i)} \left( X_{(i)}^T \beta - \log \left( \sum_{j=1}^{n} I(\tilde{T}_j \geq \tilde{T}_i) \hat{w}_j \exp(X_{(j)}^T \beta) \right) \right)$$

and then the partial score is

$$\hat{U}_n(\beta) = \frac{1}{n} \sum_{i=1}^{n} \Delta_{(i)} \hat{w}_{(i)} \left( X_{(i)} - \frac{\sum_{j=1}^{n} \hat{w}_j I(\tilde{T}_j \geq \tilde{T}_i) \exp(X_{(j)}^T \beta) X_j}{\sum_{j=1}^{n} \hat{w}_j I(\tilde{T}_j \geq \tilde{T}_i) \exp(X_{(j)}^T \beta)} \right), \quad (9)$$

To derive the asymptotic distribution of $\hat{\beta}_n$, note that

$$\hat{U}_n(\beta) - \hat{U}_n(\beta_0^*) = \left. \frac{\partial \hat{U}_n(\beta)}{\partial \beta} \right|_{\beta = \beta_0^*} (\beta - \beta_0^*) + o_P(\|\beta - \beta_0^*\|)$$

Thus, choosing $\beta = \hat{\beta}_n$ leads to

$$\sqrt{n}(\hat{\beta}_n - \beta_0^*) \approx \left( - \left. \frac{\partial \hat{U}_n(\beta)}{\partial \beta} \right|_{\beta = \beta_0^*} \right)^{-1} n^{1/2} \hat{U}_n(\beta_0^*)$$

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As a result, we just need to prove that \[-\frac{\partial \hat{U}_n(\beta)}{\partial \beta} |_{\beta = \beta_0^*} \to_p - \frac{\partial U_0(\beta)}{\partial \beta} |_{\beta = \beta_0^*} = \Sigma_0\] and \[n^{-1/2} \hat{U}_n(\beta_0^*)\] converges to a normal distribution. We prove the second convergence by showing that \[n^{1/2} \hat{U}_n(\beta_0^*)\] has a weighted asymptotically linear expansion: \[n^{1/2} \hat{U}_n(\beta_0^*) = n^{-1/2} \sum_{i=1}^{n} \hat{w}_i U_i(\beta_0^*) + o_p(1)\] with

\[U_i(\beta_0^*) = \int_0^{\tau_2} \left[ X_i(t) - \frac{s^{(1)}(\beta_0^*, t)}{s^{(0)}(\beta_0^*, t)} \right] dN_i(t) - \int_0^{\tau_2} \frac{Y_i(t) \exp(\beta_0^* T X_i(t))}{s^{(0)}(\beta_0^*, t)} \left[ X_i(t) - \frac{s^{(1)}(\beta_0^*, t)}{s^{(0)}(\beta_0^*, t)} \right] d\tilde{N}(t)\]

and \[\tilde{N}(t) = \mathbb{E}[N(t)]\]. Similar asymptotic linear expansions have appeared in Lin and Wei (1989) and Lin (2000). This weighted asymptotic linear expansion motivates the study of the IPLW empirical measure and processes.

We start by giving the weighted asymptotic linear expansion of the IPLW partial score \(\hat{U}_n(\beta)\) and subsequently give its asymptotic distribution.

**Theorem A.1** (Asymptotic linear expansion). Under assumptions (D1) - (D4), we have the following two results:

1. For each \(\beta\), \(n^{1/2} \hat{U}_n(\beta) = n^{-1/2} \sum_{i=1}^{n} \hat{w}_i U_i(\beta) + o_p(1)\) such that

   \[U_i(\beta) = \int_0^{\tau_2} \left[ X_i(t) - \frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)} \right] dN_i(t) - \int_0^{\tau_2} \frac{Y_i(t) \exp(\beta^T X_i(t))}{s^{(0)}(\beta, t)} \left[ X_i(t) - \frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)} \right] d\tilde{N}(t)\]

   with \(\tilde{N}(t) = \mathbb{E}[N(t)]\).

2. \(n^{-1/2} \hat{U}_n(\beta_0^*) \to_d N(0, \Sigma)\) with

   \[\Sigma = \text{Var}[U_1(\beta_0^*)] + \mathbb{E} \left[ U_1(\beta_0^*) U_1(\beta_0^*)^T I(Q = 0)[1 - \pi_{\gamma_0}(Z_1)] \right] \]

   \[\quad - Q_e(U_1(\beta_0^*))^T \Sigma^{-1}(\gamma_0) Q_e(U_1(\beta_0^*))\],

   where \(Q_e(U_1(\beta_0^*)) = P_0[I(Q = 0)(1 - \pi_{\gamma_0}(Z_1)) \tilde{Z}_1 U_1(\beta_0^*)^T]\).

The proof of Theorem A.1 can be found in appendix C. We first prove that the IPLW partial score can be written in the weighted asymptotic linear expansion form (first asser-
tion). Then we use the weak convergence result of the IPLW empirical process from Proposition B.2 to obtain the asymptotic distribution of $n^{1/2} \hat{U}_n(\beta)$. Next recall $-\frac{\partial \hat{U}_n(\beta)}{\partial \beta} = A_n(\beta)$ and we can write $A_n(\beta)$ equivalently as

$$A_n(\beta) = -\frac{\partial \hat{U}_n(\beta)}{\partial \beta} = \int_0^{T_2} \left\{ \frac{S_{n,w}^{(2)}(\beta, t)}{S_{0,w}^{(0)}(\beta, t)} - \left( \frac{S_{n,w}^{(1)}(\beta, t)}{S_{0,w}^{(0)}(\beta, t)} \right)^2 \right\} d\bar{N}(t) \tag{10}$$

and similarly define its population version $A(\beta)$

$$A(\beta) = -\frac{\partial U_0(\beta)}{\partial \beta} = \int_0^{T_2} \left\{ \frac{s^{(2)}(\beta, t)}{s^{(0)}(\beta, t)} - \left( \frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)} \right)^2 \right\} d\bar{N}(t) \tag{11}$$

Under assumption (D5), $A(\beta^*) = \Sigma_0$ is positive definite and we later prove that $A_n(\beta) \to_p A(\beta)$ for $\beta$ in a compact set $\mathbb{B}$ that contains $\beta_0^*$. Together with the asymptotic normality of the IPLW partial score, we can derive the asymptotic normality of the estimator $\hat{\beta}_n$.

## B Empirical process theory for an IPLW process

To study the asymptotic properties of $\hat{\beta}_n$, we need to generalize empirical process theory into an IPW scenario. We first introduce an IPLW empirical measure

$$P_n^\pi = \frac{1}{n} \sum_{i=1}^n \frac{I(L_i + Q_i > 0)}{Q_i + (1 - Q_i)\pi_{\gamma_0}(X_i)} \delta_{X_i, \hat{T}_i, \Delta_i} = \frac{1}{n} \sum_{i=1}^n w_i \delta_{X_i, \hat{T}_i, \Delta_i}$$

where $\delta_{X_i, \hat{T}_i, \Delta_i}$ is the Dirac measure placing unit mass on $(X_i, \hat{T}_i, \Delta_i)$ and $w_i = \frac{I(L_i + Q_i > 0)}{Q_i + (1 - Q_i)\pi_{\gamma_0}(X_i)}$ such that $P_n^\pi f = \frac{1}{n} \sum_{i=1}^n w_i f(X_i, \hat{T}_i, \Delta_i)$ for a function $f = f(x, \hat{T}, \delta)$. In practice, $\pi_{\gamma_0}(X_i)$ is unknown, so we introduce the IPLW empirical measure with estimated weight

$$P_n^{\pi,e} = \frac{1}{n} \sum_{i=1}^n \frac{I(L_i + Q_i > 0)}{\hat{Q}_i + (1 - Q_i)\pi_{\hat{\gamma}_n}(X_i)} \delta_{X_i, \hat{T}_i, \Delta_i} = \frac{1}{n} \sum_{i=1}^n \hat{w}_i \delta_{X_i, \hat{T}_i, \Delta_i}$$

with $\gamma_0$ replaced by $\hat{\gamma}_n$. Finally, we denote $P_0$ as the probability measure corresponding to the true distribution such that $P_0 f = \mathbb{E}[f(X, \hat{T}, \Delta)]$. Note the usual empirical measure
\( P_n = \frac{1}{n} \sum_{i=1}^{n} \delta_{X_i, \hat{t}_i, \Delta_i} \) is unobserved due to the missingness in Class 3 of Figure 1. The IPLW empirical measure leads to the IPLW empirical processes \( G_n = \sqrt{n}(P_n - P_0) \) and \( G_n^e = \sqrt{n}(P_n^e - P_0) \). It turns out that our IPLW empirical measure and empirical process also enjoy similar asymptotic properties as the usual empirical measure and empirical processes. For any \( \phi : \mathcal{F} \to \mathbb{R} \), we write \( \|\phi(f)\|_\mathcal{F} = \sup_{f \in \mathcal{F}} |\phi(f)| \). We say that \( \mathcal{F} \) is \( P \)-Glivenko-Cantelli if and only if \( \sup_{f \in \mathcal{F}} |(P_n - P)f| = o_P(1) \). We first prove that Glivenko-Cantelli property also holds for the IPLW empirical process.

**Proposition B.1** (IPLW uniform convergence). Suppose that \( \mathcal{F} = \{f(x, \hat{t}, \delta)\} \) is \( P_0 \)-Glivenko-Cantelli with an integrable envelope function \( F \) such that \( P_0 F < \infty \). Under assumption (A1-3),

\[
\|P_n - P_0\|_\mathcal{F} \to_{p*} 0.
\]

If \( \hat{\gamma}_n \to_p \gamma_0 \), then \( \|P_n^e - P_0\|_\mathcal{F} \to_{p*} 0 \) also holds.

The proof can be found in Appendix C. Recall that \( \tilde{X} = (1, X^T)^T \) and \( \tilde{x} = (1, x^T)^T \).

Now, to definite weak convergence, let \( X_n \) be a bounded process and \( X \) be a bounded process whose finite-dimensional laws correspond to the finite dimensional projections of a tight Borel law on \( \ell^\infty(\mathcal{F}) \). We say that \( X_n \rightsquigarrow X \) in \( \ell^\infty(\mathcal{F}) \) if and only if \( E^*H(X_n) \to E H(X) \) for all \( H \in C_b(\ell^\infty(\mathcal{F})) \), where \( C_b(\ell^\infty(\mathcal{F})) \) denotes all bounded continuous functions on \( \ell^\infty(\mathcal{F}) \) (Van Der Vaart and Wellner, 1996; Van der Vaart, 2000). The next theorem states that the weak convergence result for IPLW empirical process.

**Proposition B.2** (IPLW weak convergence). Under assumption (A1-3), suppose that \( \mathcal{F} = \{f(x, \hat{t}, \delta)\} \) is \( P_0 \)-Donsker with an integrable envelope function \( F \) such that \( P_0 F < \infty \), then

\[
G_n \rightsquigarrow G(g_1)
\]

\[
G_n^e \rightsquigarrow G^e = G(g_1 \cdot -g_2 Q_{g_1}(\cdot)^T g_3)
\]
in $l^\infty(\mathcal{F})$ where $g_1(l, q, x) = \frac{I(l + q > 0)}{q + (1-q)\pi_{\gamma_0}(x)}$, $g_2(l, q, x) = I(q = 0)[l - \pi_{\gamma_0}(x)]$, $g_3(x) = \Sigma_{\gamma_0}^{-1}x$ and $Q_c(f) = \mathbb{E}[I(Q = 0)(1 - \pi_{\gamma_0}(x))f(X, \tilde{T}, \Delta)]$. $G$ is the $\mathbb{P}_0$-Brownian bridge process, indexed by $\mathcal{F}$.

C Proofs

Proof of Proposition 3.1. For simplicity, denote $P(L = 1|Q = 0, X) = \pi_0(X)$. First, we have

\[
\mathbb{E}\left[\frac{I(L = 1)l(\beta, \lambda_0)}{\pi_0(X)}\bigg|Q = 0\right] = \mathbb{E}\left[\mathbb{E}\left[\frac{I(L = 1)l(\beta, \lambda_0)}{\pi_0(X)}\bigg|Q = 0, X, \tilde{T}, \Delta\right]\bigg|Q = 0\right]
\]

\[
= \mathbb{E}\left[\frac{l(\beta, \lambda_0)}{\pi_0(X)}\mathbb{E}\left[I(L = 1)\bigg|Q = 0, X, \tilde{T}, \Delta\right]\bigg|Q = 0\right]
\]

\[
= \mathbb{E}\left[l(\beta, \lambda_0)|Q = 0\right]
\]

The second to last equality holds as $l(\beta, \lambda_0)$ is a function of $\tilde{T}, X, \Delta$. The last equality holds by assumption (A1). To prove (6), we have

\[
\mathbb{E}\left[\frac{I(L + Q > 0)}{Q + (1 - Q)\pi_0(X)}l(\beta, \lambda_0)\right] = \mathbb{E}\left[\frac{I(L = 1)}{\pi_0(X)}l(\beta, \lambda_0)\bigg|Q = 0\right]P(Q = 0) + \mathbb{E}\left[l(\beta, \lambda_0)|Q = 1\right]P(Q = 1)
\]

\[
= \mathbb{E}\left[l(\beta, \lambda_0)|Q = 0\right]P(Q = 0) + \mathbb{E}\left[l(\beta, \lambda_0)|Q = 1\right]P(Q = 1) = \mathbb{E}(l(\beta, \lambda_0))
\]

We first give the asymptotic distribution of $\widehat{\gamma}_n$, the estimates of the logistic regression parameter $\gamma_0$.

Lemma C.1. Under assumptions (A1), (A2) and (A3), $\widehat{\gamma}_n$ is consistent for $\gamma_0$ and

\[
\sqrt{n}(\widehat{\gamma}_n - \gamma_0) \xrightarrow{d} N(0, \Sigma_{\gamma_0}^{-1})
\]

where $\Sigma_{\gamma_0} = \mathbb{E}\left[I(Q = 0)\frac{\exp(\tilde{X}^T\gamma_0)\tilde{X}\tilde{X}^T}{1 + \exp(\tilde{X}^T\gamma_0)^2}\right] = \mathbb{E}[I(Q = 0)\pi_{\gamma_0}(X)(1 - \pi_{\gamma_0}(X))\tilde{X}\tilde{X}^T]$. 39
**Proof of Lemma C.1.** First, the score for logistic regression converges as

\[ S_n(\gamma) = \frac{1}{n} \sum_{i=1}^{n} I(Q_i = 0) \left[ L_i \hat{\mathbf{x}}_i - \frac{\exp(\mathbf{X}_i^T \gamma) \hat{\mathbf{x}}_i}{1 + \exp(\mathbf{X}_i^T \gamma)} \right] \to_p \mathbb{E} \left[ I(Q = 0) \left( L \hat{\mathbf{x}} - \frac{\exp(\mathbf{X}^T \gamma) \hat{\mathbf{x}}}{1 + \exp(\mathbf{X}^T \gamma)} \right) \right] = S(\gamma) \]

and

\[ S(\gamma_0) = \mathbb{E} \left[ I(Q = 0) \left( L \hat{\mathbf{x}} - \frac{\exp(\mathbf{X}^T \gamma_0) \hat{\mathbf{x}}}{1 + \exp(\mathbf{X}^T \gamma_0)} \right) \right] = \mathbb{E} \left( I(Q = 0) \left[ \mathbb{E}[L|Q, \mathbf{x}] \hat{\mathbf{x}} - \mathbb{P}(L = 1|Q = 0, \mathbf{x}) \right] \right) = 0 \]

since \( \mathbb{E}[L|Q, \mathbf{x}] = I(Q = 0)\mathbb{P}(L = 1|Q = 0; \mathbf{x}) + I(Q = 1)\mathbb{P}(L = 1|Q = 1; \mathbf{x}) \). Further, by the law of large numbers,

\[ \nabla S_n(\gamma) = -\frac{1}{n} \sum_{i=1}^{n} I(Q_i = 0) \frac{\exp(\mathbf{X}_i^T \gamma) \hat{\mathbf{x}}_i \mathbf{X}_i^T}{\left( 1 + \exp(\mathbf{X}_i^T \gamma) \right)^2} \to_p -\mathbb{E} \left[ I(Q = 0) \frac{\exp(\mathbf{X}^T \gamma) \hat{\mathbf{x}} \hat{\mathbf{x}}^T}{(1 + \exp(\mathbf{X}^T \gamma))^2} \right] = -\Sigma(\gamma) \]

We assume that \( \Sigma(\gamma) \) is positive-definite, thus \( \gamma_0 \) is the unique solution for \( S(\gamma) = 0 \). Next we verify the uniform convergence condition:

\[ \sup_{\gamma} \| S_n(\gamma) - S(\gamma) \| \to_p 0 \]

Denote \( \phi_\gamma(l, q, x) = I(q = 0) \left[ l - \pi_\gamma(x) \right] \hat{x} \) and \( S_n(\gamma) - S(\gamma) = (\mathbb{P}_n - \mathbb{P}_0) \phi_\gamma \). The function class \( \{ \phi_\gamma(l, q, x) : \gamma \} \) forms a VC-subgraph class by Lemma 2.6.15, 2.6.18 of Van Der Vaart and Wellner (1996). Thus, by Theorem 5.9 of Van der Vaart (2000), we have \( \hat{\gamma}_n \to_p \gamma_0 \).

For asymptotic normality of \( \hat{\gamma}_n \), note that

\[ \| \phi_{\gamma_1}(L, Q, \mathbf{X}) - \phi_{\gamma_2}(L, Q, \mathbf{X}) \| \leq \left\| \frac{\exp(\mathbf{X}^T \gamma_1) - \exp(\mathbf{X}^T \gamma_2)}{1 + \exp(\mathbf{X}^T \gamma_1)} \hat{\mathbf{x}} \right\| \leq \frac{1}{4} \| \hat{\mathbf{x}} \| \| \mathbf{X}^T \| \| \gamma_1 - \gamma_2 \| \]

Under the assumption that \( \mathbf{X} \) is bounded, we have \( \mathbb{E}\| \hat{\mathbf{x}} \mathbf{X}^T \| < \infty \). \( \mathbb{E} \phi_\gamma(L, Q, \mathbf{X}) \) is differentiable at \( \gamma_0 \) with derivative \( \Sigma_{\gamma_0} \). By Theorem 5.21 of Van der Vaart (2000), we concluded that

\[ \sqrt{n}(\hat{\gamma}_n - \gamma_0) = \Sigma_{\gamma_0}^{-1} \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \phi_{\gamma_0}(L_i, Q_i, \mathbf{X}_i) + o_P(1) \to_d N(0, \Sigma_{\gamma_0}^{-1}) \]

40
Proof of Proposition B.1. We start with bounding the difference between the IPLW empirical measure $\mathbb{P}_n^\pi$ and the usual empirical measure $\mathbb{P}_n$. By triangle inequality,

$$\|\mathbb{P}_n^\pi - \mathbb{P}_0\|_F \leq \|\mathbb{P}_n - \mathbb{P}_0\|_F + \frac{1}{n} \sum_{i=1}^n \left( \frac{I(L_i + Q_i > 0)}{Q_i + (1 - Q_i)\pi_{\gamma_0}(X_i)} - 1 \right) \delta_{X_i, \tilde{T}_i, \Delta_i} \right\|_F$$

The first term is $o_{p*}(1)$ since $\mathcal{F}$ is Glivenko-Cantelli. For the second term, define function $g(l, q, x) = \frac{I(l + q \geq 0)}{q + (1 - q)\pi_{\gamma_0}(x)} - 1$, then consider the function class $\mathcal{F}^* = \{ [g \cdot f](l, q, x, \delta, \tilde{T}) : f \in \mathcal{F} \}$ where $f = f(x, \tilde{T}, \delta)$. By assumption (A3), $g(l, q, x)$ is bounded and $\mathcal{F}$ has an integrable envelope function $F$. These two together imply that $\mathcal{F}^*$ is $\mathbb{P}_0$-Glivenko-Cantelli by the Glivenko-Cantelli Preservation theorem (Van Der Vaart and Wellner, 2000). Then, for any $f \in \mathcal{F}$,

$$\mathbb{P}_0 g f = \mathbb{E} \left[ \mathbb{E}[g(L, Q, X) f(X, \tilde{T}, \Delta) | Q] \right]$$

$$= \mathbb{E}[g(L, Q, X) f(X, \tilde{T}, \Delta) | Q = 0] \mathbb{P}(Q = 0) + \mathbb{E}[g(L, Q, X) f(X, \tilde{T}, \Delta) | Q = 1] \mathbb{P}(Q = 1)$$

$$= \mathbb{E}[0 \cdot f(X, \tilde{T}, \Delta) | Q = 1] \mathbb{P}(Q = 1) + \mathbb{E} \left[ \left( \frac{I(L = 1)}{\pi_{\gamma_0}(X)} - 1 \right) f(X, \tilde{T}, \Delta) | Q = 0 \right] \mathbb{P}(Q = 0)$$

$$= \mathbb{E} \left[ f(X, \tilde{T}, \Delta) \mathbb{E} \left( \frac{I(L = 1)}{\pi_{\gamma_0}(X)} - 1 \right) | Q = 0, X, \tilde{T}, \Delta \right] \mathbb{P}(Q = 0) = 0$$

The last equality is due to the assumption (A1). Thus, the second term could be rewritten as

$$\left\| \frac{1}{n} \sum_{i=1}^n \delta_{X_i, \tilde{T}_i, \Delta_i, L_i, Q_i} \right\|_{F^*} = \|\mathbb{P}_n - \mathbb{P}_0\|_{F^*}$$

which is again $o_{p*}(1)$.

Now consider $\mathbb{P}_n^{\pi, e}$. Since $\hat{\gamma}_n \rightarrow^p \gamma_0$, it suffices to consider a small compact neighborhood $\mathbb{K} \subset \mathbb{R}^{p+1}$ of $\gamma_0$. Let $\xi_{\gamma}(x, q) = \frac{q + (1 - q)\pi_{\gamma_0}(x)}{q + (1 - q)\pi_\gamma(x)}$. Since $X$ is bounded and $\pi_\gamma$ is continuous in $X$, $\xi_{\gamma}(X, Q)$ is also bounded. Lemma 2.6.15 and 2.6.18 of Van Der Vaart and Wellner (1996) then imply that $\{\xi_{\gamma}(x, q) : \gamma \in \mathbb{K}\}$ is a VC-subgraph class. Next the Glivenko-Cantelli.
Preservation theorem (Van Der Vaart and Wellner, 2000) implies that

\[ G = \left\{ h_{\gamma,f}(q,x,\tilde{t},\delta) = \frac{q + (1 - q)\pi_{\gamma_0}(x)}{q + (1 - q)\pi_{\gamma}(x)} f(x,\tilde{t},\delta) : f \in \mathcal{F}, \gamma \in \mathbb{K} \right\} \]

is a \( \mathbb{P}_0 \)-Glivenko-Cantelli class as \( \mathcal{F} \) has an integrable envelope function and \( \xi_{\gamma}(x,q) \) is bounded. Then recognizing that

\[
\mathbb{P}_{n,\gamma} f = \frac{1}{n} \sum_{i=1}^{n} \frac{I(L_i + Q_i > 0)}{Q_i + (1 - Q_i)\pi_{\gamma_0}(X_i)} \left\{ Q_i + (1 - Q_i)\pi_{\gamma_0}(X_i) \right\} f(X_i,\tilde{T}_i,\Delta_i) = \mathbb{P}_{n,\gamma} \xi_{\gamma_0} f
\]

We have

\[
\| \mathbb{P}_{n,\gamma} - \mathbb{P}_0 \|_{\mathcal{F}} = \sup_{f \in \mathcal{F}} \| \mathbb{P}_{n,\gamma} \xi_{\gamma_0} f - \mathbb{P}_0 f \| \leq \sup_{f \in \mathcal{F}} \| \mathbb{P}_{n,\gamma} \xi_{\gamma_0} f - \mathbb{P}_0 \xi_{\gamma_0} f \| + \sup_{f \in \mathcal{F}} \| \mathbb{P}_0 \xi_{\gamma_0} f - \mathbb{P}_0 f \|
\]

Notice the first term is \( o_{P*}(1) \) since \( G \) is \( \mathbb{P}_0 \)-Glivenko-Cantelli. For the second term, we have

\[
\frac{1}{Q + (1 - Q)\pi_{\gamma_0}(X)} - \frac{1}{Q} = I(Q = 0) \left( 1 - \frac{1}{\pi_{\gamma_0}(X)} \right) \hat{X}^T (\hat{\gamma}_n - \gamma_0)
\]

(12)

where \( \gamma^* \) is some convex combinations of \( \gamma_0 \) and \( \hat{\gamma}_n \) and \( \gamma^* \rightarrow_p \gamma_0 \). This implies that

\[
\xi_{\gamma_n}(X,Q) - 1 = \xi_{\gamma_n}(X,Q) - \xi_{\gamma_0}(X,Q) = I(Q = 0)\pi_{\gamma_0}(X) \left( 1 - \frac{1}{\pi_{\gamma_0}(X)} \right) \hat{X}^T (\hat{\gamma}_n - \gamma_0)
\]

(13)

and the second term can be rewritten as following:

\[
\sup_{f \in \mathcal{F}} \left\| \mathbb{E} \left\{ f(X,\tilde{T},\Delta)I(Q = 0)\pi_{\gamma_0}(X) \left( 1 - \frac{1}{\pi_{\gamma_0}(X)} \right) \hat{X}^T (\hat{\gamma}_n - \gamma_0) \right\} \right\|
\]

\[
= \sup_{f \in \mathcal{F}} \left\| \mathbb{E} \left\{ f(X,\tilde{T},\Delta)I(Q = 0)\pi_{\gamma_0}(X) \left( 1 - \frac{1}{\pi_{\gamma_0}(X)} \right) \hat{X}^T \right\} \right\| \| \hat{\gamma}_n - \gamma_0 \|
\]

Further, since \( \pi_\gamma(X) \) is bounded away from zero for \( \gamma \in \mathbb{K} \) and \( \| \mathbb{P}_0 \|_{\mathcal{F}} < \infty \), the second term is now determined by \( \| \hat{\gamma}_n - \gamma_0 \| \), which is \( o_P(1) \). \( \Box \)

The proof of Proposition B.2 relies on the following lemma.
Lemma C.2. Let $\zeta_\gamma(l, q, x) = \frac{I(l+q>0)}{q+(1-q)\pi_\gamma(x)}$ and $\mathcal{F} = \{f(x, \bar{t}, \delta)\}$ be a $\mathbb{P}_0$-Glivenko-Cantelli class with an integrable envelope function $F$ such that $\mathbb{P}_0 F < \infty$. Then

$$\sup_{f \in \mathcal{F}} \left\| \sqrt{n}(\mathbb{P}_n - \mathbb{P}_0)(\gamma_n - \gamma_0) \right\| = o_{\mathbb{P}}^n(1)$$

Proof. First, recall that $\xi_\gamma(q, x) = \frac{q+(1-q)\pi_\gamma(x)}{q+(1-q)\pi_\gamma(x)}$, then we have that

$$\mathbb{P}_n \xi_\gamma f = \mathbb{P}_n^\gamma \xi_\gamma f; \quad \mathbb{P}_n \xi_\gamma f = \mathbb{P}_n^\gamma \xi_\gamma f$$

Further, since

$$\mathbb{P}_0 \xi_\gamma = \mathbb{E}_0 \left[ \frac{I(L + Q > 0)}{Q + (1-Q)\pi_\gamma(X)} \right]$$

$$= \mathbb{E}_0 \left[ \mathbb{E}_0 \left[ \frac{I(L + Q > 0)}{Q + (1-Q)\pi_\gamma(X)} \bigg| Q, X \right] \right] = \mathbb{E}_0 \left[ \frac{Q + (1-Q)\pi_\gamma(X)}{Q + (1-Q)\pi_\gamma(X)} \right] = \mathbb{P}_0 \xi_\gamma$$

We further have that

$$\mathbb{P}_0 \xi_n f = \mathbb{P}_0 \xi_n f; \quad \mathbb{P}_0 \xi_\gamma f = \mathbb{P}_0 \xi_\gamma f$$

Given above results and equation (13), we have

$$\sup_{f \in \mathcal{F}} \left\| \sqrt{n}(\mathbb{P}_n - \mathbb{P}_0)(\gamma_n - \gamma_0) \right\| = \sup_{f \in \mathcal{F}} \left\| \sqrt{n}(\mathbb{P}_n^\gamma - \mathbb{P}_0)(\xi_n f - \xi_\gamma f) \right\|$$

$$\leq \sup_{f \in \mathcal{F}} \left\| (\mathbb{P}_n^\gamma - \mathbb{P}_0) \left( I(Q = 0)\pi_\gamma(X) \left( 1 - \frac{1}{\pi_\gamma(X)} \right) f(X, \hat{T}, \Delta) \hat{x}^T \right) \right\| \sqrt{n}(\gamma_n - \gamma_0)$$

where $\gamma^*$ is a point lies between $\gamma_n$ and $\gamma_0$. Note that the consistency of $\gamma_n$ implies that $\gamma^* \overset{p}{\rightarrow} \gamma_0$ and $\gamma^*$ will fall into a compact small neighborhood $\mathbb{K}$ around $\gamma_0$ with probability 1. As a result, $\mathcal{G} = \{I(q = 0)\pi_\gamma(x) \left( 1 - \frac{1}{\pi_\gamma(x)} \right) \hat{x}^T : \gamma \in \mathbb{K} \}$ forms a VC-subgraph class by Lemma 2.6.15 and 2.6.18 of Van Der Vaart and Wellner (1996). Then by the Glivenko-Cantelli Preservation theorem (Van Der Vaart and Wellner, 2000), we have $\mathcal{F}_1 = \{fg : f \in \mathcal{F}, g \in \mathcal{G} \}$ is a $\mathbb{P}_0$-Glivenko-Cantelli class with an integrable envelope function. Then

$$\sup_{f \in \mathcal{F}} \left\| \sqrt{n}(\mathbb{P}_n - \mathbb{P}_0)(\gamma_n f - \gamma_0 f) \right\| \leq \mathbb{P}_n^\gamma - \mathbb{P}_0 \|_{\mathcal{F}_1} \sqrt{n} \| \gamma_n - \gamma_0 \|$$
By Proposition B.1 and Lemma C.1, \( \sqrt{n}\| \hat{\gamma}_n - \gamma_0 \| = O_P(1) \) and \( \| \mathbb{P}_n^\pi - \mathbb{P}_0 \|_{\mathcal{F}_1} = o_P(1) \).

**Proof of Proposition B.2.** Let \( \zeta_\gamma(l, q, x) = \frac{I(l+q>0)}{q+(1-q)\pi_\gamma(x)} \). This implies that \( \zeta_\gamma(L, Q, X) = g_1(L, Q, X) \), where \( g_1 \) is defined in Proposition B.2. Moreover, under assumption (A3) and \( \| \mathbb{P}_0 \|_{\mathcal{F}} < \infty \), \( \mathcal{F}' = \{ g_1 \cdot f : f \in \mathcal{F} \} \) is a Donsker Class by Example 2.10.10 of Van Der Vaart and Wellner (1996).

By the definition that \( G_{\pi,n} = \sqrt{n}(\mathbb{P}_{\pi,n}^\pi - \mathbb{P}_0) \), we have

\[
G_{\pi,n}f = \sqrt{n}(\mathbb{P}_{\pi,n}^\pi - \mathbb{P}_0)\zeta_\gamma f = \sqrt{n}(\mathbb{P}_{\pi,n}^\pi - \mathbb{P}_0)g_1 f.
\]

Thus, the usual Donsker theorem (see, e.g., Section 19.2 of Van der Vaart 2000) implies that \( G_{\pi,n} \Rightarrow G(g_1 \cdot) \) in \( l^\infty(\mathcal{F}) \) and

\[
\text{Var}(G(g_1 f)) = \text{Var}(f(X, \tilde{T}, \Delta)) + \mathbb{E} \left[ f(X, \tilde{T}, \Delta)^2 \frac{I(Q = 0)[1 - \pi_{\gamma_0}(X)]}{\pi_{\gamma_0}(X)} \right]
\]

Next,

\[
G_{\pi,n} \cdot e - G_{\pi,n} = \sqrt{n}(\mathbb{P}_{\pi,n}^\cdot e - \mathbb{P}_0) f - \sqrt{n}(\mathbb{P}_{\pi,n}^\pi - \mathbb{P}_0) f
\]

\[
= G_{\pi,n} (\zeta_{\gamma,n} - \zeta_{\gamma_0}) f + \sqrt{n}\mathbb{P}_0 (\zeta_{\gamma,n} - \zeta_{\gamma_0}) f \tag{14}
\]

By Lemma C.2, \( G_n (\zeta_{\gamma,n} - \zeta_{\gamma_0}) f \) is \( o_P(1) \), which bounds the first term. For the second term, note that

\[
\zeta_{\gamma,n} - \zeta_{\gamma_0} = -I(L = 1)I(Q = 0) \left( \frac{1}{\pi_{\gamma_0}(X)} - 1 \right) \tilde{X}^T(\hat{\gamma}_n - \gamma_0) + o(\| \hat{\gamma}_n - \gamma_0 \|^2)
\]

and \( \mathbb{E}[I(L = 1)|Q = 0, X] = \pi_{\gamma_0}(X) \), we can show that

\[
\sqrt{n}\mathbb{P}_0 (\zeta_{\gamma,n} - \zeta_{\gamma_0}) f = - \left\{ \mathbb{E} \left[ I(Q = 0)(1 - \pi_{\gamma_0}(X)) f(X, \tilde{T}, \Delta) \tilde{X}^T \right] \right\} \sqrt{n}(\hat{\gamma}_n - \gamma_0) + o_P(1).
\]
Together, equation (14) and Lemma C.1 implies that

$$
\mathbb{G}_n^{\pi,e} f = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left[ g_1(L_i, Q_i, X_i) f(X_i, \bar{T}, \Delta_i) - \mathbb{P}_0 f \right] \mathbb{E}^{\mathbb{G}_n} f
$$

$$
- \frac{1}{\sqrt{n}} \mathbb{E} \left[ I(Q = 0) (1 - \pi_{\gamma_0}(X)) f(X, \bar{T}, \Delta) \bar{X}^T \right] \Sigma_{\gamma_0}^{-1} \sum_{i=1}^{n} I(Q_i = 0) [L_i - \pi_{\gamma_0}(X_i)] X_i + o_p(1)
$$

$$
= \sqrt{n} \mathbb{P}_0 (\zeta_{\gamma_0} - \zeta_0)_f
$$

$$
= \mathbb{G}_n \left[ g_1 \cdot f - g_2 Q_{e}(f)^T g_3 \right] + o_p(1)
$$

where $g_1(l, q, x) = \frac{I(l + q > 0)}{q + (1 - q)\pi_{\gamma_0}(x)}$, $g_2(l, q, x) = I(q = 0) [l - \pi_{\gamma_0}(x)]$, $g_3(x) = \Sigma_{\gamma_0}^{-1} \bar{x}$ and $Q_{e}(f) = \mathbb{E}[I(Q = 0)(1 - \pi_{\gamma_0}(X)) f(X, \bar{T}, \Delta) \bar{X}]$. This proves the finite dimensional convergence of $\mathbb{G}_n^{\pi,e}$. Next, we prove the asymptotic equicontinuity of $\mathbb{G}_n^{\pi,e}$. Define $\rho(f, g) = \mathbb{P}_0 (f - g)^2$ and $\mathcal{F}_\delta = \{ f - g : f, g \in \mathcal{F}, \rho(f - g) \leq \delta \}$. First, $\mathcal{F}$ is totally bounded by the metric $\rho$ given (Van Der Vaart and Wellner, 1996, Problem 2.1.2) and $\| \mathbb{P}_0 \|_{\mathcal{F}} < \infty$. Next,

$$
\| \mathbb{G}_n^{\pi,e} \|_{\mathcal{F}_\delta} \leq \| \mathbb{G}_n^{\pi} \|_{\mathcal{F}_\delta} + \| \mathbb{G}_n^{\pi,e} - \mathbb{G}_n^{\pi} \|_{\mathcal{F}_\delta}
$$

For the first term on the right-hand side, $\mathbb{G}_n^{\pi}$ is asymptotically equicontinuous with respect to $\rho$. For the second term,

$$
\| \mathbb{G}_n^{\pi,e} - \mathbb{G}_n^{\pi} \|_{\mathcal{F}_\delta} \leq \| Q_{e}^T \mathcal{F}_\delta \sqrt{n} \bar{\gamma}_n - \gamma_0 \| + o_p(1)
$$

and

$$
\| Q_{e}^T \mathcal{F}_\delta \|_{\mathcal{F}_\delta} = \sup_{h \in \mathcal{F}_\delta} \| \mathbb{E}[I(Q = 0)(1 - \pi_{\gamma_0}(X)) h(X, \bar{T}, \Delta) \bar{X}^T] \| \leq C \sup_{h \in \mathcal{F}_\delta} (\mathbb{P}(h^2))^{1/2} \leq C \delta
$$

by the definition of $h$ and some constant $C > 0$. Thus, we have $\lim_{\delta \downarrow 0} \| \mathbb{G}_n^{\pi,e} \|_{\mathcal{F}_\delta} = 0$. Thus, by Theorem 1.5.7 of Van Der Vaart and Wellner (1996), $\mathbb{G}_n^{\pi,e} \rightsquigarrow \mathbb{G}(g_1 \cdot - g_2 Q_{e}(\cdot)^T g_3)$ in $l^\infty(\mathcal{F})$ and

$$
\text{Var}(\mathbb{G}(g_1 \cdot f - g_2 Q_{e}(f)^T g_3)) = \text{Var}(f(X, \bar{T}, \Delta))
$$

$$
+ \mathbb{E} \left[ f(X, \bar{T}, \Delta)^2 I(Q = 0) \frac{1 - \pi_{\gamma_0}(X)}{\pi_{\gamma_0}(X)} \right] - Q_{e}(f)^T \Sigma_{\gamma_0}^{-1} Q_{e}(f),
$$

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which completes the proof. □

Before proving Theorem A.1, we first introduce a useful lemma.

**Lemma C.3.** Under assumption (D2-3), for a small compact set $\mathbb{B}$ that contains $\beta_0^*$,

$$\sup_{t \in [0, \tau_2], \beta \in \mathbb{B}} \| S_{n,w}^{(k)}(\beta, t) - s^{(k)}(\beta, t) \| = o_P(1)$$

for $k = 0, 1, 2$.

**Proof of Lemma C.3.** By assumption (D2), $X(t)$ can be written as the difference of two nondecreasing processes of $t \in [0, \tau_2]$, then by Example 2.11.16 of Van Der Vaart and Wellner (1996) and the fact that $X(t)$ is bounded, $\mathcal{G}_n X \rightsquigarrow \mathcal{G}_0$ in $l^\infty([0, \tau_2])$. Now we can view $\mathcal{G} = \{ x(t) : t \in [0, \tau_2] \}$ as a function class $\{ f_t(x) = x(t); t \in [0, \tau_2] \}$. $\mathcal{G}$ is a $P_0$-Donsker class. Next, $\{ \beta : \beta \in \mathbb{B} \}$ is trivially a $P_0$-Donsker class and $\{ x(t)^T \beta : t \in [0, \tau_2], \beta \in \mathbb{B} \}$ is also a Donsker class by theorem 2.10.6 of Van Der Vaart and Wellner (1996). Similarly, we can prove that $\{ y(t) \exp(\beta^T x(t)) x(t)^{\otimes k} : \beta \in \mathbb{B}, t \in [0, \tau_2] \}$ is also a Donsker class for $k = 0, 1, 2$ as $\{ y(t) : t \in [0, \tau_2] \}$ is also a $P_0$-Donsker class by theorem 2.11.16 of Van Der Vaart and Wellner (1996). Then the result can be proved by Proposition B.1. □

**Proof of Theorem A.1.** The proof of the asymptotic linear expansion is inspired by Lin and Wei (1989). By Lemma C.3, we have

$$\sup_{\beta \in \mathbb{B}, t \in [0, \tau_2]} \| S_{n,w}^{(k)}(\beta, t) - s^{(k)}(\beta, t) \| = o_P(1) \quad k = 0, 1, 2$$

for a compact set $\mathbb{B}$ that contains $\beta_0^*$. Then we can decompose the partial score in equation
Thus, by Proposition (8) as follows:

\[
\sqrt{n} \tilde{\mathbf{U}}_n(\beta) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \Delta_i \tilde{w}_i \left\{ \mathbf{X}_i(\tilde{T}_i) - \frac{S_{n,w}^{(1)}(\beta, \tilde{T}_i)}{S_{n,w}^{(0)}(\beta, \tilde{T}_i)} \right\}
\]

\[
= \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \tilde{w}_i \int_{\tau_1}^{\tau_2} \mathbf{X}_i(t) dN_i(t) - \sqrt{n} \int_{0}^{\tau_2} \frac{S_{n,w}^{(1)}(\beta, t)}{S_{n,w}^{(0)}(\beta, t)} d\tilde{N}(t)
\]

\[
= \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \tilde{w}_i \int_{0}^{\tau_2} \mathbf{X}_i(t) dN_i(t) - \sqrt{n} \int_{0}^{\tau_2} \frac{s(1)(\beta, t)}{s(0)(\beta, t)} d[\tilde{N}(t) - \tilde{N}(t)]
\]

\[
- \sqrt{n} \int_{0}^{\tau_2} \frac{S_{n,w}^{(1)}(\beta, t)}{S_{n,w}^{(0)}(\beta, t)} d\tilde{N}(t) = - \sqrt{n} \int_{0}^{\tau_2} \left[ \frac{S_{n,w}^{(1)}(\beta, t)}{S_{n,w}^{(0)}(\beta, t)} - \frac{s(1)(\beta, t)}{s(0)(\beta, t)} \right] d[\tilde{N}(t) - \tilde{N}(t)]
\]

(15)

Term (I) and (II) are already linear expansions so we do not need to conduct any further derivation. In what follows, we will first show that term (IV) is \(o_p(1)\) and then argue that term (III) has an asymptotic linear expansion.

**Term (IV).** By assumption (D4), for large enough \(n\), both \(S_{n,w}^{(0)}(\beta, t)\) and \(s^{(0)}(\beta, t)\) are bounded away from 0, so Lemma C.3 implies that

\[
\sup_{\beta \in \mathbb{B}, t \in [0, \tau_2]} \left\| \frac{S_{n,w}^{(1)}(\beta, t)}{S_{n,w}^{(0)}(\beta, t)} - \frac{s(1)(\beta, t)}{s(0)(\beta, t)} \right\| = o_p(1)
\]

Moreover, by Proposition B.2, \(n^{1/2}(\tilde{N}(\tau_2) - \tilde{N}(\tau_2))\) converges to a mean zero normal random variable. Together, this implies that (IV) is \(o_p(1)\).

**Term (III).** Next, we have that

\[
\frac{S_{n,w}^{(1)}(\beta, t)}{S_{n,w}^{(0)}(\beta, t)} = \frac{S_{n,w}^{(1)}(\beta, t)}{s(0)(\beta, t)} \left[ 1 + \frac{S_{n,w}^{(0)}(\beta, t) - s(0)(\beta, t)}{s(0)(\beta, t)} \right] = \frac{S_{n,w}^{(1)}(\beta, t)}{s(0)(\beta, t)} \left[ 1 - \frac{S_{n,w}^{(0)}(\beta, t) - s(0)(\beta, t)}{s(0)(\beta, t)} + o_p(1) \right]
\]

\[
= \frac{1}{s(0)(\beta, t)} \left[ S_{n,w}^{(1)}(\beta, t) - \frac{s(1)(\beta, t)}{s(0)(\beta, t)} \left( S_{n,w}^{(0)}(\beta, t) - s(0)(\beta, t) \right) \right] + o_p(1)
\]

Thus,

\[
n^{1/2} \int_{0}^{\tau_2} \frac{S_{n,w}^{(1)}(\beta, t)}{S_{n,w}^{(0)}(\beta, t)} d\tilde{N}(t) = n^{1/2} \int_{0}^{\tau_2} \frac{1}{s(0)(\beta, t)} \left[ S_{n,w}^{(1)}(\beta, t) - \frac{s(1)(\beta, t)}{s(0)(\beta, t)} \left( S_{n,w}^{(0)}(\beta, t) - s(0)(\beta, t) \right) \right] d\tilde{N}(t) + o_p(1)
\]

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Taking above equation back to equation (15), we get the desired asymptotic linear expansion of $\hat{U}_n(\beta)$: $\sqrt{n}\hat{U}_n(\beta) = n^{-1/2}\sum_{i=1}^{n} \hat{w}_i U_i(\beta) + o_p(1)$ with

$$U_i(\beta) = \int_0^{\tau_2} \left[ X_i(t) - \frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)} \right] dN_i(t) - \int_0^{\tau_2} Y_i(t) \exp(\beta^t X_i(t)) \left[ X_i(t) - \frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)} \right] d\tilde{N}(t)$$

Finally, to apply Proposition B.2, note that $\pi_{\gamma_0}(X)$ needs to be replaced by $\pi_{\gamma_0}(Z)$ and $U_i(\beta)$ can be viewed as a function $\eta_\beta(\tilde{X}, \tilde{T}, \Delta)$. As a result, we have $\sqrt{n}\hat{U}_n(\beta) = n^{-1/2}\sum_{i=1}^{n} \hat{w}_i U_i(\beta) + o_p(1) = \sum_n^{\pi_{\gamma_0}}\eta_\beta + o_p(1)$. Proposition B.2 implies the asymptotic normality of $\sqrt{n}\hat{U}_n(\beta^*_0)$, which completes the proof.

**Proof of Theorem 3.2.** Based on the fact that $\hat{U}_n(\hat{\beta}_n) = 0$ and $U_0(\beta^*_0) = 0$, we have

$$\sqrt{n}(\hat{\beta}_n - \beta^*_0) = A_n(\beta^*_0)^{-1}\sqrt{n}\hat{U}_n(\beta^*_0) + o_P(\sqrt{n}\|\hat{\beta}_n - \beta^*_0\|),$$

where $A_n$ is defined in equation (10). To prove that $\hat{\beta}_n \overset{p}{\to} \beta^*_0$, we adopt the same strategy as Lemma 3.1 in Andersen and Gill (1982). From Theorem A.1, we obtained that

$$\frac{1}{n}\hat{U}_n(\beta) = \frac{1}{n} \sum_{i=1}^{n} \hat{w}_i U_i(\beta) + o_P(n^{-1/2}).$$

Then by Proposition B.1,

$$\frac{1}{n} \hat{U}_n(\beta) \overset{p}{\to} \mathbb{E} \left\{ \int_0^{\tau_2} \left[ X(t) - \frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)} \right] dN(t) - \int_0^{\tau_2} \left[ X(t) - \frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)} \right] Y(t) \exp(\beta^t X(t)) \left[ X(t) - \frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)} \right] d\tilde{N}(t) \right\}$$

It is not hard to prove that above expectation equals to $U_0(\beta) = \mathbb{E} \left[ \Delta \left( X(\tilde{T}) - \frac{s^{(1)}(\beta, \tilde{T})}{s^{(0)}(\beta, T)} \right) \right]$. By assumption (D5), $A(\beta^*_0) = - \frac{\partial U_0(\beta)}{\partial \beta} |_{\beta = \beta^*_0}$ is positive definite and by a similar argument as Lemma 3.1 in Andersen and Gill (1982), we have $\hat{\beta}_n \overset{p}{\to} \beta^*_0$. We now prove the uniform convergence of $A_n(\beta)$ to $A(\beta)$ in a small compact subset $\mathbb{B}$ that contains $\beta^*_0$.

$$\sup_{\beta \in \mathbb{B}} \| A_n(\beta) - A(\beta) \| \leq \int_0^{\tau_2} \sup_{\beta \in \mathbb{B}} \left\| \left( \frac{S^{(2)}(\beta, t)}{S^{(0)}(\beta, t)} \right) - \left( \frac{S^{(1)}(\beta, t)}{S^{(0)}(\beta, t)} \right)^{\otimes 2} \right\| \| d(\tilde{N}(t) - \tilde{N}(t)) \|$$

$$\quad + \int_0^{\tau_2} \sup_{\beta \in \mathbb{B}} \left\{ \left( \frac{S^{(2)}(\beta, t)}{S^{(0)}(\beta, t)} - \left( \frac{S^{(1)}(\beta, t)}{S^{(0)}(\beta, t)} \right)^{\otimes 2} \right)^{\otimes 2} - \left( \frac{s^{(2)}(\beta, t)}{s^{(0)}(\beta, t)} - \left( \frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)} \right)^{\otimes 2} \right)^{\otimes 2} \right\} \| d\tilde{N}(t) \|$$

(16)

---

Note: We only need the pointwise convergence result at $\beta = \beta^*_0$. 

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For the first term of (16), let
\[
\begin{align*}
  h_n(t) &= \sup_{\beta \in \mathcal{B}} \left\| \frac{S_{n,w}^{(2)}(\beta, t)}{S_{n,w}^{(0)}(\beta, t)} \right\|^2 - \left(\frac{S_{n,w}^{(1)}(\beta, t)}{S_{n,w}^{(0)}(\beta, t)}\right) \\
  h(t) &= \sup_{\beta \in \mathcal{B}} \left\| \frac{s^{(2)}(\beta, t)}{s^{(0)}(\beta, t)} \right\|^2 - \left(\frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)}\right) 
\end{align*}
\]
and
\[
\int_0^{\tau_2} |h_n(t)||d(\bar{N}(t) - \bar{\tilde{N}}(t))| = \int_0^{\tau_2} |h(t)||d(\bar{N}(t) - \bar{\tilde{N}}(t))| + o_P(1)
\]
by Lemma C.3. By Proposition B.1, sup_{t \in [0, \tau_1]} |\bar{N}(t) - \bar{\tilde{N}}(t)| = o_P(1). Thus the first term is \(o_P(1)\). The second term is also \(o_P(1)\) by Lemma C.3. By the uniform convergence of \(A_n(\beta)\) to \(A(\beta)\), we then have \(A_n(\beta_0^*) \to_P A(\beta_0^*)\). Then, by slutsky’s theorem, we obtained that
\[
\sqrt{n}(\hat{\beta}_n - \beta_0^*) \to_d \mathcal{N}(0, \Sigma_0^{-1} \Sigma \Sigma_0^{-1})
\]

\[
\Box
\]

D Doubly Robust Estimation and its limitation

Now we propose an augmented inverse probability of linkage weighting (AIPLW) estimator for estimating the long-term effect. We first need to define several outcome regression functions:

\[
m_0(X) = \mathbb{E} \left[ \Delta \left( X - \frac{s^{(1)}(\tilde{T}, \beta)}{s^{(0)}(\tilde{T}, \beta)} \right) \right | X, Q = 0, L = 1
\]

\[
= \mathbb{E} \left[ \Delta |X, Q = 0, L = 1 \right] X - \mathbb{E} \left[ \Delta \frac{s^{(1)}(\tilde{T}, \beta)}{s^{(0)}(\tilde{T}, \beta)} | X, Q = 0, L = 1 \right] m_1(X)
\]

\[
m_3(X) = \mathbb{E} \left[ I(\tilde{T} \geq t) \exp(X^T \beta) | X, Q = 0, L = 1 \right] = \mathbb{E} \left[ I(\tilde{T} \geq t) | X, Q = 0, L = 1 \right] \exp(X^T \beta)
\]
The augmented IPW partial likelihood is then as following:

\[ U_{n,AIPW} = \frac{1}{n} \sum_{i=1}^{n} \left\{ I(Q_i = 1) \Delta_i \left[ X_i - \frac{S_{n,DR}^{(1)}(\beta, \hat{T}_i)}{S_{n,DR}^{(0)}(\beta, \hat{T}_i)} \right] + I(Q_i = 0) \left[ \frac{I(L_i = 1)}{\pi_{\hat{\gamma}_n}(X_i)} \Delta_i \right] \left[ X_i - \frac{S_{n,DR}^{(1)}(\beta, \hat{T}_i)}{S_{n,DR}^{(0)}(\beta, \hat{T}_i)} \right] \right\} \]

\begin{equation}
= \frac{1}{n} \sum_{i=1}^{n} \left\{ I(Q_i = 1) I(\hat{T}_i \geq t) \exp(X_i^T \beta) + I(Q_i = 0) I(\hat{T}_i \geq t) \exp(X_i^T \beta) + \left(1 - \frac{I(L_i = 1)}{\pi_{\hat{\gamma}_n}(X_i)} \right) \hat{m}_0(X_i) \right\} X_i^\otimes k \tag{17}
\end{equation}

with

\[ S_{n,DR}^{(k)}(\beta, t) = \frac{1}{n} \sum_{i=1}^{n} \left\{ I(Q_i = 1) I(\hat{T}_i \geq t) \exp(X_i^T \beta) + I(Q_i = 0) I(\hat{T}_i \geq t) \exp(X_i^T \beta) + \left(1 - \frac{I(L_i = 1)}{\pi_{\hat{\gamma}_n}(X_i)} \right) \hat{m}_0(X_i) \right\} X_i^\otimes k \]

where \( \hat{m}_k(x) \) are certain estimators of \( m_k(x) \) for \( k = 1, 2, 3 \) such that \( \hat{m}_0(x) = \hat{m}_1(x) - \hat{m}_2(x) \). Let \( \hat{\beta}_{AIPW} \) be the solution to \( U_{n,AIPW} = 0 \). \( \hat{\beta}_{AIPW} \) is a doubly robust estimator in the sense that either \( \pi_{\hat{\gamma}_n}(x) \) being consistent for \( \pi_0(x) = P(L = 1|x, Q = 0) \) or \( \hat{m}_k(x) \) being consistent for \( m_k(x) \) for \( k = 1, 2, 3 \) will guarantee that \( \hat{\beta}_{AIPW} \) is a consistent estimator for \( \beta_0^* \). Informally, to prove the doubly-robust property of \( \hat{\beta}_{AIPW} \), we need to prove that the population version of the estimating equation (17) have the same root \( \beta_0^* \) as the IPLW estimation equation.

We first argue that \( S_{n,DR}^{(k)}(\beta, t) \) is a doubly-robust estimator of \( s_{(k)}(\beta, t) \) in the above sense. It is not hard to see that \( S_{n,DR}^{(k)}(\beta, t) \) converges to \( s_{DR}^{(k)}(\beta, t) \) with

\[ s_{DR}^{(k)}(\beta, t) = \mathbb{E} \left\{ \left( I(Q = 1) I(\hat{T} \geq t) \exp(\mathbf{X}^T \beta) + I(Q = 0) \left[ \frac{I(L = 1)}{\pi_{\hat{\gamma}_0}(\mathbf{X})} I(\hat{T} \geq t) \exp(\mathbf{X}^T \beta) \right] \right) \mathbf{X}^\otimes k \right\} \]

where \( \hat{m}_3(x) \rightarrow_p m_3^*(x) \) and \( \pi_{\hat{\gamma}_0}(x) \rightarrow \pi_{\gamma_0}(x) \). \( m_3^*(x) \) is not necessarily \( m_3(x) \) and similarly \( \pi_{\gamma_0}(x) \) might not be \( \pi_0(x) \). Then when \( \pi_0(x) = \pi_{\gamma_0}(x) \) and \( m_3^*(x) \neq m_3(x) \), we have

\[ s_{DR}^{(k)}(\beta, t) = \mathbb{E} \left\{ I(Q = 1) I(\hat{T} \geq t) \exp(\mathbf{X}^T \beta) + I(Q = 0) \frac{I(L = 1)}{\pi_0(\mathbf{X})} I(\hat{T} \geq t) \exp(\mathbf{X}^T \beta) \right\} \mathbf{X}^\otimes k \]

\[ = s^{(k)}(\beta, t) \]
according to Proposition 3.1 and assumption (A1). On the other hand, when \( \pi_{\gamma_0}(x) \neq \pi_0(x) \) and \( m_k^*(x) = m_3(x) \), we can rewrite \( s_{DR}^{(k)}(\beta, t) \) as

\[
\mathbb{E} \left\{ \begin{array}{c}
I(Q = 1) I(T \geq t) \exp(X^T \beta) + I(Q = 0) \frac{I(L = 1)}{\pi_{\gamma_0}(x)} \left( I(T > t) \exp(X^T \beta) - m_3(x) \right) \\
+ I(Q = 0) m_3(x) \cdot x^{0_k}
\end{array} \right\}
\]

and term \( I \) is 0 by law of total expectation. Thus, again we have \( s_{DR}^{(k)}(\beta, t) = s^{(k)}(\beta, t) \).

Similarly, it is not hard to prove that the population version of the above estimating equation (17)

\[
U_{AIPW} = \mathbb{E} \left\{ I(Q = 1) \Delta \left[ X - s_{DR}^{(1)}(\beta, \tilde{T}) \right] + I(Q = 0) \Delta \left[ X - \frac{s_{DR}^{(1)}(\beta, \tilde{T})}{s_{DR}(\beta, \tilde{T})} \right] \\
+ \left( 1 - \frac{I(L = 1)}{\pi_{\gamma_0}(x)} \right) m_0^*(x) \right\}
\]

where \( \hat{m}_0(x) \to m_0^*(x) \). Then when we have \( \pi_{\gamma_0}(x) = \pi_0(x) \), \( U_{AIPW} \) becomes

\[
\mathbb{E} \left\{ \left[ I(Q = 1) + I(Q = 0) \frac{I(L = 1)}{\pi_{\gamma_0}(x)} \right] \Delta \left[ X - s^{(1)}(\beta, \tilde{T}) \right] \right\}
\]

which is the same as the IPLW estimating equation according to Proposition 3.1 and assumption (A1). On the other hand, if we have \( \pi_{\gamma_0}(x) \neq \pi_0(x) \) and \( m_k^*(x) = m_k(x) \) for \( k = 1, 2, 3 \), then using the same argument as above, we have that \( U_{AIPW} \) becomes

\[
E \left\{ \Delta \left[ X - s^{(1)}(\beta, \tilde{T}) \right] \right\}
\]

which is just the original partial likelihood estimating equation for Cox model. Thus, \( \hat{\beta}_{AIPW} \) is doubly-robust.

### D.1 Difficulty of Estimation of Doubly-Robust Estimator

Based on (17), we need to estimate \( m_k(x) \) for \( k = 1, 2, 3 \) to solve for \( \hat{\beta}_{AIPW} \). However, there are major difficulties with estimating these three regression functions. To estimate
$m_k(x)$, we need to estimate

\[ m_1(X) = \mathbb{E}[\Delta|X; Q = 0, L = 1]X = P(T \leq C|X, Q = 0, L = 1)X \]
\[ m_2(X) = \mathbb{E}\left[ \frac{s^{(1)}(\tilde{T}, \beta)}{s^{(0)}(T, \beta)} X, Q = 0, L = 1 \right] \]
\[ m_3(X) = P(\tilde{T} \geq t|X; Q = 0, L = 1)\exp(X^T\beta) \]

We have a couple modeling strategies. We use $m_1(x)$ as an example to illustrate the modeling details. For the first modeling strategy, we can try to estimate $m_k(x)$ through modeling the distribution of $C_1, C_2, T$. More specifically, for $P(T \leq C|X, Q = 0, L = 1)$, it is not hard to get that

\[ P(T \leq C|X, Q = 0; L = 1) = \frac{P(T \leq C_2, T \geq C_1|X, L = 1)}{P(T \geq C_1|X, L = 1)} \]

For the numerator, we have

\[ P(T \leq C_2, T \geq C_1|X, L = 1) = \int_0^{\tau_2} P(C_2 \geq s, C_1 \leq s|T = s, X, L = 1)f_T(s|X, L = 1)ds \]

Thus, we need to model the joint distribution of $C_1$ and $C_2$ given $T, X$ and $L = 1$. Note here with the independent censoring assumption, we have $(C_1, C_2) \perp T|X$. Together with assumption (A1), it is not clear if we also have $(C_1, C_2) \perp T|X, L = 1$. Next, even if we make the further assumption that $(C_1, C_2) \perp T|X, L = 1$. It still requires us to model the joint distribution of $C_1$ and $C_2$ given $X$ and $L = 1$. Another thing is that this also requires us to model the distribution of failure time $T$ given $X$ and $L = 1$, which need careful modeling to avoid model conflict with the Cox model for $T$ given $X$ alone. Similar modelings are required for estimating $m_2(X)$ and $m_3(X)$.

For a second modeling strategy, we can directly model $P(\Delta = 1|X, Q = 0, L = 1)$ with a logistic regression as $\Delta$ is binary variable. Similarly, we can estimate $m_3(X)$ by directly modeling the distribution of the observed time $\tilde{T}$ given $X, Q = 0$ and $L = 1$ through Cox
regression. To estimate \( m_2(X) \), we need to either model the distribution of \( \tilde{T} \) given \( \Delta = 1, Q = 0 \) and \( L = 1 \) or model the distribution of \( \Delta \) given \( T, X, Q = 0 \) and \( L = 1 \). Take all things into consideration, very careful modelings need to be carried out to ensure model congeniality and whether such models exist is not clear to us.

Finally, to avoid the potential model congeniality issue, non-parametric estimation technique might be applied. However, nonparametric estimation in general suffers from the curse of dimensionality issue, which might require a very large number of samples to get a good estimate.

### E Linkage assumption and NLAC method

Note that one sufficient condition for CLAR is

\[
L \perp (T, C)|Q = 0, X.
\]

Technically, we can also modify the CLAR assumption such that linkage also depends on the censoring time in clinical trial \( C_1 \):

\[
P(L = 1|\tilde{T}, \Delta, Q = 0, X, C_1) = P(L = 1|Q = 0, X, C_1)
\]

as \( C_1 \) is always observed when \( Q = 0 \). One sufficient assumption for this modified CLAR assumption is

\[
L \perp (T, C_2)|Q = 0, X, C_1.
\]

We now discuss some other potential assumptions for linkage. For an alternative approach, we might assume that

\[
L \perp (T, C)|X.
\]

However, the IPW type method for this assumption suffers from the same issue as the
complete-case analysis in that unlinked participants that are diagnosed with PC within the clinical trial will not be included in analysis.

As our main goal is to deal with the missing survival outcome $T$ and $C_2$ and the missingness only happens when a participant is not linked and censored in the clinical trial, an alternative approach would be to directly model $P(L = 0, Q = 0|X, T, C_1, C_2)$ and a MAR type assumption would be

$$P(L = 0, Q = 0|X, T, C_1, C_2) = P(L = 0, Q = 0|X)$$

since only $X$ is always observed. However, this MAR assumption would never hold as we always have $Q = 0$ when $T \geq C_1$. Thus, we choose to model linkage alone as the CLAR assumption. Next, we give the proof for Proposition 6.1.

**Proof of Proposition 6.1.** The NLAC method modifies the censoring time $C$ compared to the oracle method. To prove the consistency of the estimator obtained by naive method, we only need to prove that the population version of the partial likelihood for NLAC method has a solution at $\beta = \beta_0$. The rest is the same as the consistency proof in Andersen and Gill (1982). For notational simplicity, we illustrate the proof with time-independent covariates only.

Recall for NLAC method, we have

$$\tilde{T}_j = \begin{cases} T_j & L_j + Q_j > 0 \\ C_{1j} & L_j + Q_j = 0 \end{cases}$$

and $\Delta_j = 0$ if $L_j + Q_j = 0$. Thus, the partial likelihood for NLAC method solves

$$\hat{U}_{naive}(\beta) = \frac{1}{n} \sum_{i=1}^{n} I(L_i + Q_i > 0) \Delta_i \left[ X_i - \frac{S_{n,w}^{(1)}(\beta, \tilde{T}_i)}{S_{n,w}^{(0)}(\beta, \tilde{T}_i)} \right] = 0$$

with

$$S_{n,w}^{(k)}(\beta, t) = \sum_{j=1}^{n} \left[ I(L_j + Q_j > 0) I(\tilde{T}_j \geq t) \exp(X_j^T \beta) + I(L_j + Q_j = 0) I(C_{1j} \geq t) \exp(X_j^T \beta) \right] X_j^{\otimes k}$$
Then, by similar technique in Andersen and Gill (1982), we can prove that

\[
\hat{U}_{\text{naive}}(\beta) \rightarrow_p U_0(\beta) = \mathbb{E} \left[ \Delta I(L + Q > 0) \left( X - \frac{S^{(1)}(\beta, \tilde{T})}{S^{(0)}(\beta, \tilde{T})} \right) \right]
\]

with \( S^{(k)}(\beta, t) = \mathbb{E} \left[ \left\{ I(L + Q > 0)I(\tilde{T} > t) \exp(X^T \beta) + I(L = 0)I(Q = 0)I(C_1 \geq t) \exp(X^T \beta) \right\} X^{\otimes k} \right] \).

Next, we prove that \( \beta = \beta_0 \) solves \( U_0(\beta) = 0 \). We first have that

\[
\mathbb{E}[\Delta I(L + Q > 0)X] = \mathbb{E}[\Delta I(Q = 1)X] + \mathbb{E}[\Delta I(L = 1)I(Q = 0)X]
\]

Further, we have

\[
\mathbb{E}[\Delta I(Q = 1)X] = \mathbb{E}[I(T \leq C)I(T \leq C_1)X] = \mathbb{E}[I(T \leq C_1)X] = \int_0^\tau \mathbb{E}[P(C_1 \geq t|X)f_T(t|X)]dt
\]

\[
= \int_0^\tau \mathbb{E}[X|I(C_1 \geq t)I(T \geq t) \exp(X^T \beta_0)]\lambda_0(t)dt
\]

since \( \lambda_T(t|X) = \lambda_0(t) \exp(X^T \beta_0) \) and \( C_1 \perp T|X \). Next, we have

\[
\mathbb{E}[\Delta I(L = 1)I(Q = 0)X] = \mathbb{E}[I(T \leq C)I(T \geq C_1)I(L = 1)X]
\]

\[
= \mathbb{E}[I(T \leq C_2)I(T \geq C_1)I(L = 1)X]
\]

\[
= \mathbb{E}[X\pi(X, C_1, C_2)I(T \geq C_1)I(T \leq C_2)]
\]

\[
= \mathbb{E}[X\mathbb{E}[\mathbb{E}[I(T \geq C_1)I(T \leq C_2)\pi(X, C_1, C_2)|T, X]|X]]
\]

where \( \mathbb{E}[I(L = 1)|T, Q = 0, C_1, C_2, X] = \pi(X, C_1, C_2) \). Next, denote \( g(T, X) = \mathbb{E}[I(T \geq C_1)I(T \leq C_2)\pi(X, C_1, C_2)|T, X] \), we further have

\[
g(s, X) = \mathbb{E}[I(T \geq C_1)I(T \leq C_2)\pi(X, C_1, C_2)|T = s, X] = \mathbb{E}[I(C_1 \leq s)I(C_2 \geq s)\pi(X, C_1, C_2)|X]
\]
Then we are done. We prove this by proving the following two equalities:

\[
E[\Delta I(L = 1)I(Q = 0)X] = E[XE[g(T, X)|X]] = E \left[ X \int_0^{T_2} g(s, X)f_T(s|X)ds \right] \\
= \int_0^{T_2} E[XE[I(C_1 \leq s)I(C_2 \geq s)\pi(X, C_1, C_2)|X]f_T(s|X)] ds \\
= \int_0^{T_2} E[XI(C_1 \leq s)I(C_2 \geq s)\pi(X, C_1, C_2)P(T \geq s|X)\exp(X^T\beta_0)] \lambda_0(s)ds \\
= \int_0^{T_2} E[XI(C_1 \leq s)I(C_2 \geq s)\pi(X, C_1, C_2)\E[I(T \geq s)|X]\exp(X^T\beta_0)] \lambda_0(s)ds \\
= \int_0^{T_2} E[XI(C_1 \leq s)I(C_2 \geq s)I(T \geq s)\pi(X, C_1, C_2)|X] \exp(X^T\beta_0)] \lambda_0(s)ds \\
= \int_0^{T_2} E[XI(C_1 \leq s)I(C_2 \geq s)I(T \geq s)\pi(X, C_1, C_2) \exp(X^T\beta_0)] \lambda_0(s)ds
\]

Thus, together, we have

\[
E[\Delta I(L + Q > 0)X] = \\
\int_0^{T_1} E[X\{I(C_1 \geq s)I(T \geq s) + \pi(X, C_1, C_2)I(C_1 \leq s)I(C_2 \geq s)I(T \geq s)\} \exp(X^T\beta_0)] \lambda_0(s)ds \\
+ \int_{T_1}^{T_2} E[X\pi(X, C_1, C_2)I(C_2 \geq s)I(T \geq s) \exp(X^T\beta_0)] \lambda_0(s)ds \\
as C_1 \in [0, T_1]. Similarly, we have

\[
E \left[ \Delta I(L + Q > 0) \frac{S^{(1)}(\beta, T)}{S^{(0)}(\beta, T)} \right] = \\
\int_0^{T_1} E[\{I(C_1 \geq s)I(T \geq s) + \pi(X, C_1, C_2)I(C_1 \leq s)I(C_2 \geq s)I(T \geq s)\} \exp(X^T\beta_0)] \lambda_0(s) \frac{S^{(1)}(\beta, s)}{S^{(0)}(\beta, s)} ds \\
+ \int_{T_1}^{T_2} E[\pi(X, C_1, C_2)I(C_2 \geq s)I(T \geq s) \exp(X^T\beta_0)] \lambda_0(s) \frac{S^{(1)}(\beta, s)}{S^{(0)}(\beta, s)} ds
\]

Now as long as we can prove that

\[
E[\Delta I(L + Q > 0)X] - E \left[ \Delta I(L + Q > 0) \frac{S^{(1)}(\beta_0, T)}{S^{(0)}(\beta_0, T)} \right] = 0
\]

Then we are done. We prove this by proving the following two equalities:

\[
\int_0^{T_1} E[X\{I(C_1 \geq s)I(T \geq s) + \pi(X, C_1, C_2)I(C_1 \leq s)I(C_2 \geq s)I(T \geq s)\} \exp(X^T\beta_0)] \lambda_0(s)ds - \\
\int_0^{T_1} E[\{I(C_1 \geq s)I(T \geq s) + \pi(X, C_1, C_2)I(C_1 \leq s)I(C_2 \geq s)I(T \geq s)\} \exp(X^T\beta_0)] \lambda_0(s) \frac{S^{(1)}(\beta, s)}{S^{(0)}(\beta, s)} ds = 0
\]

(19)
and
\[
\int_{\tau_1}^{\tau_2} \mathbb{E}[X \pi(X, C_1, C_2) I(C_2 \geq s) I(T \geq s) \exp(X^T \beta_0)] \lambda_0(s) ds - \\
\int_{\tau_1}^{\tau_2} \mathbb{E}[\pi(X, C_1, C_2) I(C_2 \geq s) I(T \geq s) \exp(X^T \beta_0)] \lambda_0(s) \frac{S^{(1)}(\beta, s)}{S^{(0)}(\beta, s)} ds = 0
\]  
(20)

We first prove equation (19). For \( s \in [0, \tau_1] \), we have

\[
S^{(0)}(\beta, s) = \mathbb{E}[I(\tilde{T} \geq s) \exp(X^T \beta)[I(Q = 1) + I(L = 1)I(Q = 0)] \\
+ I(C_1 \geq s)I(L = 0)I(Q = 0) \exp(X^T \beta)] \\
= \mathbb{E}[I(\tilde{T} \geq s) \exp(X^T \beta)I(Q = 1) + I(C_1 \geq s) \exp(X^T \beta)I(Q = 0)] \\
+ \mathbb{E}[I(L = 1)I(Q = 0) \exp(X^T \beta)[I(\tilde{T} \geq s) - I(C_1 \geq s)]]
\]

Further,

\[
\mathbb{E}[I(\tilde{T} \geq s) \exp(X^T \beta)I(Q = 1) + I(C_1 \geq s) \exp(X^T \beta)I(Q = 0)] \\
= \mathbb{E}[I(T \geq s)I(T \leq C_1) \exp(X^T \beta)] + \mathbb{E}[I(C_1 \geq s)I(T \geq C_1) \exp(X^T \beta)] \\
= \mathbb{E}[I(T \geq s)I(C_1 \geq s) \exp(X^T \beta)]
\]

and

\[
\mathbb{E}[I(L = 1)I(Q = 0) \exp(X^T \beta)[I(\tilde{T} \geq s) - I(C_1 \geq s)]] \\
= \mathbb{E}[I(L = 1)I(Q = 0) \exp(X^T \beta)I(T \geq s)I(C_2 \geq s)I(C_1 \leq s)] \\
= \mathbb{E}[\pi(X, C_1, C_2)I(T \geq s)I(C_2 \geq s)I(C_1 \leq s) \exp(X^T \beta)]
\]  
(21)

Similarly, we can prove that

\[
S^{(1)}(\beta, s) = \mathbb{E}[X \{I(C_1 \geq s)I(T \geq s) + \pi(X, C_1, C_2)I(C_1 \leq s)I(C_2 \geq s)I(T \geq s)\} \exp(X^T \beta)]
\]

All these results suggest that when \( \beta = \beta_0 \), equation (19) is 0. When \( s \in [\tau_1, \tau_2] \), we have

\[
S^{(0)}(\beta, s) = \mathbb{E}[I(\tilde{T} \geq s) \exp(X^T \beta)I(L = 1)I(Q = 0)] \\
= \mathbb{E}[I(T \geq s)I(C_2 \geq s) \exp(X^T \beta)I(T \geq C_1)\pi(X, C_1, C_2)] \\
= \mathbb{E}[\pi(X, C_1, C_2)I(T \geq s)I(C_2 \geq s) \exp(X^T \beta)]
\]
as $C_1 \in [0, \tau_1]$. By the same idea, we can prove that equation (20) is 0. Then we have finished the proof. \qed

Note that we only uses assumption (N4) in (18) and (21) and in fact, we can further assume that

\[(\text{N5}) \quad L \perp T|(X, Q = 0, C_1, C_2, \Delta)\]

and NLAC method still gives consistent estimate in this scenario. Finally for the case of time-dependent covariates, we can get similar results under the assumption that

$$P(T \geq s|C_1, C_2, \bar{X}(\tau)) = P(T \geq s|\bar{X}(s)) \quad P(C_k \geq s|T, \bar{X}(\tau)) = P(C_k \geq s|\bar{X}(s)), k = 1, 2.$$ 

The proof is overall very similar to the case when there are only time-independent covariates and we omit it.

### F Relaxation of the “no gap” assumption

So far we have made the “no gap” assumption to focus on the right censoring problem. Now we consider relaxations of this assumption as it is quite common that a participant might not be under observation for some time in practice. This allows for the possibility of interval censoring as a participant might be diagnosed with the event of interest during the gap when he is not under observation. Further, this creates a situation that we have both right censored and interval-censored data, which is also known as partly interval-censored data (Turnbull, 1976).

Partly interval-censored data for Cox regression has been studied in Kim (2003), Cai and Betensky (2003) and the estimation is more difficult than right-censored data. For simplicity, we do not deal with interval-censoring in the current paper and leave that to
future work. Instead we consider an alternative approach that transforms the interval-censored data to right-censored data. This approach is in the same spirit as the NLAC approach. However, one has to be careful with the transformation. We first discuss an intuitive but problematic approach.

**F.1 A problematic approach**

For illustration, we consider the oracle setting such that each participant is linked to the observational follow-up datasets. For participants that are known to be interval-censored during the gap between clinical trial and observational follow-up, we treat such participants as being right censored at the last recorded date of clinical trial. Thus, we transform the partly interval-censored problem to a right-censored only problem. On the other hand, for participants with gaps, it is also possible that they might not be interval-censored. It is then tempting to use their survival information in the observational dataset, i.e, failure time $T$ or the censoring time $C_2$. However, this approach is problematic as this would lead to biased estimates. To see the effect of bias with this approach empirically, we conducted a simulation study\(^6\) with approximately 4.5% of the participants being interval-censored. The coverage of the 95% confidence interval for parameter $\beta_1$ is only about 65% with $n = 10,000$ and 1,000 repetitions.

To see why we cannot use the survival information in the observational follow-up dataset for a participant with gap and not interval-censored, we need to think about the corresponding censoring distribution. Considering participants with gaps, effectively the censoring

\(^6\)The detailed simulation setting is provided in the appendix G.
time $C$ is set as

$$C = \begin{cases} 
C_1 & \text{if } C_1 < T < C_1 + U \\
\max(C_1, C_2) & \text{if } C_1 + U \leq T
\end{cases},$$

where $U$ is a random variable for the length of the gap between the clinical trial and the start of observational follow-up dataset. Thus, it is clear that the censoring time $C$ now depends on the failure time $T$ and violates the independent censoring assumption.

**F.2 A remedy**

We now propose a remedy approach that properly transforms the partly interval-censored data to right-censored data and conventional statistical software can then be applied to estimate the parameter for Cox models. Again we consider the oracle setting that each participant is linked to the observational follow-up dataset. For participants with gaps and censored in the clinical trial, we simply view them as being right censored at the last recorded date of clinical trial. Thus, we set $C = C_1$ whenever there is a gap between a participant’s last recorded date in clinical trial and the start time of observational follow-up. Let $G$ denotes whether gap exists for a participant. Equivalently, the censoring time $C$ is set as

$$C = I(G = 1)C_1 + I(G = 0)\max(C_1, C_2).$$

Thus, similar to the linkage assumption for the NLAC method, above proposed method works if $G \perp T|X, C_1, C_2$, under the oracle setting that each participant is linked.

For the more practical setting with incomplete linkages, we can similarly apply the methods developed in the current paper. To be more specific, for NLAC, the censoring time $C$ can be written as

$$C = I(L = 1)[I(G = 1)C_1 + I(G = 0)\max(C_1, C_2)] + I(L = 0)C_1$$
Thus, NLAC again sets the censoring time as $C_1$ for participants that are not linked and censored in the clinical trial. One sufficient condition for NLAC to work is

$$L \perp T|X, C_1, C_2, G,$$

which is similar to assumption (N1). For the IPLW method, we might modify the CLAR assumption as

$$P(L = 1|X, Q = 0, \bar{T}, \Delta, G) = P(L = 1|X, Q = 0, G).$$

We present relevant simulation results in appendix G due to space limit. The limitation of this remedy approach is similar to NLAC: it only works when Cox model is correctly specified; when Cox model is mis-specified, our proposed approach will no longer work as we modify the censoring times.

G More simulation results

We now present the simulation results when there are gaps between the clinical trial and the observational follow-up dataset. We consider the following simulation scenario. The hazard function is $\lambda(t|X; \beta_0) = \lambda_0(t) \exp(\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3)$ and $\beta_0 = (\beta_1, \beta_2, \beta_3)^T = (-\log(2), \log(2), 0.2)^T$. $X_1$ is a Bernoulli variable that takes value 1 with probability 0.5. $X_2$ is a normal random variable with mean -1 and standard deviation 1. $X_3$ is a normal random variable with mean 1 and standard deviation 2. The baseline hazard function is $\lambda_0(t) = 0.15$. The censoring time in clinical trial $C_1$ is uniformly distributed between 0 and 3.5.

For each patient, the probability for a gap between clinical trial and the observational follow-up dataset to exist is 0.5 and the length of the gap $U$ is set as a uniform random variable between 1 and 2. Thus, the starting time of the observational follow-up period for
a participant is set as $C_1$ plus $U$. $C_2$ is set as start time of the observational follow-up time plus an exponential random variable with rate $0.8 \cdot X_1 + 0.03$. We further set $\tau_1 = 3.5$ and $\tau_2 = 16^7$. The percentage of interval-censored patient is approximately 4.5%. This is the scenario we used in section F.

I consider the same three mechanisms for linkage to the medicare data as the simulations with time-dependent covariates in Section 4. The only difference is that for LCAR, we have $P(L = 1) = 0.4$. When Cox model is correctly specified, one additional mechanism for linkage is considered as

$$P(L = 1|X, C_2, \Delta; Q = 0) = \frac{\exp(-0.25 + 0.5 \cdot X_1 + 0.5 \cdot X_2 - 0.1 \cdot C_2 - 0.1 \cdot \Delta)}{1 + \exp(-0.25 + 0.5 \cdot X_1 + 0.5 \cdot X_2 - 0.1 \cdot C_2 - 0.1 \cdot \Delta)}$$

$$P(L = 1|Q = 1) = 0.5.$$ 

This leads to a more serious violation of the CLAR assumption (A1) and linkage now depends on the censoring time in clinical trial $C_2$ conditional on $X$. As expected, NLAC should still work under this linkage mechanism as linkage does not depend on the failure time $T$. We again consider sample sizes $n = 500, 1,000, 1,500, \ldots, 10,000$. For each simulation setting, we generate 1,000 repetitions. The simulation results are given in Table 5 to Table 6. As the results are similar to the simulation studies in the main text, we omit the discussion here.

H Simulation setting in section 2.3

Now we present the simulation setting for the motivating example in section 2.3. The hazard function is $\lambda(t|x) = \lambda_0(t) \exp(\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_2^2)$ and $\beta_0 = (\beta_1, \beta_2, \beta_3)^T = (-\log(2), \log(2), 0.2)^T$. $X_1$ is a Bernoulli variable that takes value 1 with probability 0.5.

\footnote{\textit{C} \textsubscript{1} and \textit{C} \textsubscript{2} will be administratively censored by $\tau$ or $\tau_M$}
$X_2$ is a normal random variable with mean -1 and standard deviation 1. $X_3$ is a normal random variable with mean $X_2$ and standard deviation 2. The baseline hazard function is $\lambda_0(t) = 0.05$. The censoring time in clinical trial $C_1$ is exponentially distributed with rate $0.1 \times X_1 + 0.05$. The censoring time $C_2$ is defined as $C_1$ plus an exponential random variable with rate $0.8 \times X_1 + 0.03$. Further, we set $\tau_1 = 3$ and $\tau_2 = 16$. 
Table 5: Simulation results for linkage mechanism (LCAR) and (CLAR).

| Mechanism | Method | n   | $\beta_1$ (Mean SE) | $\beta_2$ (Mean SE) | $\beta_3$ (Mean SE) | Coverage of 95% CI |
|-----------|--------|-----|---------------------|---------------------|---------------------|-------------------|
| LCAR      | Oracle | 500 | -0.01 (0.219)       | 0.01 (0.095)        | 0.00 (0.045)        | 0.96 0.94 0.95    |
|           |        | 2000| -0.00 (0.108)       | 0.00 (0.047)        | 0.00 (0.022)        | 0.94 0.95 0.94   |
| CC        | 500    | -0.03 (0.355)       | 0.02 (0.155)        | 0.01 (0.073)        | 0.97 0.94 0.96    |
|           | 2000   | -0.01 (0.172)       | 0.00 (0.075)        | 0.00 (0.036)        | 0.96 0.96 0.94   |
| CC+       | 500    | 0.11 (0.241)        | -0.06 (0.111)       | -0.02 (0.054)       | 0.92 0.91 0.934  |
|           | 2000   | 0.12 (0.118)        | -0.07 (0.054)       | -0.02 (0.026)       | 0.81† 0.72† 0.86† |
| NLAC      | 500    | -0.01 (0.240)       | 0.01 (0.112)        | 0.00 (0.054)        | 0.96 0.95 0.95    |
|           | 2000   | -0.00 (0.118)       | 0.00 (0.055)        | 0.00 (0.026)        | 0.94 0.95 0.94   |
| IPLW      | 500    | -0.02 (0.271)       | 0.02 (0.125)        | 0.01 (0.060)        | 0.95 0.92 0.93    |
|           | 2000   | -0.01 (0.134)       | 0.00 (0.063)        | 0.00 (0.030)        | 0.95 0.95 0.93   |
| CLAR      | Oracle | 500 | -0.01 (0.219)       | 0.01 (0.095)        | 0.00 (0.045)        | 0.96 0.94 0.95    |
|           |        | 2000| -0.00 (0.108)       | 0.00 (0.047)        | 0.00 (0.022)        | 0.94 0.95 0.94   |
| CC        | 500    | -0.18 (0.320)       | -0.14 (0.153)       | 0.00 (0.070)        | 0.92 0.83† 0.95    |
|           | 2000   | -0.16 (0.156)       | -0.15 (0.074)       | -0.00 (0.034)       | 0.80† 0.45† 0.95  |
| CC+       | 500    | -0.08 (0.239)       | -0.22 (0.117)       | -0.02 (0.054)       | 0.95 0.51† 0.94   |
|           | 2000   | -0.07 (0.118)       | -0.23 (0.057)       | -0.02 (0.027)       | 0.89† 0.03† 0.88† |
| NLAC      | 500    | -0.01 (0.238)       | 0.01 (0.114)        | 0.00 (0.054)        | 0.95 0.95 0.95    |
|           | 2000   | -0.00 (0.117)       | 0.00 (0.056)        | 0.00 (0.027)        | 0.95 0.95 0.94   |
| IPLW      | 500    | -0.02 (0.263)       | 0.02 (0.134)        | 0.01 (0.063)        | 0.94 0.91 0.93    |
|           | 2000   | -0.00 (0.130)       | 0.01 (0.069)        | 0.00 (0.032)        | 0.95 0.95 0.94   |

We use † to highlight settings with coverage below 90%.
Table 6: Simulation results for linkage mechanism (LNAR(\(\hat{T}\))) and (LNAR(\(C_2\))).

| Mechanism   | Method | n  | \(\beta_1\) (Mean SE) | \(\beta_2\) (Mean SE) | \(\beta_3\) (Mean SE) | Coverage of 95% CI |
|-------------|--------|----|------------------------|------------------------|------------------------|-------------------|
| LNAR(\(\hat{T}\)) | Oracle | 500 | -0.01 (0.219)          | 0.011 (0.095)          | 0.00 (0.045)          | 0.96 0.94 0.95    |
|             |        | 2000 | -0.00 (0.108)          | 0.00 (0.047)          | 0.00 (0.022)          | 0.94 0.95 0.94    |
| CC          | 500    | -0.20 (0.320)         | -0.16 (0.154)         | 0.00 (0.071)          | 0.92 0.80† 0.95     |
|             |        | 2000 | -0.19 (0.156)         | -0.17 (0.074)         | -0.01 (0.034)         | 0.77† 0.38† 0.94  |
| CC+         | 500    | -0.10 (0.239)         | -0.24 (0.118)         | -0.02 (0.055)         | 0.94 0.47† 0.94     |
|             |        | 2000 | -0.1 (0.118)          | -0.24 (0.058)         | -0.02 (0.027)         | 0.87† 0.02† 0.86† |
| NLAC        | 500    | -0.01 (0.238)         | 0.01 (0.114)          | 0.00 (0.055)          | 0.95 0.95 0.95      |
|             |        | 2000 | -0.01 (0.118)         | 0.00 (0.056)          | -0.00 (0.027)         | 0.94 0.95 0.94    |
| IPLW        | 500    | -0.02 (0.265)         | 0.01 (0.137)          | 0.01 (0.064)          | 0.94 0.92 0.92      |
|             |        | 2000 | -0.01 (0.131)         | 0.00 (0.070)          | -0.00 (0.032)         | 0.94 0.95 0.94    |
| LNAR(\(C_2\)) | Oracle | 500 | -0.01 (0.219)          | 0.01 (0.095)          | 0.00 (0.045)          | 0.96 0.94 0.95    |
|             |        | 2000 | -0.00 (0.108)          | 0.00 (0.047)          | 0.00 (0.022)          | 0.94 0.95 0.94    |
| CC          | 500    | -0.63 (0.340)         | -0.27 (0.176)         | -0.02 (0.082)         | 0.55† 0.63† 0.95    |
|             |        | 2000 | -0.60 (0.165)         | -0.28 (0.083)         | -0.02 (0.039)         | 0.04† 0.09† 0.91  |
| CC+         | 500    | -0.46 (0.248)         | -0.35 (0.127)         | -0.05 (0.060)         | 0.54† 0.24† 0.87†   |
|             |        | 2000 | -0.44 (0.122)         | -0.36 (0.061)         | -0.05 (0.029)         | 0.04† 0.00† 0.62† |
| NLAC        | 500    | -0.01 (0.246)         | 0.01 (0.123)          | 0.00 (0.059)          | 0.96 0.95 0.95      |
|             |        | 2000 | -0.01 (0.121)         | 0.00 (0.060)          | 0.00 (0.029)          | 0.94 0.95 0.95    |
| IPLW        | 500    | -0.04 (0.316)         | 0.04 (0.180)          | 0.02 (0.088)          | 0.94 0.87† 0.89†    |
|             |        | 2000 | -0.01 (0.157)         | 0.01 (0.101)          | 0.01 (0.047)          | 0.94 0.91 0.91    |

We use † to highlight settings with coverage below 90%.