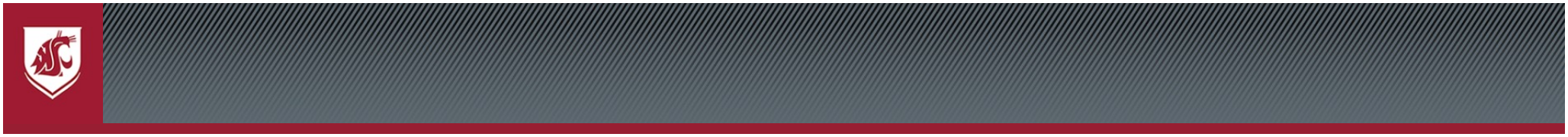
Competing Risks & Alternative Adjustment Strategies



Questions from Last Class?

PS 3

- On testing the proportional hazards assumption: As some of you noted, the diagnostic plots are “Okay-ish”
- That’s alright – you just want to avoid clear departures, temporal trends, etc.

PS 3 Cont.

- Don't necessarily rely on goodness-of-fit tests (like AIC) to determine whether to include something as a confounder
- Generally, these are better for determining the *form* a variable takes – should you include a squared term, or just the linear one? Is an exponential fit okay, or should you use a Weibull?

Competing Risks

- We assumed in the last class that there's a single outcome of interest
- What if that's not true?
- A competing risk is another mutually exclusive outcome that may be of interest

Ways of Ignoring Competing Risks

- If you don't care about them, treat them as censored
- You can roll them into one outcome measure – for example, AIDS defining illness OR Death
- This muddies the waters a little bit as to what you're estimating, but is by far the most straightforward

Cause-Specific Analysis

- But what if you're interested in both?
- Cause-Specific Analysis analyzes each competing risk, while treating the other one as censored
- "What is the time to Event 1 if Event 2 never happened, and what is the time to Event 2 if Event 1 never happened?"
- This *can* be sensible, but isn't always
- "What is the time to death if no one was ever discharged from the hospital, and what is the time to discharge from the hospital if no one ever died?"

Subdistribution Hazard

- Individuals who experience Event 1 remain in the risk set for Event 2, and vice versa
- This places a constraint on the estimated hazard function, as a number of people in the risk set cannot have the outcome

Parametric Mixture Models

- Model both outcomes as parametric models as well as the proportion of individuals experiencing each outcome
- This is very good for prediction, but the usual problems of parametric models applies here
- It's also a pain to implement

Alternative Methods of Confounding Control

Why?

- Thus far, when we've controlled for confounding, we've been breaking the relationship between the confounder and the outcome
- But you could *also* break the relationship between the confounder and exposure
- Perhaps we have more information on that relationship?

Propensity Scores

- Predict the probability of having the exposure
  - PS = P(X=1|Z)
- Logistic regression is most often used for this
- This is your “propensity score”
- You can “trim” extreme values from your data
- Propensity scores can be used as a covariate (estimating the exposure-outcome relationship among those equally likely to have the exposure)

Propensity Score Matching

- Match pairs (or sets) of exposed and unexposed with equal (or nearly equal) propensity scores
- *In theory* this feels like it's emulating a clinical trial – equal likelihoods of being exposed, just happen to not be
- Wildly popular
- Some suggestion that this is a bad idea
  - https://gking.harvard.edu/publications/why-propensity-scores-should-not-be-used-formatching

Inverse Probability of Treatment Weights

- Similar to propensity scores
- Model the probability of exposure
  - $W = 1/P(X=x|Z)$
- Take the inverse of this probability
  - Often stabilized with the marginal probability of your exposure
    - $SW = P(X=x)/P(X=x|Z)$
- This is now the "weight" of the observation
- Conduct your analysis on the weighted population
  - **Use robust variance/bootstrapping/etc.**

Why Weight?

- What are you estimating?
- Regression: Estimate is conditional on the modeled covariates
- Propensity: Estimate is conditional on the propensity score
- Weighting: Estimating the marginal effect
  - This is helpful if you *don't* want conditional estimates (see: mathematical modeling)
  - Weighted data sets can be used to create covariate-adjusted KM curves

"Doubly Robust"

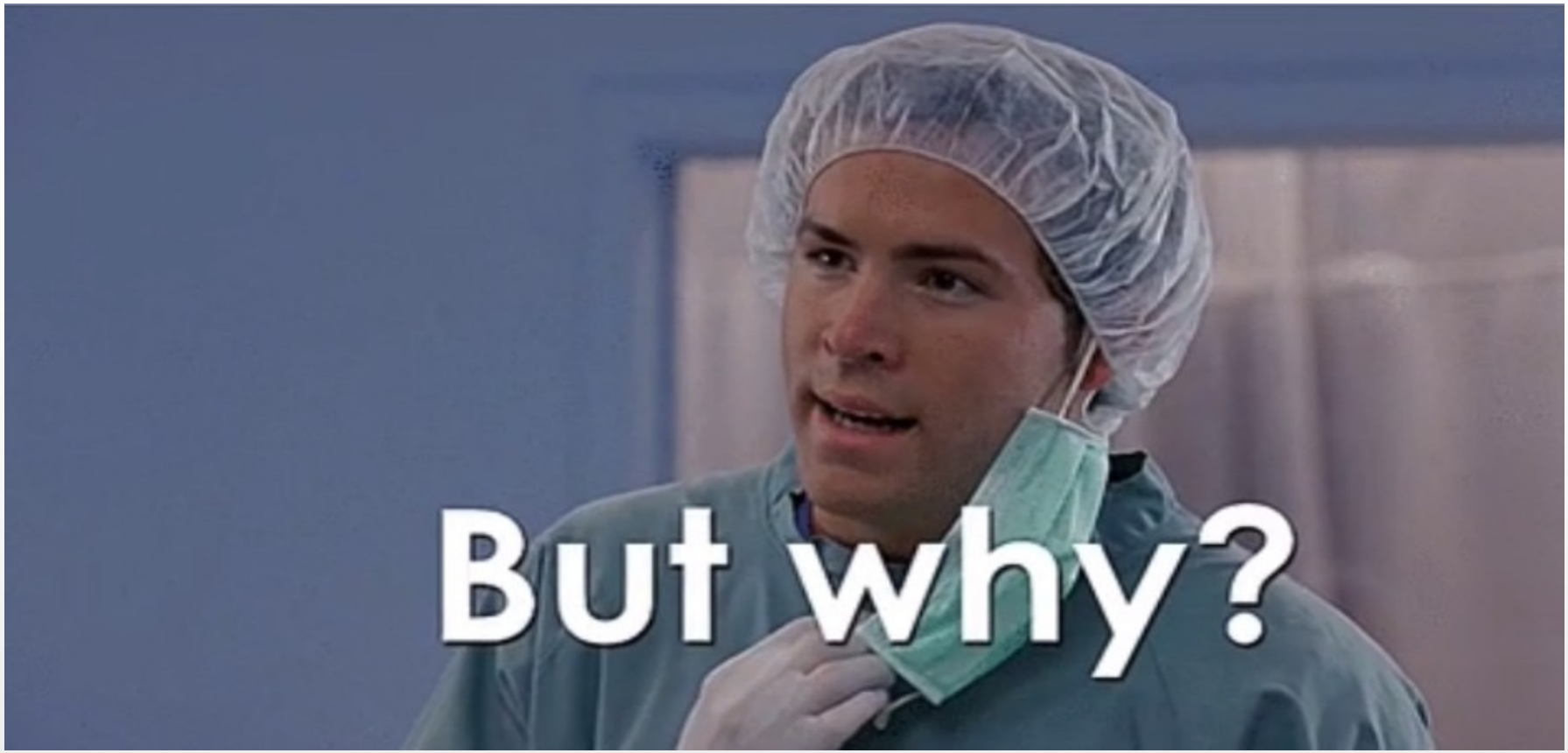
- If you see something referred to as "doubly robust", it means they're using PS/IPTW *and* regression adjustment to try and adjust for confounding
- "Getting two swings at the ball"
- Theoretically, this should help protect you if one model is misspecified
- Some practical question as to whether or not this gets you very much, as your p(misspecification) is probably not independent
- Can't save you from unmeasured confounding

Cautions

- These methods only really work if there is substantial overlap between exposure groups
- Average weight should be ~ 1
- No weights above 20, below 1/20
- Graph the distribution of propensity scores

Running these Into Each Other

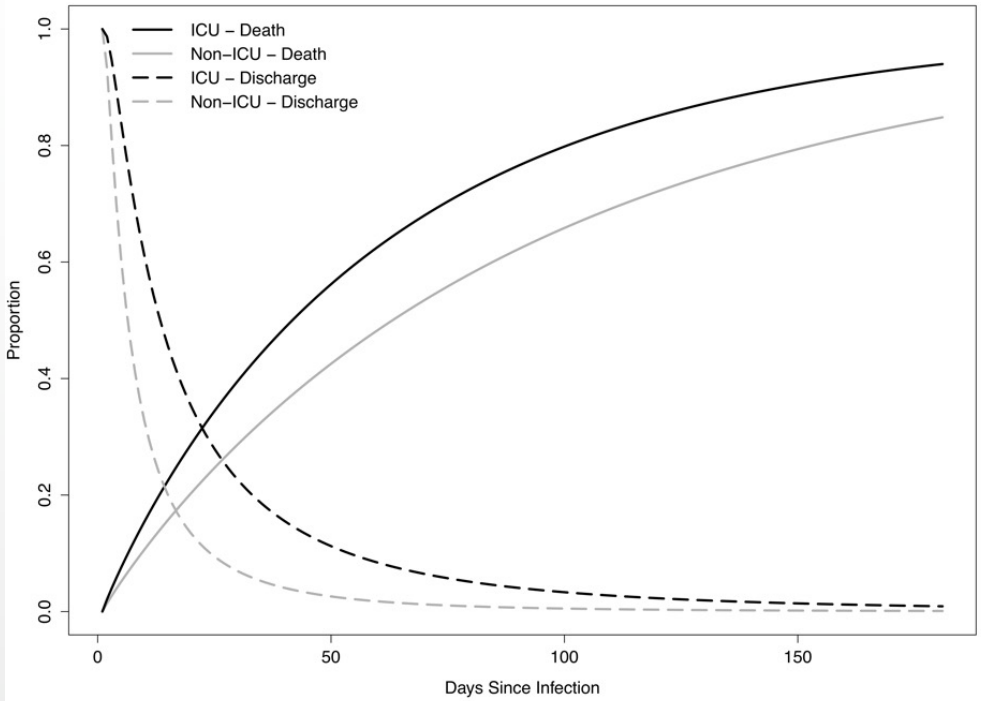
- Lofgren ET, SR Cole, DJ Weber, DJ Anderson and RW Moehring. Hospital-acquired *Clostridium difficile* Infections: Estimating All-Cause Mortality and Length of Stay. *Epidemiology* 2014; 25: 570-75


But why?

Study Design is Driven by the Question

- Parametric survival models: Needed to use these in mathematical models where being able to draw from a parametric distribution was important
- IPTW: I didn't want to keep track of patient covariates, just the difference between ICU and non-ICU patients, so I needed marginal estimates of that effect
- Competing Risks: I needed to know the survival curves for both death and discharge, and I needed to know them in the presence of the other

$RT_D = 0.65\ (0.36, 1.17)$
$RT_N = 2.30\ (1.66, 3.18)$



$RT_D = 1.97\ (0.96, 4.01)$
$RT_N = 1.88\ (1.40, 2.51)$