WEB-APPENDIX for "Comparison of Statistical Approaches Dealing with Immortal Time Bias in Drug Effectiveness Studies"

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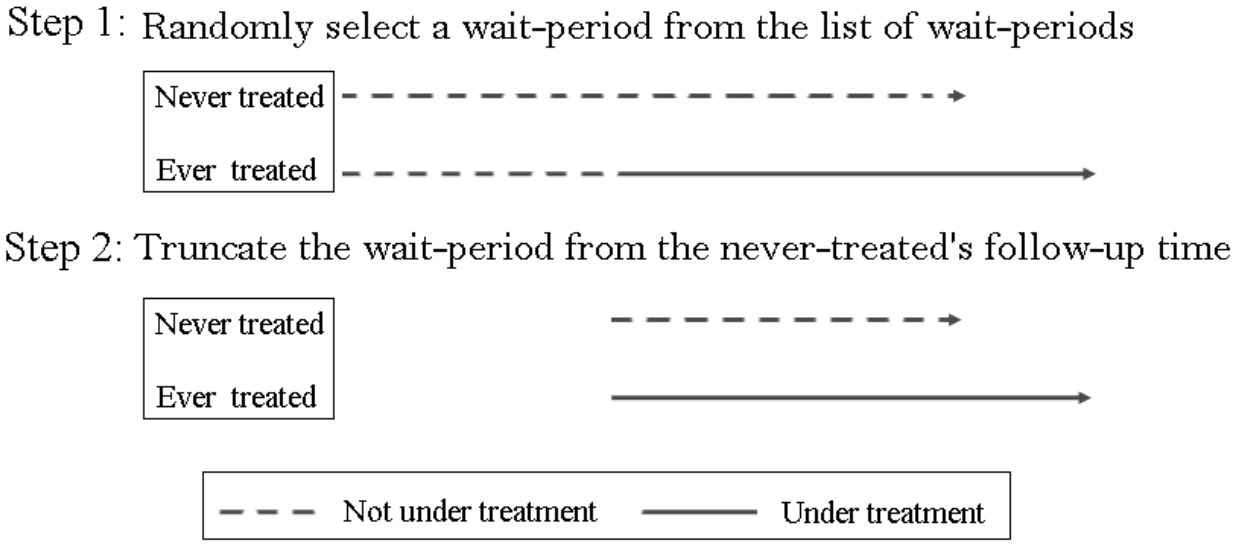
Web-Appendix 1: Quantification of the Bias from PTDM

We use the same notations here as defined in the section 2.1. Let $T'_1 = T_1 - T_{IT} = (1 - f) \times T_1$ denote the person-time under treatment in the ever-treated group. The total person-time not under treatment is $T'_0 = T_0 + T_{IT} = r \times T_1 + f \times T_1 = T_1(r + f)$, where T_0 and T_{IT} are contributed by the never-treated and ever-treated subjects respectively. Under the assumption of constant hazard of failure, the failure rate is calculated by the number of failures divided by the corresponding follow-up person-time. Thus, the failure rate ratio obtained from a time-dependent analysis is (1):

$$RR = \frac{N_1/T'_1}{N_0/T'_0} = \frac{N_1/(T_1 - T_{IT})}{N_0/(T_0 + T_{IT})}. \quad \text{(A.1)}$$

For PTDM, after excluding the observed and assigned immortal times from both groups (see Web-Figure 1), the unexposed time under consideration is $T''_0 = T_0 - T'_{IT} - T_x = T_0 - q \times T_{IT} - x \times T_1$ and the exposed time under consideration is $T'_1 = T_1 - T_{IT}$. The failure rate ratio from PTDM is calculated as

$$RR''' = \frac{N_1/T'_1}{(N_0 - N'_{IT})/T''_0} = \frac{N_1/(T_1 - T_{IT})}{(N_0 - N'_{IT})/(T_0 - T'_{IT} - T_x)}$$



Web-Figure 1: An illustration of prescription time-distribution matching

Comparing RR''' with the correct rate ratio RR in equation (A.1) yields:

$$\begin{aligned}
\frac{RR'''}{RR} &= \frac{\frac{N_1/(T_1-T_{IT})}{(N_0-N'_{IT})/(T_0-T'_{IT}-T_x)}}{\frac{N_1/(T_1-T_{IT})}{N_0/(T_0+T_{IT})}} \\
&= \left(\frac{N_0}{N_0-N'_{IT}}\right)\frac{T_0-T'_{IT}-T_x}{T_0+T_{IT}} \\
&= \left(\frac{N_0}{N_0-N'_{IT}}\right)\frac{T_0-q\times T_{IT}-x\times T_1}{T_0+T_{IT}} \\
&= \left(\frac{N_0}{N_0-N'_{IT}}\right)\frac{r-q\times f-x}{r+f} \qquad \text{(A.2)}
\end{aligned}$$

We see that RR'''/RR can be expressed as a function of r, f, x and q.

The equation (A.2) and Figure 1 show the general pattern of bias and allow general statements about the PTDM approach. A stochastic evaluation of the PTDM approach is provided in Web-Appendix 3. To take into account additional specific details of a more realistic epidemiological setting, such as censoring, different rates of failures, covariates under consideration, etc, we carry out simulation studies.

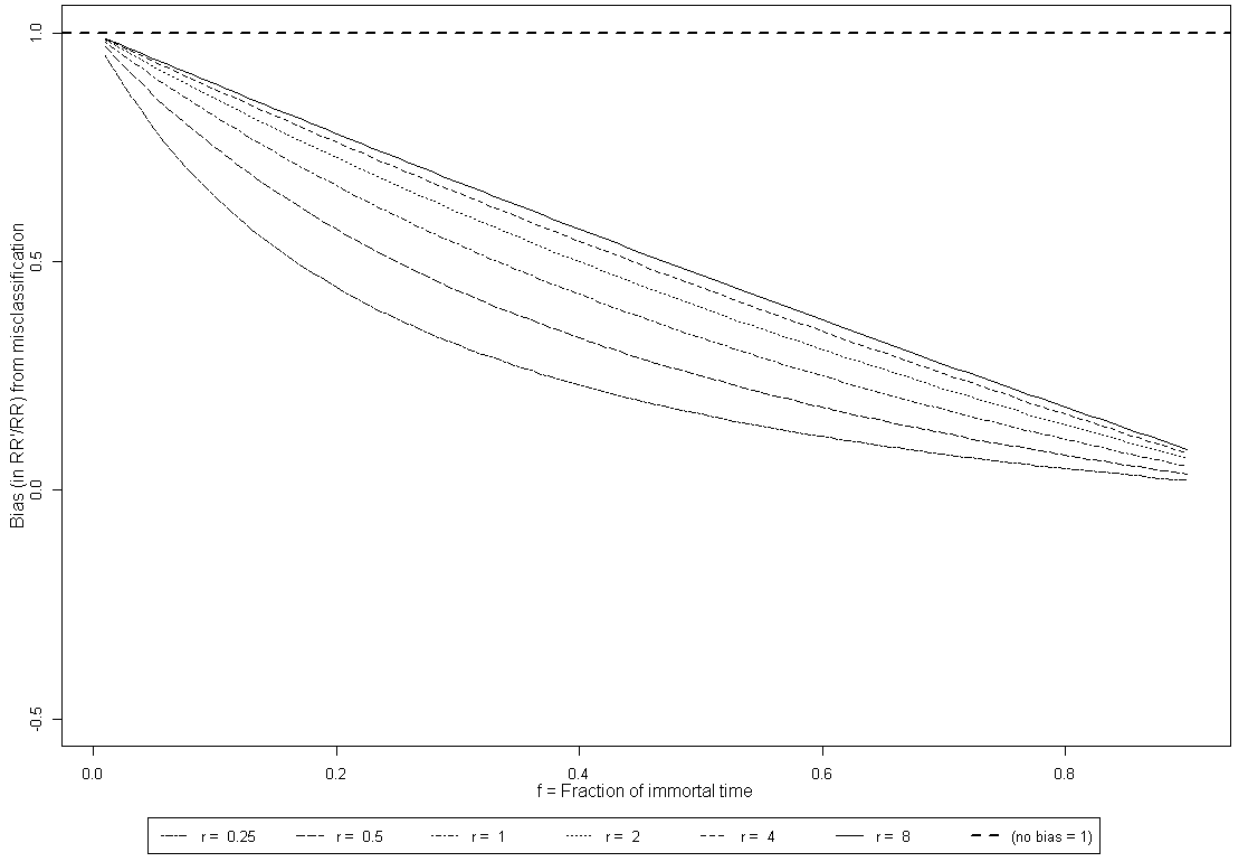
Web-Appendix 2: Bias due to Incorrect Handling of Immortal Time

For the sake of simplicity, many researchers often improperly define the treatment exposure. For example, it is popularly assumed that the subjects are on treatment immediately after joining a study cohort, when in reality, there may be a delay period to initiate treatment for some of the subjects. Not properly accounting for the delay period creates an immortal time bias.

2.1 Misclassifying Immortal Time

Misclassifying the observed immortal time T_{IT} as treated time leads to the failure rate of N_1/T_1 for the ever-treated subjects, and the failure rate ratio,

$$RR' = \frac{N_1/T_1}{N_0/T_0}.$$



Web-Figure 2: Risk ratios of PTDM (RR') method compared to RR of a time-dependent analysis as a function of the fraction of immortal time f and for various ratios r. The bias is the deviation of RR'/RR from the null value 1.

Comparing RR' with the correct rate ratio RR yields (2) (r and f are defined in Web-Appendix 1):

$$\begin{aligned} \frac{RR'}{RR} &= \frac{\frac{N_1/T_1}{N_0/T_0}}{\frac{N_1/(T_1-T_{IT})}{N_0/(T_0+T_{IT})}} \\ &= (1-f) \times \frac{r}{(r+f)}. \end{aligned} \qquad \text{(B.1)}$$

Under the assumption of constant hazard, this approach, therefore, always underestimates the correct failure rate ratio, thus overestimating (inflating) the treatment effect; see Web-Figure 2. We can see a larger downward bias (in RR'/RR) for increasing values of f, the fraction of the immortal person-time in the ever-treated subjects. For different ratios $r = T_0/T_1$ (r = 0.25, 0.5, 1, 2, 4, 8), the pattern of RR'/RR looks similar. The higher values of r yield slightly less bias (in RR'/RR).

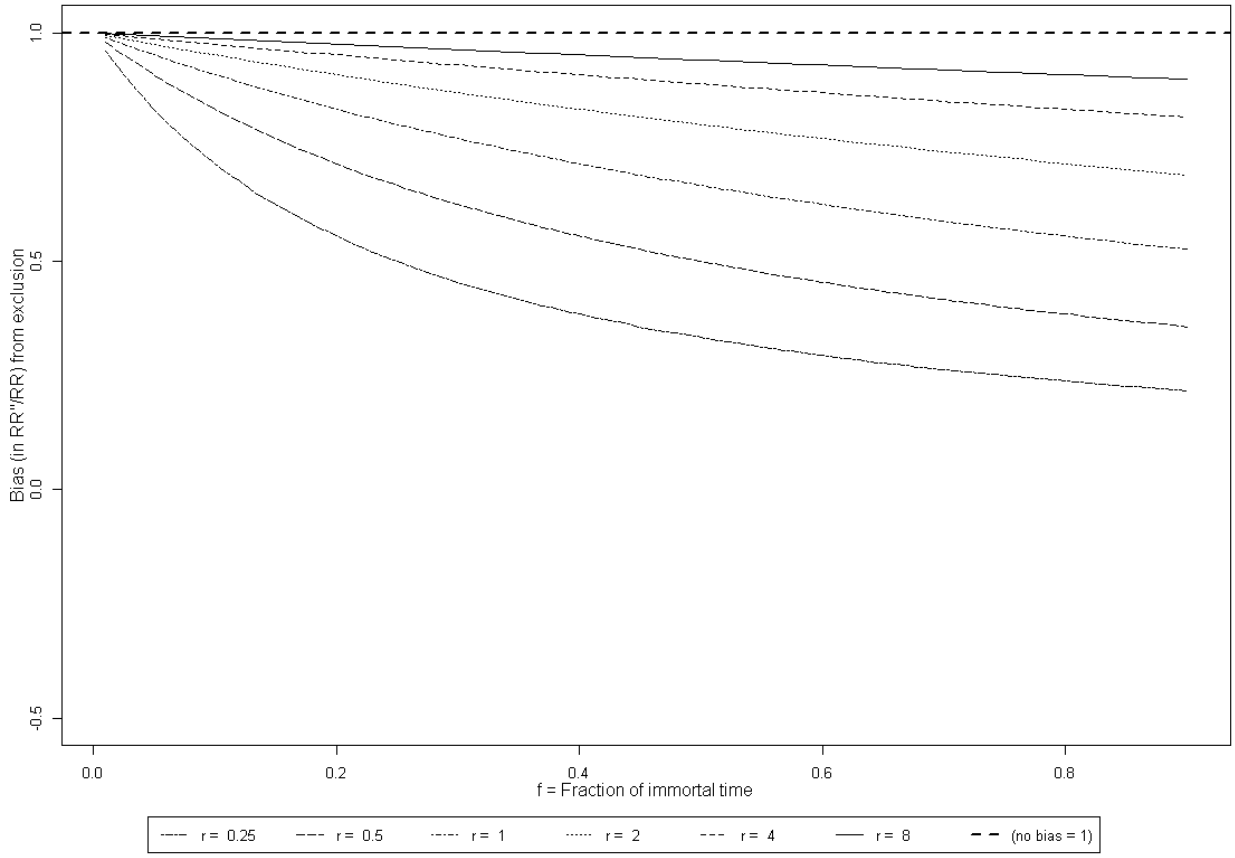
2.2 Excluding Immortal Time

Exclusion of the immortal time yields the failure rate under treatment of N_1/T'_1, and the failure rate ratio

$$RR'' = \frac{N_1/T'_1}{N_0/T_0}.$$

Comparing RR'' to the correct rate ratio RR yields (2):

$$\begin{aligned} \frac{RR''}{RR} &= \frac{(N_1/T'_1)/(N_0/T_0)}{(N_1/T'_1)/(N_0/T'_0)} \\ &= \frac{r}{r+f} \end{aligned} \qquad \text{(B.2)}$$



Web-Figure 3: Risk ratios of PTDM (RR'') method compared to RR of a time-dependent analysis as a function of the fraction of immortal time f and for various ratios r. The bias is the deviation of RR''/RR from the null value 1.

As in the previous situation, this approach, therefore, always underestimates the correct failure rate ratio, overestimating the effect of treatment; see Web-Figure 3. This also shows a downward bias (in RR''/RR) for increasing values of f, the fraction of the immortal person-time in the ever-treated subjects. However, the bias (in RR''/RR) is

significantly reduced for the higher values of *r*, the ratio of the person-times in the never-treated and ever-treated subjects. If the ever-treated cohort is much smaller than the never-treated cohort, the bias from this approach may be negligible, even for large fractions of immortal time *f*. Therefore, use of this approach may be reasonable in some settings (3).

Web-Appendix 3: Quantification of the Bias from PTDM under Simple Distributional Assumptions

Let S be the time from cohort entry to the treatment initiation, T be the time from cohort entry to the study outcome if untreated, and W be the time from treatment initiation to the study outcome.

For simplicity, let (S,T,W) be mutually independent, each with exponential distributions, with hazard rates γ, λ and η respectively. The time from treatment initiation to study outcome for a subject in the treatment group would correspond to a realization from $W|S < T$. Under the independence assumption, $W|S < T$ is exponentially distributed with hazard η. Note that, (S,T,W) are defined as potential outcomes (or counterfactuals or latent variables), and we only observe some functions of these variables.

To describe a subject belonging to the control group, consider two independent copies of the potential outcomes (S,T,W): (S_1,T_1,W_1) for the subject from the control group and (S_2,T_2,W_2) for the treated subject with whom the control subject was matched. In the PTDM setting, an untreated subject belongs to the control group if the following conditions are met: the untreated subject does not initiate treatment before he reaches the outcome ($T_1 < S_1$), the matched treated subject initiates treatment before his outcome is observed ($S_2 < T_2$), and the untreated subject develops his outcome after his matched treated subject initiates treatment ($S_2 < T_1$). Thus, the time from treatment initiation to study outcome for a control

subject is a realization of $T_1 - S_2 | T_1 < S_1, S_2 < T_2, S_2 < T_1$.

Now, for $z > 0$, we have

$$\begin{aligned} &Pr(T_1 - S_2 > z | T_1 < S_1, S_2 < T_2) \\ &\quad = \int_0^\infty \left(\int_{s_2+z}^\infty (\gamma+\lambda) \exp\left[-(\gamma+\lambda)t_1\right] dt_1 \right) (\gamma+\lambda) \exp\left[-(\gamma+\lambda)s_2\right] ds_2 \\ &\quad = (\gamma+\lambda) \int_0^\infty \exp[-(s_2+z)(\gamma+\lambda)] \exp[-s_2(\gamma+\lambda)] ds_2 \\ &\quad = \exp[-(\gamma+\lambda)z]/2 \end{aligned}$$

In this probability calculation, we used the fact that for any two independent exponential random variables, the distribution of one given it is smaller than the other is also exponential, with hazard being the sum of the two individual hazards, i.e., $T_1 | T_1 < S_1 \sim$ exponential$(\gamma + \lambda)$ and $S_2 | S_2 < T_2 \sim$ exponential$(\gamma + \lambda)$.

Then we obtain:

$$\begin{aligned} &Pr(T_1 - S_2 > z | T_1 < S_1, S_2 < T_2, S_2 < T_1) \\ &\quad = \frac{Pr(T_1 - S_2 > z, T_1 < S_1, S_2 < T_2)}{Pr(T_1 < S_1, S_2 < T_2, S_2 < T_1)} \\ &\quad = \frac{Pr(T_1 - S_2 > z | T_1 < S_1, S_2 < T_2)}{Pr(S_2 < T_1 | T_1 < S_1, S_2 < T_2)} \\ &\quad \propto \exp[-(\gamma+\lambda)z], \end{aligned}$$

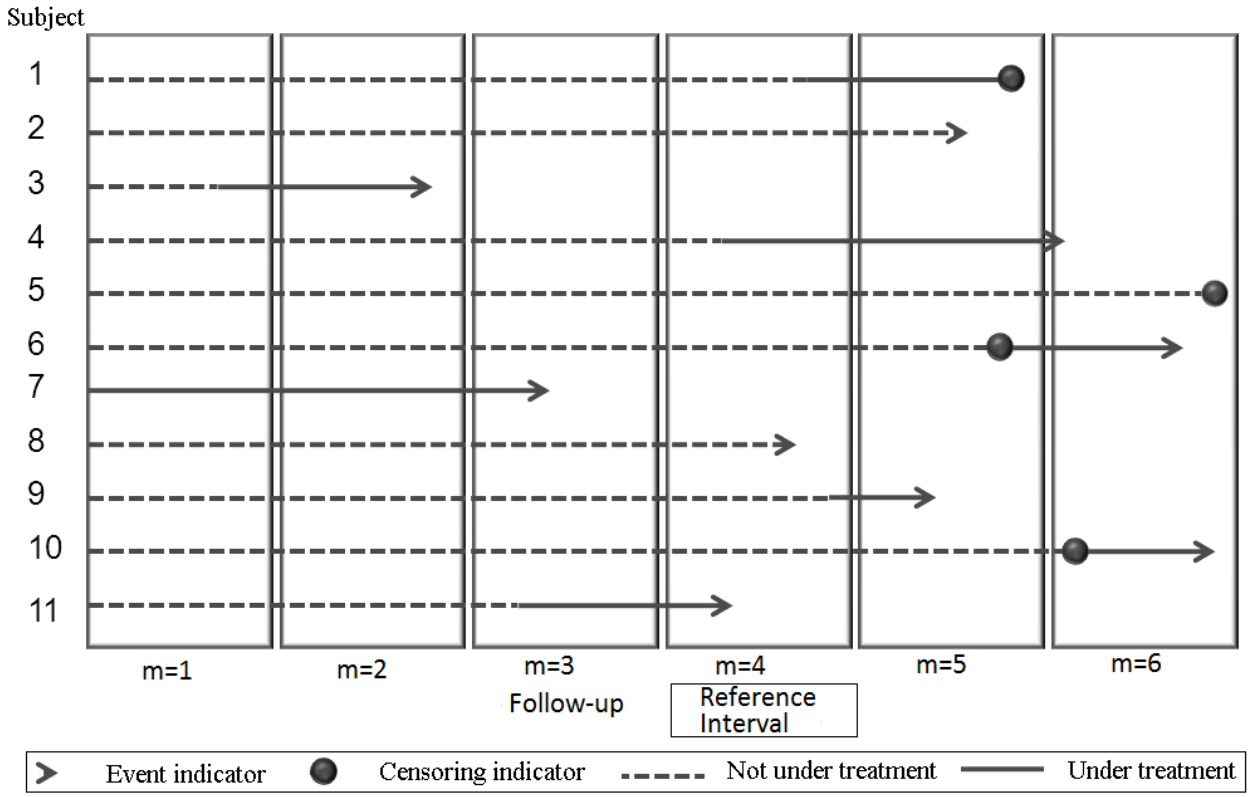
where the last step follows from the earlier calculation. We see that $T_1 - S_2 | T_1 < S_1, S_2 < T_2, S_2 < T_1$ is exponentially distributed with hazard $(\lambda + \gamma)$.

Based on our assumptions, when a subject initiates treatment, the hazard for the outcome changes from λ to η. Then η/λ is the hazard ratio parameter of interest. But the above calculation shows that we will be mistakenly targeting $\eta/(\gamma + \lambda)$ if we use PTDM approach. Therefore, the PTDM approach is shown to be biased in the framework under consideration.

As the PTDM approach estimates a lower hazard ratio, the direction of the bias should be negative. This phenomenon is observed in all our simulations (see Tables 1-6 and 8). For example, let $\lambda = .01$ (mimicking the rare event condition in our simulation) and $\gamma = 1/15$ (mean initiation time of 15 months) yields a predicted bias in the log-HR of $-\log[(\lambda + \gamma)/\lambda]$ = -2.04. Similarly, for the more frequent event condition ($\lambda = .10$), the predicted bias is = -0.51. Our simulation studies also take into account of additional covariates and censoring, which are not accounted for in this simplistic calculation, but those results indicate that the large bias of the PTDM approach seen in Tables 1 and 4 (-1.411 and -0.522 respectively) should not be surprising.

Web-Appendix 4: Implementing the Sequential Cox Approach

4.1 Constructing a mini-trial



Web-Figure 4: An illustration of the sequential Cox approach

To illustrate the method, consider Web-Figure 4, where the follow–up times for 11 subjects are outlined. Patient 1 was not under treatment when entering the study. This individual started taking the treatment in the m = 4th month and was censored during the 5th month. Similarly subject 5, who was never under treatment was censored during the 6th month. Now, suppose we want to create the mimicked trial considering the 4th month

as the reference interval. We eliminate the subjects who received treatment before the 4th month, i.e., the 3rd, 7th and 11th subjects will be discarded. The subjects who started treatment after the 4th month are censored at the time of treatment start i.e., the 6th and 10th subjects are censored at the 5th and 6th months respectively. Under the assumption that treatment status remains the same for the entire month, subjects 1, 4 and 9 will be considered the treated group and subjects 2, 5, 6, 8 and 10 will be considered the control group, for the mimicked trial starting at the beginning of 4th month. In this mimicked trial, a subject is either on treatment or off treatment during the entire follow-up.

4.2 Constructing pseudo-data

Similarly, we can identify the subjects for the treatment and control groups in the mimicked mini-trials starting at the beginning of other months. This yields multiple mimicked mini-trials, one for each of the time intervals (say, months) of treatment start. The intervals in which no subject initiates treatment do not have a corresponding mimicked mini-trial. Combining all these mimicked mini-trials (corresponding to all months of treatment start), we obtain the pseudo-data.

4.3 Implementation details

The treatment effect is estimated by fitting a stratified Cox model on the combined data of all mini-trials (pseudo-data), stratified by the treatment initiation time. Unlike the original implementation of the sequential Cox approach, we did not consider any time-dependent

covariates or confounders in our data analyses or simulations. Therefore, we fit the stratified Cox model, adjusting for only the baseline confounders.

4.4 Implementing in R

The coxph function in the survival package is used to fit the Cox model. In the coxph function, the option strata is set to fit a stratified Cox model for the sequential Cox approach. Also, the options such as cluster and robust = TRUE are set to obtain the robust (sandwich) variance estimate. Aalen's additive regression model is fitted using the aalen function in the timereg package to estimate the IPCWs. The data can be coded in either wide or long form (i.e., time-dependent or counting process formulation of the Cox model).

Web-Appendix 5: Survival Data Simulation via a Permutation Algorithm

In this algorithm, a permutation probability law based on the Cox model partial likelihood (4) is used as a basis for performing matching as follows. If a subject with a given set of covariates remains at risk until interval *m*, then the probability of that subject reaching the outcome at interval *m* is proportional to the subject's current hazard. This algorithm simulates survival data following specified distributions of survival time conditional on any number of fixed or time-dependent covariates. This algorithm has been validated for generating survival times conditional on time-dependent treatment (5) as well as being used in several other studies dealing with generating survival data with time-dependent covariates (see for example (1, 6, 7, 8, 9)).

The algorithm has following steps:

1. For each subject $i = 1, 2,\ldots,n$, we generate the survival time T_i using a specified distribution.
2. For each subject *i*, we generate the censoring time T_{iC} using a specified distribution.
3. We find the observed survival time $T_i^* = min(T_i, T_{iC})$ and the binary censoring indicator $C_i = I(T_i \geq T_{iC}) = 1$ if censored and 0 otherwise.
4. Repeat steps 1-3 *n* times and sort survival status tuples (T_i^*, C_i) with respect to T_i^* in increasing order.
5. We generate *n* covariate matrices $X_i = (A_{im}, L_{i0}, L_{im})$ with dimensions $(m \times p)$, where the $m = 0, 1,\ldots,K$ rows correspond to the different time intervals or visits when

measurements are taken and the p columns correspond to the predictor variables, including treatment (A_m), time-fixed and/or time-varying covariates (L_0 and/or L_m). For subject i, X_{im}, the m-th row of X_i, is a vector of variable values at time m.

6. According to the ordered T_i^* listed in step 3, we begin assigning the survival status tuple (T_i^*,C_i) to covariate values from X_{im} as follows. At time T_i^*, variable values (treatment and covariate) are sampled with probabilities p_{im} defined below based on the Cox model's partial likelihood:

$$p_{im} = \begin{cases} \frac{\exp(\psi X_{im})}{\sum_{j \in r_i} \exp(\psi X_{jm})}, & \text{if } C_i = 0 \\ \frac{1}{\sum_{j \in r_i} I(j \in r_i)}, & \text{if } C_i = 1, \end{cases}$$

where ψ is the vector of log-HRs for the corresponding variables and $I(j \in r_i)$ indicates whether a subject is within a given riskset r_i for time T_i^*.

7. The subject i with the covariate values X_{im} is assigned the observed time T_i^*. The selected X_{im} is removed from further calculation.

The permutation algorithm is implemented in the PermAlgo package in R (10).

Additional Simulation Results

Web-Table 1: Comparison of the analytical approaches to adjust for immortal time bias from simulation - I (one baseline covariate and time-dependent treatment exposure) of 1, 000 datasets, each containing 2, 000 subjects followed for up to 30 time-intervals. Event times were generated from a gamma distribution with parameters 1/0.01 and 0.4 (Simulation - V).

Approach§	Bias($\widehat{\psi_1}$)	$SD(\widehat{\psi_1})$	$\widehat{se(\psi_1)}$	CP	MSE($\widehat{\psi_1}$)
TD-Cox	-0.001	0.085	0.083	0.942	0.007
Included IT	-2.350	0.075	0.073	0.000	5.53
Excluded IT	-1.631	0.070	0.067	0.000	2.665
PTDM	-1.305	0.097	0.096	0.000	1.711
Sequential Cox†‡	-0.014	0.109	0.105	0.936	0.012

TD-Cox, Cox proportional hazards model with time-dependent exposure; PTDM, Prescription time distribution matching; IT, Immortal time.

§ When estimating the treatment effect, the baseline covariate L_0 is included in all the models under consideration.

† In the sequential Cox approach, the corresponding IPCW model is fitted using Aalen's additive regression model adjusting for A_{t_m} and L_0 to predict future censoring status.

‡ Robust (sandwich) estimate is used to obtain the SE.

Web-Table 2: Comparison of the analytical approaches to adjust for immortal time bias from simulation - I (one baseline covariate and time-dependent treatment exposure) of 1, 000 datasets, each containing 2, 000 subjects followed for up to 30 time-intervals. Event times were generated from a Weibull distribution with parameters 1/0.01 and 2 (Simulation - VI).

Approach§	Bias($\widehat{\psi_1}$)	$SD(\widehat{\psi_1})$	$\widehat{se(\psi_1)}$	CP	MSE($\widehat{\psi_1}$)
TD-Cox	0.003	0.239	0.237	0.954	0.057
Included IT	-2.142	0.221	0.217	0.000	4.636
Excluded IT	-0.819	0.213	0.212	0.044	0.717
PTDM	-1.281	0.275	0.274	0.012	1.718
Sequential Cox†‡	0.013	0.293	0.285	0.942	0.086

TD-Cox, Cox proportional hazards model with time-dependent exposure; PTDM, Prescription time distribution matching; IT, Immortal time.

§ When estimating the treatment effect, the baseline covariate L_0 is included in all the models under consideration.

† In the sequential Cox approach, the corresponding IPCW model is fitted using Aalen's additive regression model adjusting for A_{t_m} and L_0 to predict future censoring status.

‡ Robust (sandwich) estimate is used to obtain the SE.

Web-Appendix 6: Summary of the Selected Cohorts, Selection and Exclusion Criteria

In this study, the eligibility criteria for β-IFN treatment are: patients have to be at least 18 years old, have an Expanded Disability Status Scale (EDSS; (11)) score of 6.5 or below (i.e., able to walk 20 meters without resting with constant bilateral support) and have definite MS with a relapsing-onset disease course. In total, 2, 671 patients met the eligibility criteria to receive β-IFN treatment between July 1995 and December 2004, as outlined previously (12, 13). Follow-up (study end) was to December 2008.

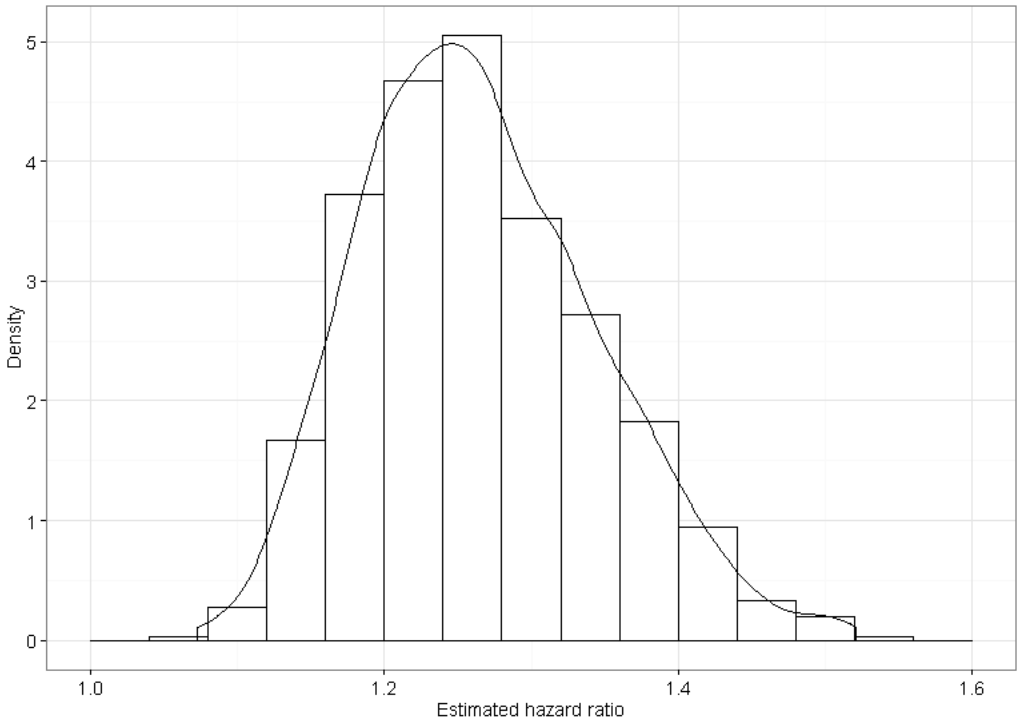
Web-Table 3: Characteristics of the selected cohort of patients with relapsing-onset multiple sclerosis (MS), British Columbia, Canada (1995-2008).

Baseline characteristics	Ever-β-IFN exposed	Never-β-IFN unexposed
Women, *n* (%)	660 (76.0)	637 (76.8)
Age, average (SD)	38.1 (9.2)	41.3 (10.0)
Disease duration, average (SD)	5.8 (6.6)	8.3 (8.5)
EDSS score, median (range)	2.0 (0-6.5)	2.0 (0-6.5)

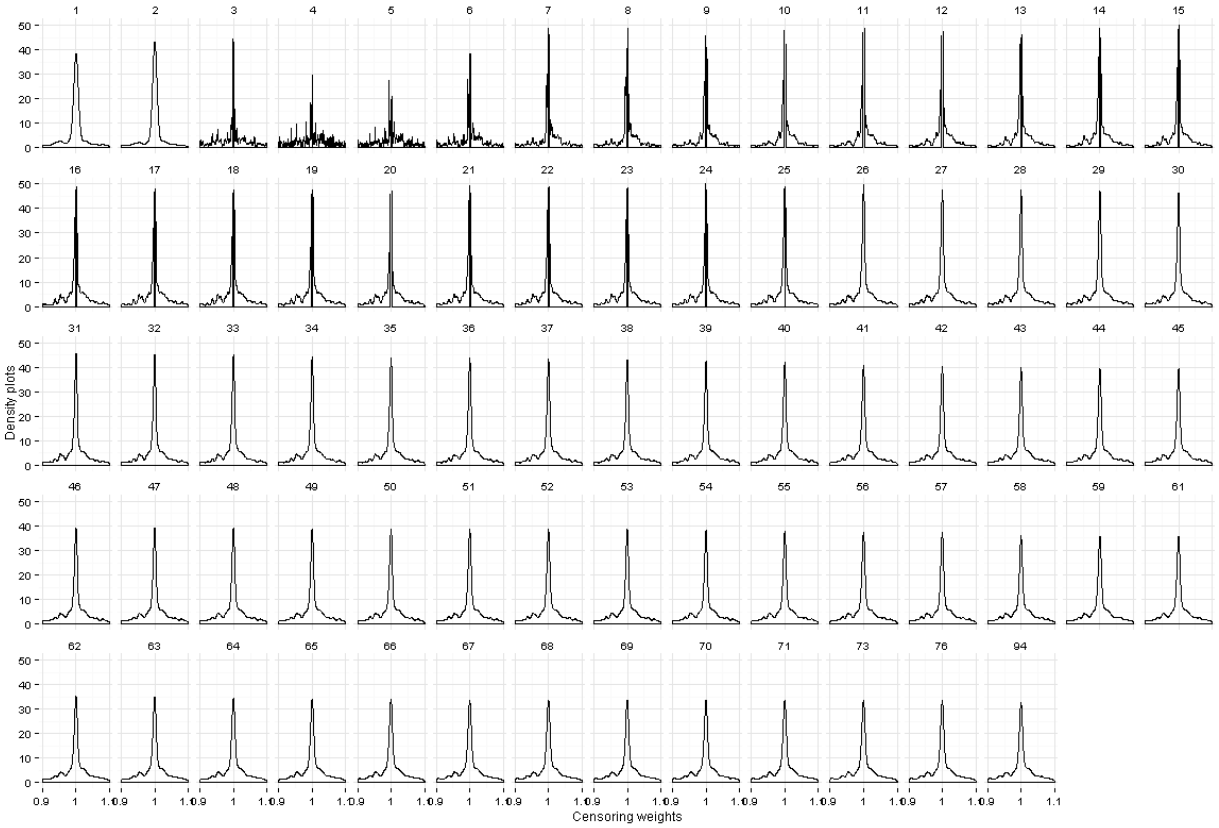
Patients who were exposed to a non-β-IFN immunomodulatory drug, a cytotoxic immunosuppressant for MS (n = 172), or were enrolled in a drug-related MS clinical trial (n = 21) prior to baseline were excluded from the analysis. If such exposures occurred after

baseline, data were censored at the start of the exposure to the non-β-IFN treatment (or clinical trial). Further exclusion criteria included unknown MS onset date (n = 10), insufficient EDSS measurements (n = 436), reaching of the outcome (n = 218) or the secondary progressive stage before the eligibility date (n = 217). Some patients met multiple exclusion criteria. As a result, 1, 697 patients were selected and among them, 829 patients remained untreated during follow-up. A summary of their characteristics are reported in Web-Table 3.

Application to the Multiple Sclerosis Cohort



Web-Figure 5: Density (gaussian kernel with bandwidth selected from Silverman's 'rule of thumb' (14)) plot of estimated hazard ratios from the prescription-time distribution matching (PTDM) method using 1, 000 different seeds for random sampling of the control subjects to estimate the causal effect of β-IFN on time to sustained EDSS 6 for patients with relapsing-onset multiple sclerosis (MS), British Columbia, Canada (1995-2008).



Web-Figure 6: Density plots of the estimated IPC weights from patients with relapsing-onset multiple sclerosis (MS), British Columbia, Canada (1995-2008) in all the reference (treatment initiation) intervals using the sequential Cox approach

Web-Appendix 7: Specifications for Simulation Inspired by the Multiple Sclerosis Cohort

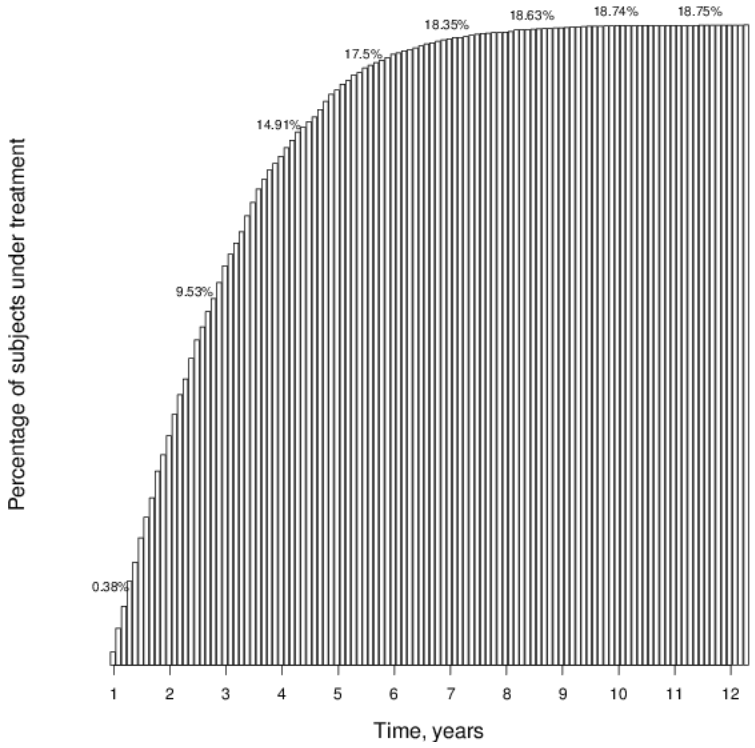
In this Monte Carlo study, we generated $N = 1,000$ datasets each with $n = 1,700$ subjects followed for up to $m = 150$ subsequent months. These numbers were selected based on the multiple sclerosis data used in this paper.

We assume an exponential distribution for generating failure times T with the constant $\lambda_0 = 0.01$ rate of monthly events throughout the follow-up. A gamma distribution with shape 3.5 and rate 0.01 (with mean 35 months) is assumed to generate censoring times T_C. Treatment initiation time T_A is generated from a uniform distribution $U(0, 150)$ (in months). To focus on the immortal time issue, we again assumed that there are no discontinuations or interruptions for those who initiate treatment. Additionally, we consider sex, age, disease duration and EDSS scores as baseline confounders L_0 in these data. A subject's sex is generated based on a Bernoulli distribution where the probability of being male is 0.3. Age is generated based on a normal distribution with mean 40 and standard deviation 10. Disease duration is generated based on a exponential distribution with rate 0.14. Baseline EDSS score is generated based on a binomial distribution with size 10 and probability 0.1. These distributions and corresponding parameters were chosen based on the data characteristics outlined in Web-Table 1.

After generating values for the survival time T_i, the censoring time T_i^C, and the treatment and covariate matrix $X_{im} = (A_{im}, L_{i0})$ for each subject $i = 1, 2, \ldots, n$ for up to $m = 150$ months, the permutation algorithm (15) is used to generate survival data where treatment A_{t_m} is time-dependent but the confounder L_0 is fixed at baseline value. The effect parameters for treatment and sex on the survival outcome are set such that the treatment did not have a beneficial effect (a log-HR of $\psi_1 = 0.25$), males are at a lower risk than females (a log-HR of $\psi_2 = -0.2$), an older age at baseline are associated with a higher risk (a log-HR of $\psi_3 = 0.05$), a shorter disease duration is associated with a lower risk (a log-HR of $\psi_4 = -0.02$) and a higher EDSS score at baseline is associated with a higher risk (a log-HR of $\psi_5 = .5$). These log-HRs were chosen based on the coefficients from the Cox model fit with the time-dependent treatment from the multiple sclerosis data (β-IFN: 0.25, sex: -0.22, age: 0.54, disease duration: 0.03 and baseline EDSS: -0.019; which are similar to the earlier reported coefficients (13)). A summary of the simulated cohort characteristics are reported in Web-Table 4. Web-Figure 7 shows the barchart of the percentage of cohort cumulatively receiving treatment over the follow-up period.

Web-Table 4: Characteristics of the simulated cohort of 10, 000 patients.

Baseline characteristics	Ever-β-IFN exposed	Never-β-IFN unexposed
Women, %	0.76	0.76
Age, average (SD)	39.03 (9.86)	40.17 (9.91)
Disease duration, average (SD)	6.98 (7.09)	6.96 (7.01)
EDSS score, median (range)	1.0 (0-6)	2.0 (0-7)



Web-Figure 7: Barchart of the cumulative percentages of the cohort of 10, 000 subjects having initiated treatment over the follow-up periods.

Web-References

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