The Prevalent New User Design and You

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METHODOLOGIC TOPICS OF CURRENT INTEREST SESSION

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Our main context

A **comparative study** of the **causal effect** of two distinct therapeutic alternatives that include a **treatment of interest A** and a single **comparator treatment B**.

Other use cases for the design also exist and will be discussed at the end of the presentation!

Five core questions

1. Why avoid the inclusion of prevalent users in cohort studies of drug safety and effectiveness?
2. What are prevalent new users (vs prevalent users) and how can we identify them?
3. What does the PNU design estimate?
4. What are some analytic strategies for PNU design studies?
5. How is the PNU design evolving?

Why avoid prevalent users in studies of drug safety and effectiveness?

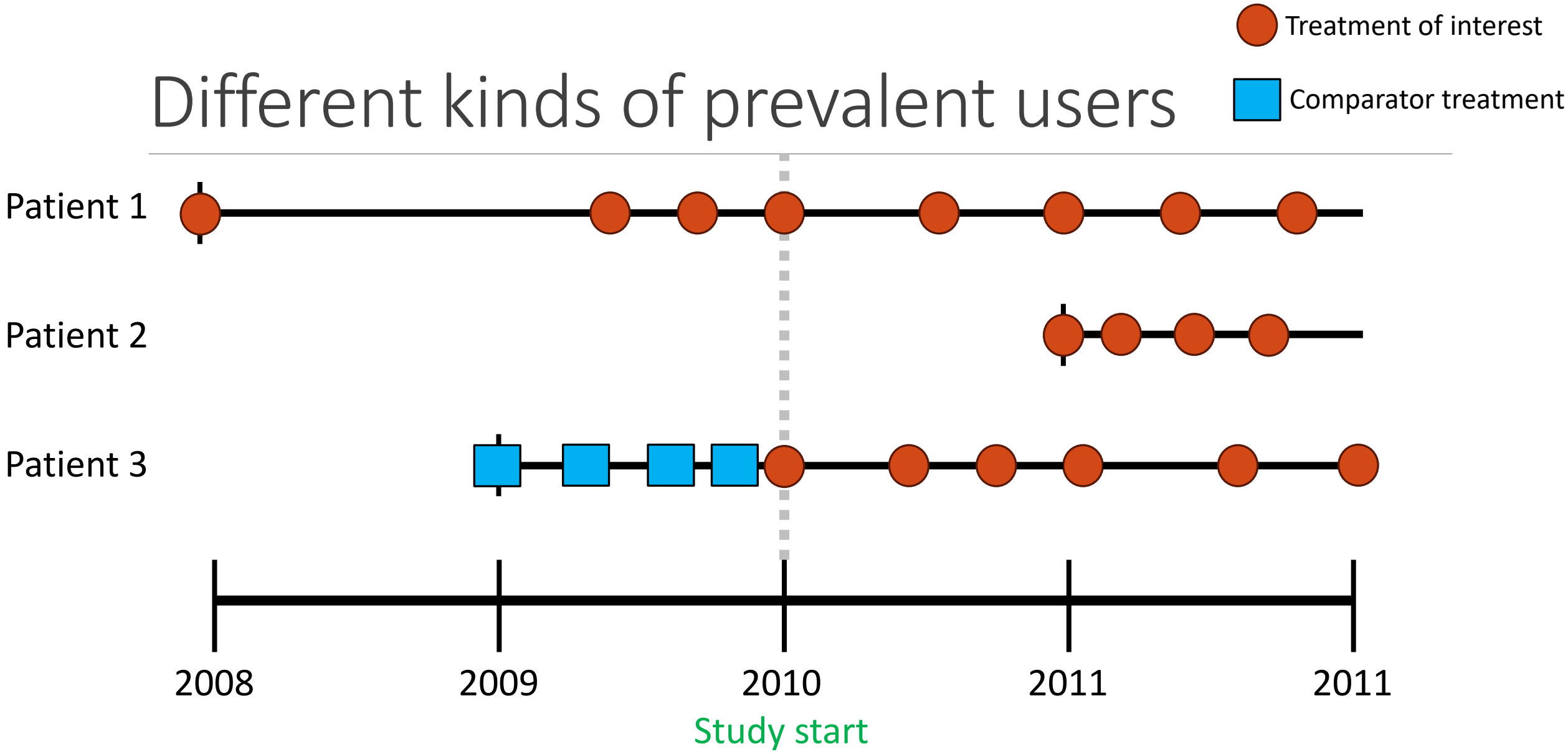
What are prevalent users?

Prevalent users are people who, when we could start follow-up, are already taking or may have been taking the treatment of interest or comparator

For example…

- Sally switches to a new private health insurance provider one year after starting a new type of birth control
- Sharif obtains public health insurance coverage for the first time at age 65 when he has been taking statins since a myocardial infarction at the age of 50
- Samar moves to a new country halfway through receiving chemotherapy for colon cancer
- Neda was enrolled in our prospective study of the benefits of different types of electric toothbrushes years after starting to use an electric toothbrush

Different kinds of prevalent users



Problem #1: Time-varying treatment effects

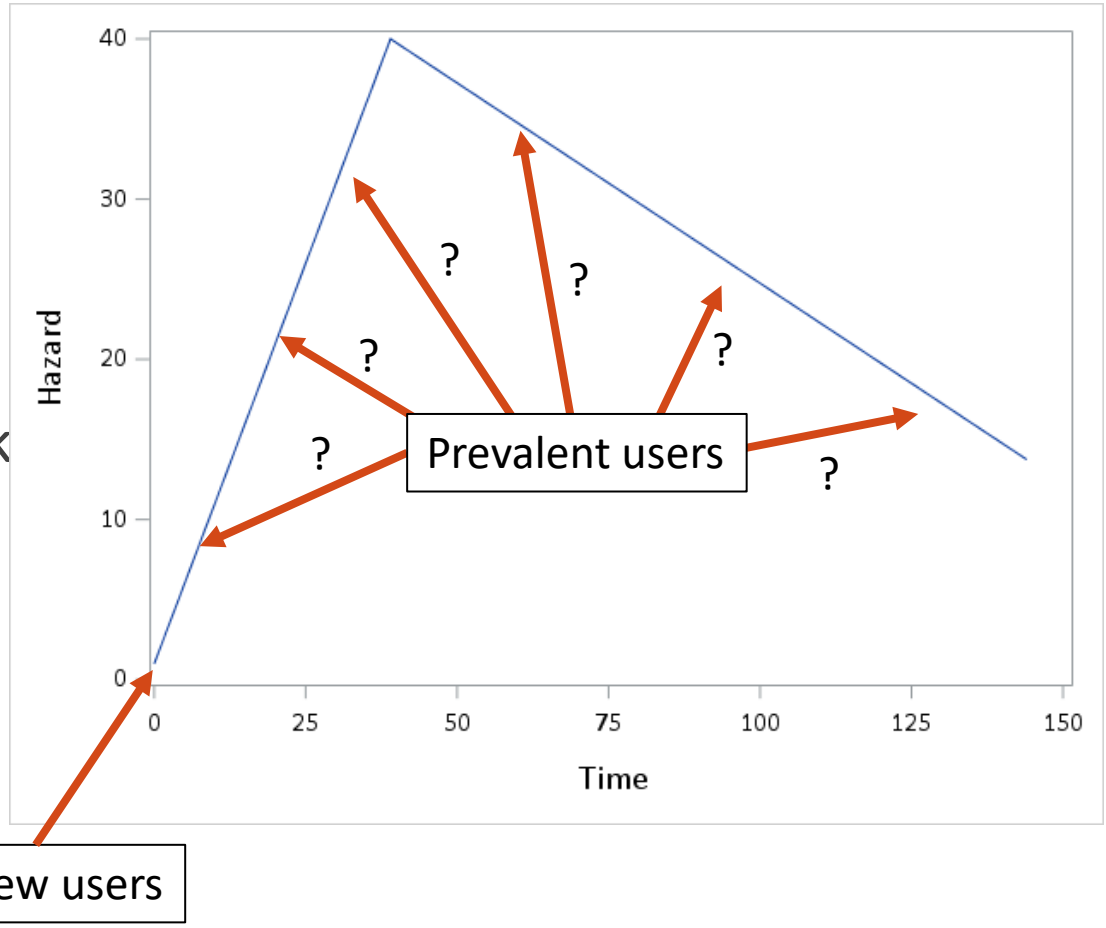
What if the risk of the outcome changes over the course of treatment?

- Anaphylaxis
- Rhabdomyolysis
- Adverse events from chemotherapy

Prevalent users will have a different risk at the start of follow-up

Improperly allocating their follow-up can bias treatment effect estimates

Even worse for non-point treatments



Problem #2: Prevalent user bias and filtering

Prevalent users are not a random sample of new users

Many characteristics are associated with remaining on treatment, including:

- Age
- Healthcare utilization
- Health literacy
- Number of other medications

Prevalent users and new users will have different distributions of these variables

Sometimes called “healthy adherer bias”

The oldest solution: restriction/washouts

Popularized by Olli Miettinnen

What if we only included true/“incident” new users of the treatment of interest and the comparator?

We will partially control for confounding by indication

Everyone will start follow-up from time 0, meaning they all start on the same point of the hazard function

There won’t be any selection processes that could generate prevalent user bias

But restriction is not always a good fit

When studying new treatments, restriction to new users:

- Reduces sample size
- Excludes a clinically relevant population (switchers)
- Prevents any study of switching effects

For a long time, this was generally accepted as a necessary price to pay

What if we could exclude prevalent users but still avoid some of these issues?

What are prevalent new users and how can we identify them?

What are prevalent new users?

Prevalent new users are individuals who receive the treatment of interest after known **new use** of the comparator treatment

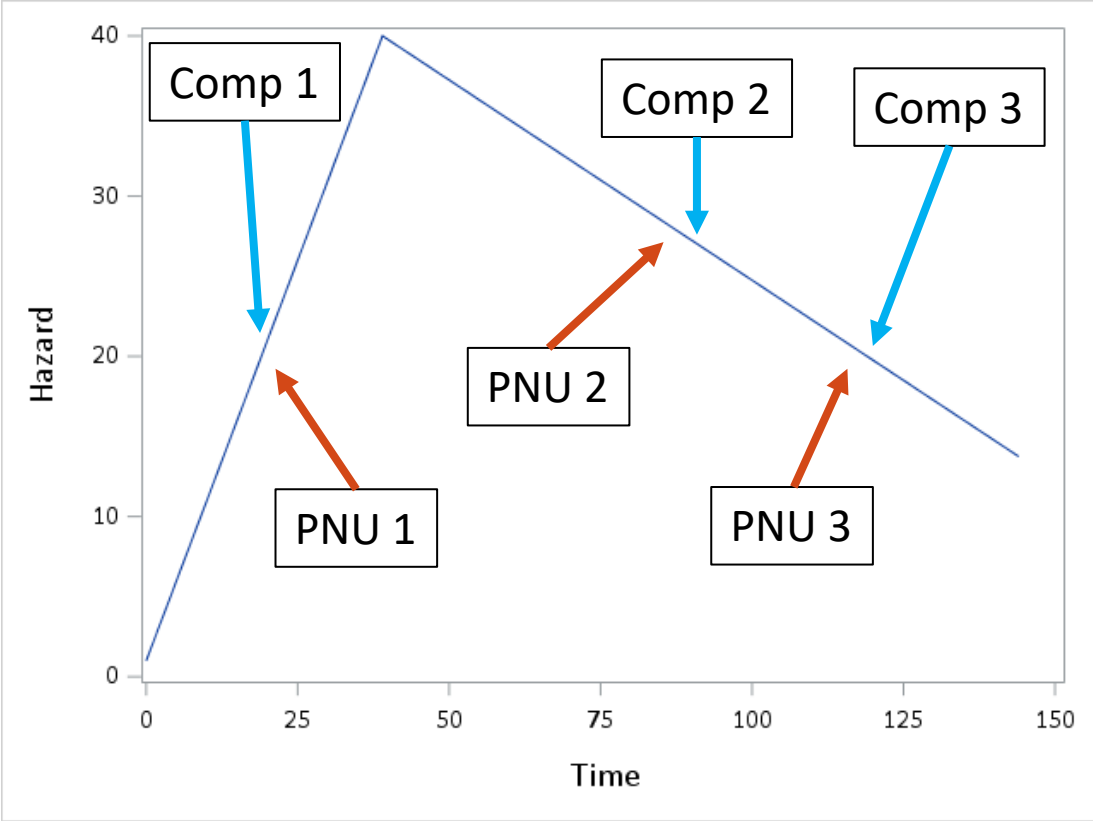
For example…

- Patricia started estrogen-only hormone replacement therapy two years ago and is switching to combination estrogen-progesterone
- Pablo was diagnosed with atrial fibrillation four months ago and started warfarin therapy, but is now switching to dabigatran due to unstable INR values
- Phyo started lisinopril for hypertension, but after two weeks reports a chronic cough and is switched to valsartan

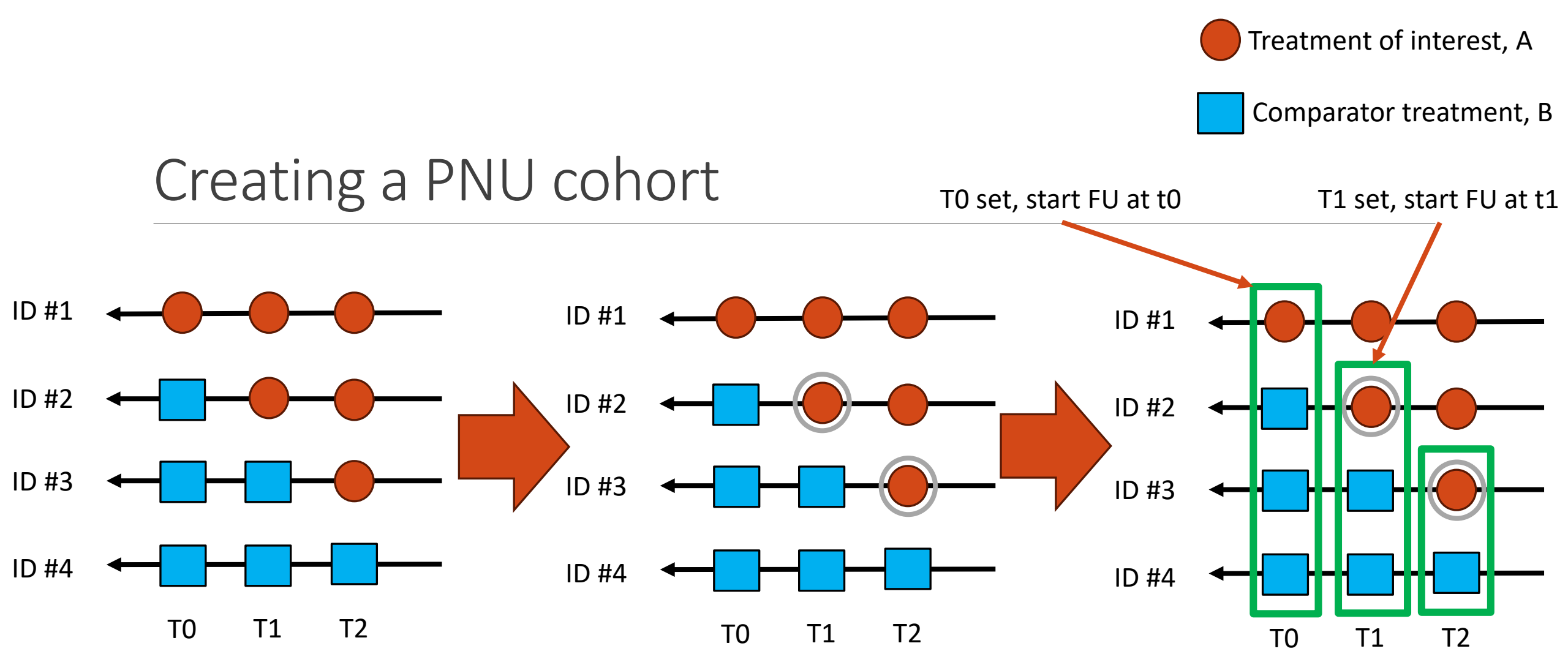
What does the “new user” part add?

Prevalent new users have known **index dates** for the comparator, so:

- We can (kind of) place them on the hazard function
- We can compare them with other **new users** of the comparator who took the comparator when the prevalent new users started the treatment of interest



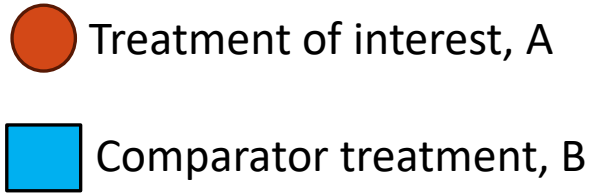
Creating a PNU cohort



Identify incident new users of the treatment of interest (A) or comparator (B)

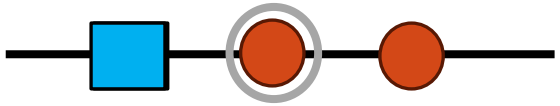
Follow incident new users of B and identify those who later initiate A (prevalent new users)

Create exposure sets of prevalent new users of A and B continuers



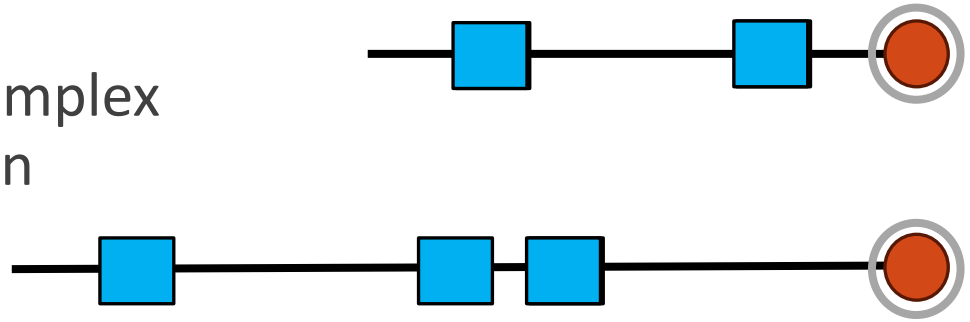
Types of prevalent new users

Direct switchers: people who initiate treatment B and then start A, with no break in between



Delayed switchers: people who initiate treatment B, stop for a period of time, and after a "holiday" switch to A

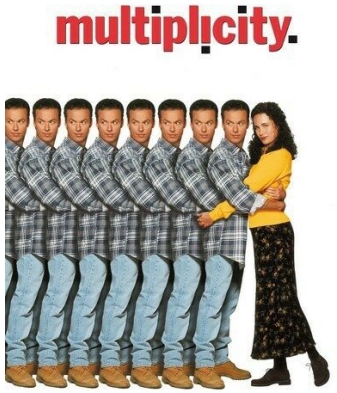
Complicated switchers: people with more complex histories (e.g., restarting B, stopping, and then restarting this time with A)



Potential pain points

While everyone contributes at most 1 observation to "treatment A" they may create multiple "comparator/continuer" observations

- All prevalent new users will contribute at least 1 observation to both groups



Defining exposure sets and distinguishing PNU types can be tricky

- Prescription fills?
- Calendar time?
- Calendar time + RX fill?
- Complete exposure history-based?

Exclusion criteria should be re-assessed within each exposure set

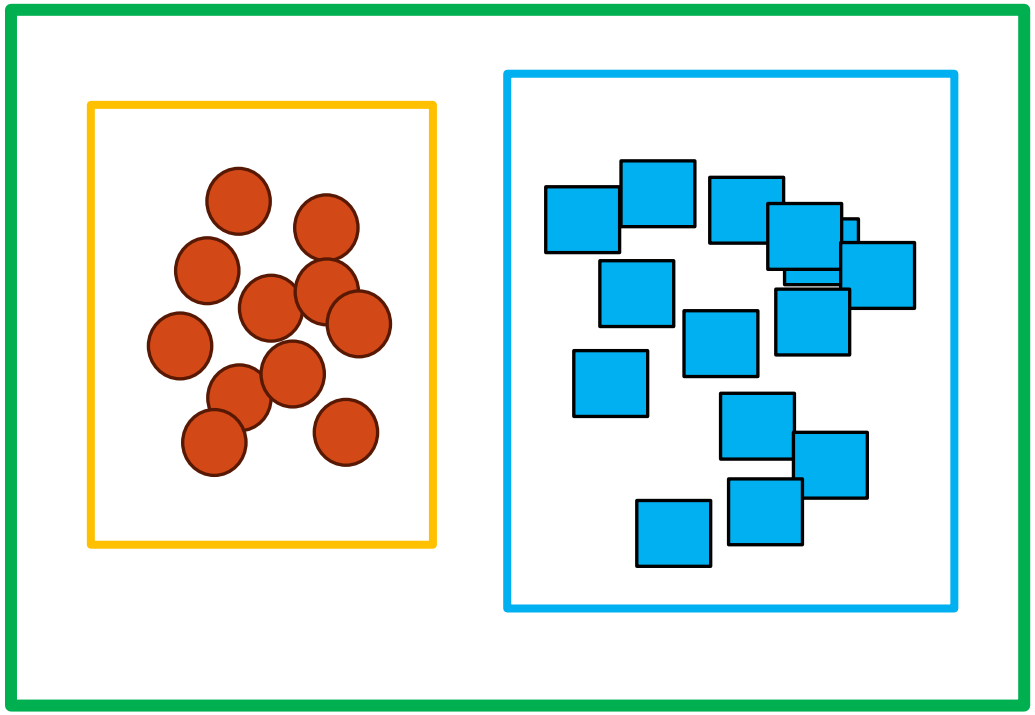
Avoid using future information

What does the PNU design estimate?

First, what can the active comparator new user design estimate?

Restriction to true/ “incident” new users means we can estimate:

- The effect of **initiating** **treatment A** vs **initiating** **treatment B** among people who initiate **A?**
- The effect of **initiating** **treatment A** vs **initiating** **treatment B** among people who initiate **B?**
- The effect of **initiating** **treatment A** vs **initiating** **treatment B** among people who initiate **A or B?**



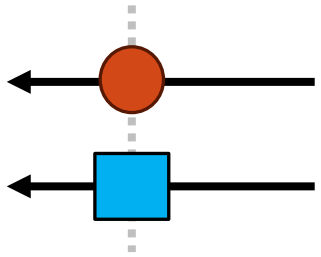
What changes with prevalent new users?

We are estimating the effect of **initiating** A vs **taking** B among initiators of A

Because we make sure exposure to B is equivalent within exposure sets…

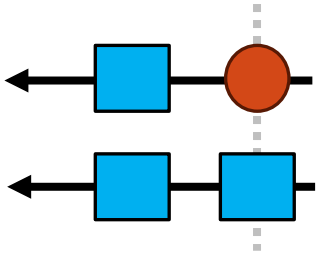
- **Incident new users** of A are compared to B **incident new users**
- **Direct switchers** to A are compared to B **continuers**
- **Delayed switchers** to A are compared to B **restarters**
- Complicated switchers to A are compared to people with equivalent histories taking B

Incident users of A



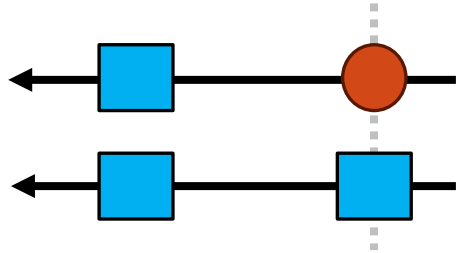
Incident users of B

Direct switchers to A



B continuer

Delayed switchers to A



B restarter

We can’t easily swap treatment and comparator

If we set up our active comparator study to estimate the effect of A vs B, it’s trivial to flip treatment and comparator

- For ratio measures: divide 1 by your estimate
- For difference measures: multiply by negative 1

Switching treatment and comparator in a PNU study requires the creation of a new cohort

- Because we are comparing **initiators** with **takers** rather than **initiators** with **initiators**
- Or, prevalent new users of B are a completely separate target population from prevalent new users of A

The quantity is very population-specific

Prevalent new users of A are still entering at different points in the hazard function

- Even if we are comparing them with the correct people taking B

Different A initiator populations may have different exposure history distributions

When treatment effects vary over time, two groups of A initiators with identical “baseline” characteristics may experience different effects

What are some analytic strategies for PNU design studies?

Time-conditional propensity score matching

1. Identify all prevalent new users of A
2. Take random samples of the B observations (e.g., 10 per prevalent new user) from the same exposure set
3. Fit a multivariable conditional logistic regression predicting A vs B, conditioning on match group
4. Obtain propensity scores for the whole population of B observations using the regression parameters
5. Match prevalent new users of A to takers of B based on both exposure set and propensity score

More on matching

With replacement vs without replacement?

If without replacement, **essential** not to avoid future info

- Find matches for people earlier in calendar time first
- Do not start by finding matching for those with the most follow-up

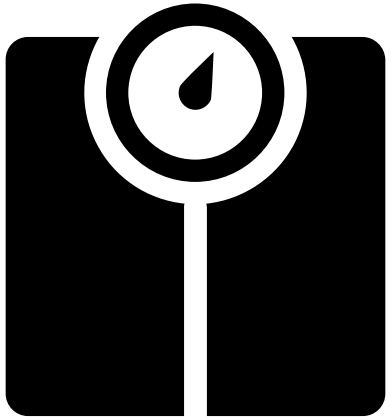
Can make it tricky to handle selection bias due to censoring

- Can only rely on censoring matched pairs when estimating HRs
- Otherwise will need weights

Very efficient if you do not need to bootstrap for CIs

Time-stratified odds/SMR weighting

1. Identify all of the exposure sets with prevalent new users
2. Fit an exposure-set stratified multivariable logistic regression model predicting A vs B
3. Use this propensity score to assign those taking B weights equal to their covariate-conditional odds of taking A
4. Assign the prevalent new users of A weights of 1
5. Analyze the weighted population



More on weighting

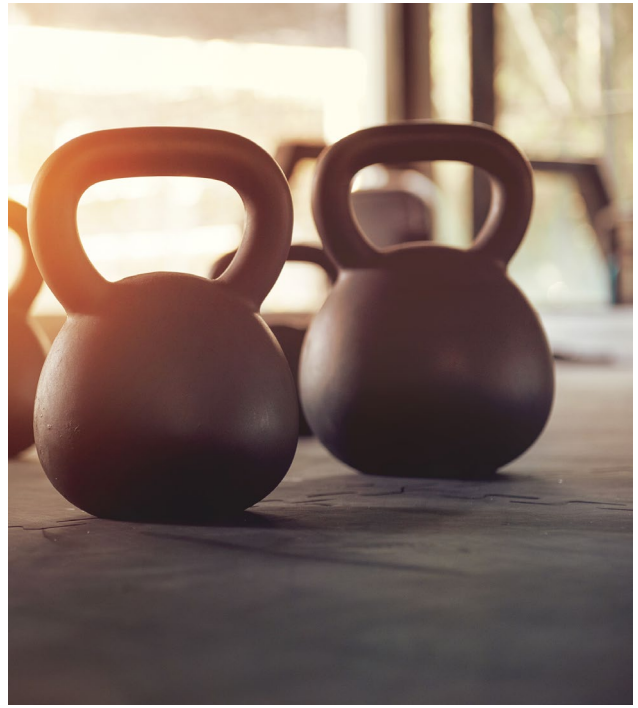
Uses more information than matching

Small exposure sets may make stratification difficult, requiring either pooled models or coarser strata

May encounter extreme weights in some cases

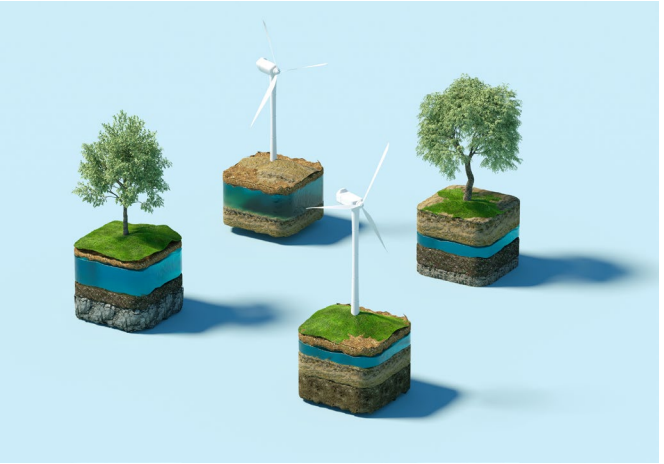
- While other types of weights (e.g., overlap weights) can be used, very difficult to articulate what they estimate

Typically require bootstrapping to obtain confidence intervals, meaning they may take longer than matching



Time-stratified outcome modeling

1. Identify all of the exposure sets with prevalent new users of A
2. Fit an exposure-set stratified model predicting the probability of the outcome among patients taking B
3. Use this model to predict the probability of the outcome among the prevalent new users of A
4. Compare original outcomes of the prevalent new users of A and outcomes from the model built in the patients taking B



More on outcome modeling

Often very efficient vs other methods

Optional to fit models in those taking the treatment of interest

- Very beneficial if there are few prevalent new users

Can be combined with weighting to create doubly robust methods

More complex diagnostics than other methods

Also requires bootstrapping to obtain confidence intervals

Limitations of all methods

All assume you can predict when patients will initiate A vs initiate, continue on, or restart B

Predicting why people have switched using commonly available data is difficult

Rely on correctly fitting prediction models

Errors in identifying exposure sets can lead to biased treatment effect estimates estimates

Can conflate “new use” and “switching” effects

How is the PNU design evolving?

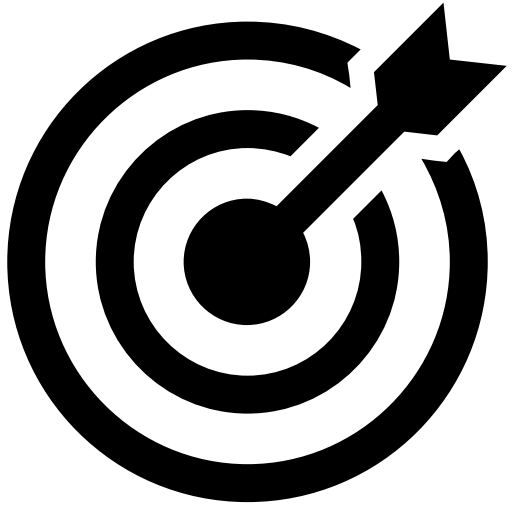
Integration with target trial emulation

What target trial is being emulated?

1. Enroll patients who are starting A, regardless of past exposure to B
2. Randomize them to either start A or take B instead
3. Follow each group for the outcomes

Is that trial an informative one?

- It's informative enough to do in oral anticoagulant trials!



Applications to therapeutic augmentation

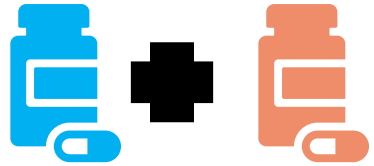
What if, instead of the treatment of interest **replacing** the comparator, the treatment of interest is **added to** the comparator?

Effect shifts from "the effect of initiating A vs taking B in those initiating A" to "the effect of **adding** A vs continuing with B alone in those adding A"

Particularly helpful when everyone **must** initiate B alone due to formulary or payer restrictions

Very sensitive to confounding by indication

VS



Applications to discontinuation

What if the treatment of interest was stopping treatment with the comparator?

We would estimate the effect of stopping treatment with B in the population of patients who stop treatment with B

We would still need to identify and predict **when** people will stop treatment, which is very challenging

Some limited success studying statin discontinuation, though frailty is a major residual confounder

Incorporating as-treated follow-up

Most early applications involved short-term outcomes

What about studying 1-year, 5-year, 20-year risks?

We might be interested in two effects:

- The effect of initiating A vs taking B
- The effect of initiating **and continuing** A vs taking **and continuing to take** B

Answering the latter requires us to censor observations

- Those who initiate A at the time they switch back to B or stop taking A
- Those who take B if they eventually initiate A or stop taking B

This censoring can lead to **selection bias** that must be addressed via some analytic method

A few references

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Thank you!

Please feel free to contact me at mawcpharmdphd@gmail.com with questions!