# Session 2.3

Target trial situations

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# Grace periods

When treatment initiation isn't immediate, a **grace period** can be used:

- A window of time after time zero during which treatment initiation is allowed
  - If untreated, clones contributed to both the treated and the untreated arms
  - If treated, clones censored in the untreated arm at treatment initiation
  - If untreated at the end of the grace period, clones censored in the treated arm

# Grace periods

This is what we were missing in our week-by-week analysis.

- When we defined people as exposed or unexposed at the beginning of the week, we should have actually had them cloned until they reached the end of the week, were exposed, or had an event, so that they contributed to both arms until they were classified as exposed or unexposed.

We can do this with larger timespans as well!

# Example: trimester-specific exposures

Let's imagine we want to study treatment vs. no treatment in trimester 1 or 2 of pregnancy.

- In our target trial, people would be randomized at 6 weeks and must start treatment by week 14
- Or they could join the second semester trial at week 14, in which case they must start treatment by week 20 (because we're still thinking about pregnancy loss)

# Time to start treatment

We could also specify a time to start treatment that happens after randomization.

- For example, we could randomize people at 6 weeks with several treatment arms:
  - start treatment *at* week 7
  - start treatment *at* week 8
  - start treatment *at* week 9
  - and so on

We would then need to clone people at randomization into each of these arms, and censor them if they start treatment do early, or don't start it at the assigned week

# Time to start treatment - clinical

Similarly, we could assign people to start treatment at the time of a clinical event.

This isn't a pretedetermined time, but it is still a well-defined intervention.

- When blood pressure reaches a certain level
- When a glucose test reaches a certain level
- When a certain number of symptoms are reported

If people never have that clinical event, they would never start treatment – that's ok!

# Time to start treatment - threshold

We could compare different strategies to find the optimal level at which to start treatment:

- ≥160/110
- ≥155/105
- ≥150/100
- ≥145/95
- ≥140/90

# Joint treatment and monitoring

- Censor people when they don't follow the treatment strategy
- Also when they don't get monitored often enough (or whatever the strategy is)

This can help ensure you have the data you need

Caniglia et al. (2019)

# For all of these types of questions we can use the clone-censor-weight approach

Avalos, Lyndsay A., Romain S. Neugebauer, Nerissa Nance, Sylvia E. Badon, T. Craig Cheetham, Thomas R. Easterling, Kristi Reynolds, et al. 2023. “Maternal and Neonatal Outcomes Associated with Treating Hypertension in Pregnancy at Different Thresholds.” *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 43 (5): 381–90. https://doi.org/10.1002/phar.2778.

Caniglia, Ellen C., James M. Robins, Lauren E. Cain, Caroline Sabin, Roger Logan, Sophie Abgrall, Michael J. Mugavero, et al. 2019. “Emulating a Trial of Joint Dynamic Strategies: An Application to Monitoring and Treatment of HIV-positive Individuals.” *Statistics in Medicine* 38 (13): 2428–46. https://doi.org/10.1002/sim.8120.