Causal Inference Workshop
R version

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Exercise 1: Drawing your directed acyclic graph

The data for these exercises is a simulated version of the Coronary Drug Project trial[1] (`trial1.csv`). The outcome of interest is all-cause mortality over 5 years of follow-up (`death`).

1 Coronary Drug Project

The US National Heart Blood and Lung Institute sponsored the Coronary Drug Project, a double-blind placebo-controlled randomized trial conducted between 1966-75, to determine the safety and efficacy of a set of drugs for secondary prevention of mortality among men with a history of myocardial infarction (heart attacks)[1].

The trial initially compared 5 active treatments, high- and low-dose equine estrogen, dextrothyroxine, nicotinic acid, and clofibrate, to placebo. However, three treatment arms (high- and low-dose estrogen, and dextrothyroxine) were stopped early for high risk of adverse events. We focus here on the comparison between **clofibrate** and **placebo** [2].

Clofibrate is a lipid-lowering agent first created in 1966 that works to increase lipoprotein lipase activity to decrease high cholesterol and triglyceride levels. In the U.S. it was initially sold under the trade name "Atromid-S", but in 2002, FDA approval was revoked due to adverse effects [7]. In the trial, patients were instructed to take 600mg 3x per day. Placebo here was sugar pills, designed to look like clofibrate, and taken on the same schedule.

Adherence to treatment in this trial was defined by the physician at each quarterly visit throughout follow-up, who visually inspect the bottle of pills to describe the adherence as "good" ($\geq$ 80% of pills used) versus "poor" (<80% of pills used).

Table 1 below describes relevant design components of the Coronary Drug Project protocol.

Table 1: Trial Description

Protocol	Description
Eligibility criteria	Men with a history of myocardial infarction in previous 3 months, 30-64 years old at baseline
Treatment arms	5 lipid-lowering active drugs vs placebo
Follow-up	Begins: at randomization Ends: earliest of 5 years after baseline, loss to follow-up, or death
Outcome	All-cause mortality within 5 years
Causal contrasts of interest	1) Intention-to-treat effect 2) Effect of good adherence to trial protocol versus poor adherence in the placebo arm

2 Simulated data

The Coronary Drug Project is real patient data, so sharing is restricted. Instead, we simulated a data set based on the relationships between a subset of the variables recorded in the Coronary Drug Project. Table 2 below describes the variables that you can use in your analyses with this simulated data.

Although the original trial had loss to follow-up, for simplicity we have chosen to simulate data with no loss to follow-up. Therefore, everyone is in the trial for the full five years, or follow-up ends due to death.

3 Directed acyclic graphs for pragmatic trials

A pragmatic trial is a trial designed to study long-term effects of sustained clinical interventions in typical patients and care settings. Per-protocol effects are often estimated in pragmatic trials because patients and providers want a measure of effectiveness that is not influence by adherence. Analyses of pragmatic trials can be especially challenging because they are susceptible to confounding and selection bias often associated with observational data analyses.

In this workshop, we are interested in two types of causal effects in pragmatic trials: the intention-to-treat effect, and the effect of good adherence versus poor adherence on mortality in the placebo arm. Although the Coronary Drug Project was not designed as a pragmatic trial, it shares many of the same features as these trials, especially the relatively high degree of non-adherence, and both the intention-to-treat effect and the placebo arm adherence effect are interesting in this trial [2, 3, 4, 5].

Before we can estimate these causal effects, we need to think about the structure of relationships between variables in our trial. Using a directed acyclic graph (DAG) can be a helpful way to visualize the potential for bias due to confounding and selection bias [6].

3.1 DAG for the intention-to-treat effect

By convention, we use the following notation for drawing DAGs for randomized trials: Z for randomization; A, A_0 and A_t for treatment or adherence; L, L_0, and L_t for measured covariates; U for unmeasured covariates; and Y for the outcome, where the subscripts indicate baseline (0) or time-varying (t) variables.

Table 2: Data Description

Variable	Notation	Definition	Values
simID	id	ID variable	Range: 0 to 4042
rand	Z	Randomization group	0: placebo; 1: clofibrate
visit	t	Visit number: visits occur quarterly	Range: 0 to 14
death	Y	Death recorded at visit t	0: alive; 1: died T $\in [t, t+1)$
adhpre0bin	A_0	Adherence to placebo during pre-randomization run-in period	0: adherence $\geq$ 80%; 1: adherence $<$ 80%
adhr	A_t	Adherence to assigned treatment at visit t	0: adherence $\geq$ 80%; 1: adherence $<$ 80%
mi_bin	L	Myocardial infarction at baseline	0: $<$2; 1: $\geq$2
AntiHyp	L	Antihypotensive medication use at visit t	0: no; 1: yes
AnyQQS	L	ECG findings: Q/QS pattern at visit t	0: no; 1: yes
AnySTDep	L	ECG findings: ST depression at visit t	0: no; 1: yes
AP	L	Angina pectoris at visit t	0: no; 1: yes
CardioM	L	Cardiomegaly at visit t	0: no; 1: yes
CHF	L	Coronary heart failure at visit t	0: no; 1: yes
DIUR	L	Diuretic use at visit t	0: no; 1: yes
FVEB	L	ECG finding: Frequent ventricular beats at visit t	0: no; 1: yes
HiHeart	L	High heart rate at visit t	0: $<$70 bpm; 1: $\geq$ 70 bpm
HiSerChol	L	High serum cholesterol at visit t	0: $<$250; 1: $\geq$ 250
HiSerTrigly	L	High serum triglyesterol at visit t	0: $<$5.0; 1: $\geq$ 5.0
IC	L	Intermittent claudication at visit t	0: no; 1: yes
NIHA	L	New York Heart Association class at visit t	0: none; 1: any limitation
OralHyp	L	Oral hypoglycemic agents use at visit t	0: no; 1: yes
VCD	L	ECG finding: Ventricular conduction defect at visit t	0: no; 1: yes

In the space below, use this notation to draw a DAG representing the intention-to-treat effect in the Coronary Drug Project. In thinking about which variables to include in your DAG, remember the intention-to-treat effect is the effect of randomization Z on the outcome Y. Your DAG can, but need not, include A. Examples of intention-to-treat effects (at the end of follow-up) are

$$\text{Additive: } \text{RD} = \Pr[Y^{z=1} = 1] - \Pr[Y^{z=0} = 1]$$

$$\text{Multiplicative: } \text{RR} = \frac{\Pr[Y^{z=1} = 1]}{\Pr[Y^{z=0} = 1]}$$

3.2 DAG for the per-protocol effect

The per-protocol effect is the effect of receiving treatment according to the trial protocol. In this workshop, we will look at a special type of per-protocol effect – the effect of good versus poor adherence to placebo.

This placebo per-protocol effect can be defined as

$$\text{Additive: RD} = \Pr[Y^{\bar{a}=1} = 1 \mid Z = 0] - \Pr[Y^{\bar{a}=0} = 1 \mid Z = 0]$$
$$\text{Multiplicative: RR} = \frac{\Pr[Y^{\bar{a}=1} = 1 \mid Z = 0]}{\Pr[Y^{\bar{a}=0} = 1 \mid Z = 0]}$$

By convention, we use the following notation for drawing DAGs for randomized trials: Z for randomization; A,A_0 and A_t for treatment or adherence; L, L_0, and L_t for measured covariates; U for unmeasured covariates; and Y for the outcome, where the subscripts indicate baseline (0) or time-varying (t) variables.

In the space below, use this notation to draw a DAG representing the per-protocol effect in the Coronary Drug Project. In thinking about which variables to include in your DAG, remember the per-protocol effect is the effect of time-varying adherence A_t on the outcome Y. Accordingly, your DAG should include common causes of A_t and Y at each time point. Common causes may include L_t, U, and Z.

Exercise 2: Intention-to-treat effects

In this coding exercise, we will work through estimating the intention-to-treat effect. The intention-to-treat effect is the effect of randomization on the outcome, `death`, regardless of whether individuals adhered to the treatment protocol they were assigned to. This effect can be quantified using several different kinds of statistics: 1) cumulative incidence ratio, 2) hazard ratio, or 3) risk difference at a specified time. Each of these statistics can be calculated using a variety of methods, including those that allow us to control for confounding by indication. In this section, we will implement these methods and compare and contrast the results.

1 Data exploration

Run the code in **Code Section 1** and answer the following questions:

- How many person-visits are in this dataset?
- How many individuals are in this dataset?
- How many individuals had at least 10 visits?
- In the example trial, individuals could be randomized to either placebo (`rand = 0`) or active treatment (`rand = 1`). The variable `rand` is constant within individuals across all visits. How many individuals were randomized to each trial arm?
- How many individuals died overall? How many individuals died in each treatment arm? What was the cumulative probability of surviving at 14 visits in each treatment arm?

2 Estimating the ITT hazard ratio

We would like to calculate estimates that account for varying amounts of person-time from each individual, especially because our outcome, `death`, *necessarily* affects the amount of time each individual contributes to the study.

2.1 Kaplan-Meier survival curves (non-parametric estimate)

To begin, we will use the Kaplan-Meier method to non-parametrically estimate survival separately in each trial arm. Run the code in **Code Section 2** to create the estimates at each visit, and plot the estimated survival curves.

- How does the estimate of survival at visit 14 (from the command `summary(kmfit)`) compare to the proportion of individuals who died in each arm separately, as estimated in bullet 5 after Code Section 1?

- Based on the graph you created and the summary of the Kaplan-Meier fit, do you think there is a difference in survival at 14 visits between the treated and placebo arms? Is this a statistically significant difference? A clinically relevant difference?

2.2 Unadjusted and adjusted hazard ratios to estimate conditional causal effects

We can estimate the unadjusted intention-to-treat hazard ratio by comparing survival among the two trial arms using either a Cox proportional hazards model or a pooled logistic regression model. We expect that the hazard ratios will be very close to identical using these methods. Pooled logistic regression is very similar to a Cox model, but it allows us to more easily estimate the baseline hazard and therefore calculate the predicted risk, risk ratio, and/or risk difference.

Unadjusted models

$$\text{Cox PH Model: } \lambda(t \mid Z) = \lambda_0(t)\exp(\alpha_1 Z)$$
$$\text{PLR Model: } logit[\Pr(Y_{it} = 1 \mid Z)] = \beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 Z$$

We can also estimate adjusted intention-to-treat hazard ratios using a Cox model or a pooled logistic model. We will adjust for the baseline measurements of the covariates listed in Table 2. Baseline covariates all have a suffix of `_b` to denote they were measured at baseline.

Adjusted models

$$\text{Cox PH Model: } \lambda(t \mid Z, L_0) = \lambda_0(t)\exp(\alpha_1 Z + \alpha_2 L_0)$$
$$\text{PLR Model: } logit[\Pr(Y_{it} = 1 \mid Z, L_0)] = \beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 Z + \beta_2 L_0$$

The coefficients α_1 and β_3 from the adjusted models can be interpreted as the **conditional** causal hazard ratio comparing individuals on clofibrate with those on placebo, *holding* L_0 *constant.*

To use a pooled logistic regression model, we must include time as a covariate in our model. However, because estimating the baseline hazard is generally difficult, we want to allow time to be included in a very flexible manner (polynomials, splines, categorical). In our trial, the time scale was `visit`, which numbered from 0 to 14 and occurred every 3 months. In this workshop, we have chosen to include `visit` as a quadratic polynomial.

Note 1: We must report *robust* standard errors when using pooled logistic regression because the data is in person-time format - observations from the same individual are highly correlated. In `R`, this is done using the functions `'vcovHC'` from the `'sandwich'` package and `'coeftest'` from the `'lmtest'` packages after the initial model fitting.

Note 2: The option `'breslow'` used in the fitting of the Cox model refers to how the model handles ties. This option matches the default in `SAS` and `Stata`.

Run the code in **Code Section 3**, fill in this table and answer the following questions.

		Cox proportional hazards	Pooled logistic regression
Unadjusted	Coef		
	SE		
	HR		
Adjusted	Coef		
	SE		
	HR		

- Do the results from the *unadjusted* Cox proportional hazards model and the *unadjusted* pooled logistic regression model match? What is the causal interpretation of these hazard ratios? What assumptions are we making to give this hazard ratio a causal interpretation?

- What is the causal interpretation of the hazard ratio from the adjusted Cox model? What is the causal interpretation of the hazard ratio from the adjusted pooled logistic regression model? What assumptions do we make to give each of these hazard ratios a causal interpretation? Are these assumptions different?

3 Standardizing over baseline covariates to estimate marginal causal effects

If we want to adjust for covariates but retain the interpretation as an average causal effect without making additional assumptions about effect homogeneity, we can standardize our estimates across baseline covariates. This amounts to calculating marginal effects, instead of conditional effects, as we did in part 3. (We will use the terms "marginal" and "standardized" interchangeably here.)

When we use Cox proportional hazards models, we do not explicitly model the baseline hazard. Therefore, we will use a pooled logistic regression to calculate standardized results (hazard ratio, risk differences, and survival curves). Again, we need to be sure that we have a flexible estimate of the baseline hazard, so we will include time (`visit`) as a quadratic polynomial, as well as interaction terms between randomization and the time variables (`randvisit` and `randvisit2`).

We will calculate standardized survival curves (one for survival if everyone was treated, one for survival if everyone received placebo), overall marginal hazard ratio, and the marginal risk difference at 14 visits. To do this, we will follow 6 steps:

(1) **Data processing.** Add interaction terms `randvisit` and `randvisit2` to the `trial` dataset.

(2) **Pooled logistic regression with interaction terms.** Estimate the parameters of a pooled logistic regression model including interaction terms created above. The code below is exactly the same as the adjusted pooled logistic regression model we ran in Code Section 3, except that we have added our interaction terms. Save the model fit as `adj_plr_ix_fit` [read: adjusted pooled logistic regression interaction fit], which includes coefficient estimates among other things.

$$logit[\Pr(Y_{it} = 1 \mid Z, L_0)] = \beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 Z + \beta_4 Zt + \beta_5 Zt^2 + \beta_6 L_0$$

(3) **Simulated data: treated.** Create a new dataset which includes 1 copy of every person at baseline, and force everyone in this dataset to get treatment (don't forget to recreate the interaction terms between the exposure and time!). We also assume that each person was observed for the complete 14 visits. Your complete simulated data will include `simID`, `visit`, `rand`, and all baseline covariates (see Table (6)). We then can calculate the predicted survival `p` at each person-time observation, and survival (`s`) by taking the cumulative product of `p` at each visit. This is equivalent to using the Kaplan-Meier method ($s = s * (1 - p)$) to calculate survival. (*Note:* Cumulative incidence can be calculated here as $ci = 1 - s$. We chose not to do this.)

(4) **Simulated data: placebo.** Repeat step 3, but assign everyone to receive placebo. Don't forget to recreate the interaction terms!

(5) **Standardized survival curves.** First, concatenate your two simulated datasets into one dataset, only keeping `s`, `visit`, and `rand` in the new dataset called `both`. To calculate average survival at each visit, we have to average over all individuals separately for each new trial arm (uses the `aggregate` function, and outputs a dataframe called `results`). We then have

a dataset that has 30 observations and 3 variables, an estimate of the average `s` for each individual at each `visit` under each hypothetical treatment assignment `rand`. Plot these results.

(6) **Standardized hazard ratio and marginal risk difference at 14 weeks.** To make these computations easier, we create a dataframe called `wideres` that contains 15 observations of 3 variables: `visit`, `Placebo`, and `Treated`. `Placebo` and `Treated` contain the average standardized survival at each visit. We calculate risk differences `RD` at each visit by subtracting estimated survival in the `Treated` from that in `Placebo`. We can then estimate the standardized hazard ratio at each visit during follow-up (`log(Treated) / log(Placebo)`). To calculated the overall HR, we average the HR over the whole study period [this is just one option].

Original Data

simID	visit	rand	mi_bin	NIHA_b	Y
9	0	1	0	0	0
9	1	1	0	0	0
9	2	1	0	0	0
9	3	1	0	0	0
9	4	1	0	0	0
9	5	1	0	0	0
9	6	1	0	0	0
9	7	1	0	0	1

$\Longrightarrow$

Simulated Data - `rand` = 1

simID	visit	rand	mi_bin	NIHA_b
9	0	1	0	0
9	1	1	0	0
9	2	1	0	0
9	3	1	0	0
9	4	1	0	0
9	5	1	0	0
9	6	1	0	0
9	7	1	0	0
9	8	1	0	0
9	9	1	0	0
9	10	1	0	0
9	11	1	0	0
9	12	1	0	0
9	13	1	0	0
9	14	1	0	0

$+$

Simulated Data - `rand` = 0

simID	visit	rand	mi_bin	NIHA_b
9	0	0	0	0
9	1	0	0	0
9	2	0	0	0
9	3	0	0	0
9	4	0	0	0
9	5	0	0	0
9	6	0	0	0
9	7	0	0	0
9	8	0	0	0
9	9	0	0	0
9	10	0	0	0
9	11	0	0	0
9	12	0	0	0
9	13	0	0	0
9	14	0	0	0

Table 3: Visualization of Simulation Process

Run the code in **Code Section 4**, fill in this table and answer the following questions.

`visit` (t)	$\hat{S}^{z=0}(t)$	$\hat{S}^{z=1}(t)$	std. RD	std. HR
0				– – –
1				– – –
2				– – –
3				– – –
4				– – –
5				– – –
6				– – –
7				– – –
8				– – –
9				– – –
10				– – –
11				– – –
12				– – –
13				– – –
14				– – –
15				

- What is the standardized risk difference at the end of follow-up? What is the standardized intention-to-treat hazard ratio at the end of follow-up?

- How does this compare with the *conditional* unadjusted intention-to-treat hazard ratio? What about the *conditional* covariate adjusted hazard ratio?

- What is the causal interpretation of this standardized hazard ratio?

- What assumptions are we making to give the standardized hazard ratio a causal interpretation?

Exercise 3: Inverse probability weighting for treatment-confounder feedback

1 Background

In this exercise, we will estimate the "placebo effect" - the effect of actually adhering to the placebo treatment on overall mortality in the placebo trial arm. This effect is a special case of a `per-protocol` effect. Because adhering to placebo is time-varying, we will need to use inverse probability weighting to adjust for treatment-confounder feedback (where treatment in this case is adherence). Examples of placebo effects (at the end of follow-up) are

$$\text{Additive: RD} = \Pr[Y^{\bar{a}=1} = 1] - \Pr[Y^{\bar{a}=0} = 1]$$
$$\text{Multiplicative: RR} = \frac{\Pr[Y^{\bar{a}=1} = 1]}{\Pr[Y^{\bar{a}=0} = 1]}$$

Here we will restrict our analysis to the placebo arm. Among people who were assigned to placebo, we expect that their mortality risk over 5 years is not affected by whether they actually did or did not take their placebo pills. Therefore, we hypothesize that we will find a null effect estimate if we compare placebo arm adherers to non-adherers. Whenever you have a placebo arm, comparing adherers to non-adherers can be a good way to assess whether you have collected enough post-randomization confounders to be able to estimate a per-protocol effect. In our example, adherence is recorded at baseline (adhr_b) and at each follow-up visit (adhr).

There are two main approaches that we can use to test this hypothesis. We want to estimate the effect of adherence to placebo on mortality if everyone continuously adhered versus if everyone continually did not adhere. We can do this by:

- Determining whether each individual is adherent or not at baseline and then artificially censoring them if and when they switch adherence status.
- Determining whether each individual is adherent or not at every time point and modeling adherence as a continuous variable.

In both approaches, inverse probability weighting is then used to adjust for the potential selection bias induced by the artificial censoring, creating a counterfactual world where everyone either continuously adheres or continually does not adhere to the placebo.

In this exercise, we will use the first approach. For an example of the second approach, see [5].

2 Data cleaning and Exploration

We will again need to use a function of time. If you're starting from here, go up to **Code Section 1** and run all of the provided code through **Code Section 4**, this will ensure that your dataset `trial` is properly cleaned to complete the next sections.

Next, we need to identify the time that each individual changes adherence status, so that we can appropriately censor them. We do this by creating a new variable that is 0 if an individual's adherence is the same as it was at baseline, or 1 once it has changed. We will also drop all individuals in the treatment arm from our dataset, and create our interaction terms between exposure and time here.

Finally, we will calculate the Kaplan-Meier curve for survival separately in adherers and non-adherers. This will require us to recreate the `maxVisit` variable (so it only includes person-time that is not censored), and subsequently the `deathOverall` variable.

Run the code in **Code Section 5** and answer the following questions.

- How many individuals are in the `placebo` dataset? How many are adherers at baseline? Non-adherers at baseline?

- Print a few lines of your new dataset and take a look at whether the new variable has been created correctly.

- Comment on the Kaplan-Meier curves you generated. After visually inspecting the data, do the curves look similar?

3 Estimate inverse probability of adherence weights

To estimate the effect of adherence on all-cause mortality in the placebo arm, we first need to create **inverse probability of adherence weights**. These weights will create a pseudo-population where the association between adherence and time-varying covariates is removed, allowing adherence to appear to be randomized with respect to the observed time-varying covariate distribution. Although there are many methods to calculate weights (unadjusted, stabilized, normalized, truncated), we prefer to use stabilized weights to avoid extreme weight values, which can lead to unstable effect estimates.

$$\omega_{it} = \prod_{j=0}^{t} \frac{f_N(A_{ij} \mid L_0)}{f_D(A_{ij} \mid L_0, L_t)}$$

Using these weights ensures that we are weighting people based only on their time-varying characteristics, not their baseline characteristics, and can improve the efficiency of our estimates. To calculate stabilized weights, we follow these steps:

- Fit the model for the numerator: estimate the probability of adherence at time t conditional on baseline covariates only

$$logit(\Pr[A_{it} = 1 \mid L_0]) = \gamma_0 + \gamma_1 t + \gamma_2 t^2 + \gamma_3 L_0$$

- Fit the model for the denominator: estimate the probability of adherence at time t conditional on baseline *and time-varying* covariates

$$logit(\Pr[A_{it} = 1 \mid L_0, L_t]) = \gamma_0^* + \gamma_1^* t + \gamma_2^* t^2 + \gamma_3^* L_0 + \gamma_4^* L_t$$

- From each model, predict the probability of adherence at time t in the data.
- Calculate the appropriate contribution to the weight from each model fit.

$$f_N(A_{it} \mid L_0) = A_{it}\Pr(A_{it} = 1) + (1 - A_{it})\Pr(A_{it} = 0)$$
$$f_D(A_{it} \mid L_0, L_t) = A_{it}\Pr(A_{it} = 1) + (1 - A_{it})\Pr(A_{it} = 0)$$

- Take the product of the ratio of the numerator and denominator contributions up to time t^* to calculate the stabilized weights at time t^*. Truncate if needed (usually at 99^{th} percentile)

Run the code in **Code Section 6**, fill in the table, and answer the following questions.

	Unstabilized	Stabilized	Truncated Stabilized (99^{th} percentile)
Mean (SD)			
Range			
Median (IQR)			
99th Percentile			

- What was the mean of your stabilized weights after truncation? What did you expect it to be? Did stabilizing the weights (compared to unstabilized) change the mean of the weights? How did truncating change the mean and range of the weights?

4 Estimating the weighted conditional hazard ratio

Now, we can use the stabilized inverse probability of adherence weights to estimate the hazard ratio for overall mortality comparing adherers versus non-adherers in the placebo arm. This is a `per-protocol` effect, where our protocols are 1) continually adhere to the protocol ("take at least 80% of assigned placebo pills"), versus 2) continually do not adhere to the protocol ("take less than 80% of assigned placebo pills"). We will censor individuals when they deviate from their protocol (`maxVisit`).

We will use a pooled logistic regression model to estimate this per-protocol effect. Since we are using a censoring based approach (1 from above), our outcome model will be created in the person-time where adherence status is unchanged from baseline (`t` $\leq$ `maxVisit`). We then use baseline adherence (`adhr_b`) as our exposure and the baseline covariates included above (since we stabilized over them) as covariates in the model.

$$logit[\Pr(Y_{it} \mid A_0, L_0, \omega_{it}, t \leq \texttt{maxVisit})] = \beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 A_0 + \beta_4 L_0$$

Run the code in **Code Section 7** and answer the following questions. Here, we will only consider a stabilized truncated weighting procedure (`stabw_t`). If you would like to see the instability from unstabilized or stabilized weights, replace the weights argument with `unstabw` or `stabw`.

adhr_b	Stabilized (Truncated)
Coef.	
SE	
Hazard Ratio	

- What is the estimated hazard ratio using stabilized (truncated) weights? How do you interpret this hazard ratio?

- What assumptions does your interpretation rely upon?

5 Estimating inverse probability weighted survival curves

Finally, we can estimate per-protocol effects for survival in adherers and non-adherers in the placebo arm. To do this, we could use the same weighted pooled logistic regression model as above, but to allow for greater flexibility in estimating the baseline hazard, we choose to refit this model including a product term between adherence (`adhr_b`) and time (`visit`) to our outcome model.

To standardize our estimate so we can have marginal estimates, we will use the same approach as we used when we were estimating the standardized ITT (see Code Section 4). We will need to adapt our code so that we assign everyone to be adherent and non-adherent to our placebo protocol continuously from baseline.

Note: You may be wondering where the time-varying covariates have gone. We only use the weights to get the correct coefficients from the outcome regression model, we do not need weights to do any predicting. For prediction, we only need the variables on the right-hand side of the model statement, which in our case are all time-fixed (except for time and its spline term, which we can create ourselves in the simulated data). Therefore, we can take the same strategy as in Code Section 4 to create our simulated dataset.

Run the code in **Code Section 8**, fill in thes table, and answer the following questions. Here, $S^0(t)$ refers to non-adherers, and $S^1(t)$ refers to adherers.

`visit` (t)	$S^0(t)$	$S^1(t)$	std. RD	std. HR
0				– – –
1				– – –
2				– – –
3				– – –
4				– – –
5				– – –
6				– – –
7				– – –
8				– – –
9				– – –
10				– – –
11				– – –
12				– – –
13				– – –
14				– – –
15				

- What is the overall standardized hazard ratio? Standardized risk difference at the end of follow-up?

- How do you interpret the standardized survival curves?

- What assumptions does your interpretation rely upon?

References

[1] Coronary Drug Project Research Group (1973). The coronary drug project. Design, methods, and baseline results. *Circulation* **47**: 11-150.

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[4] Murray EJ, Hernan MA (2016). Adherence adjustment in the Coronary Drug Project: A call for better per-protocol effect estimates in randomized trials. *Clinical Trials* **13(4)**: 372-378.

[5] Murray EJ, Hernan MA (2018). Improved adherence adjustment in the Coronary Drug Project. *Trials* **19**: 158-162.

[6] Hernan MA, Robins JM (2016). Per-protocol analyses of pragmatic trials. *New England Journal of Medicine* **377(14)**: 1391-1398.

[7] Wikipedia (2018). Clofibrate. *https://en.wikipedia.org/wiki/Clofibrate*.