



A Structural Description of Biases That Generate Immortal Time

Hernán MA et al. *Epidemiology*. 2025

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What is immortal time?

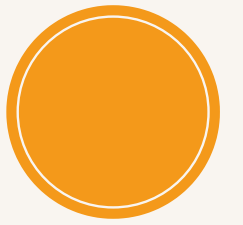
- Event -free time
- A period in survival analysis where individuals cannot experience the event of interest by definition
- If the event is death, the person is “immortal”.
- Not truly immortal

Why is it important?

- Survival analyses with immortal time yield biased effect estimates.



Two situations that produce immortal time



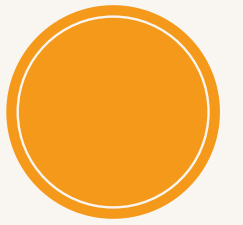
Due to **selection**

When an eligibility criteria is (incorrectly) applied after the start of follow-up.



Due to **misclassification**

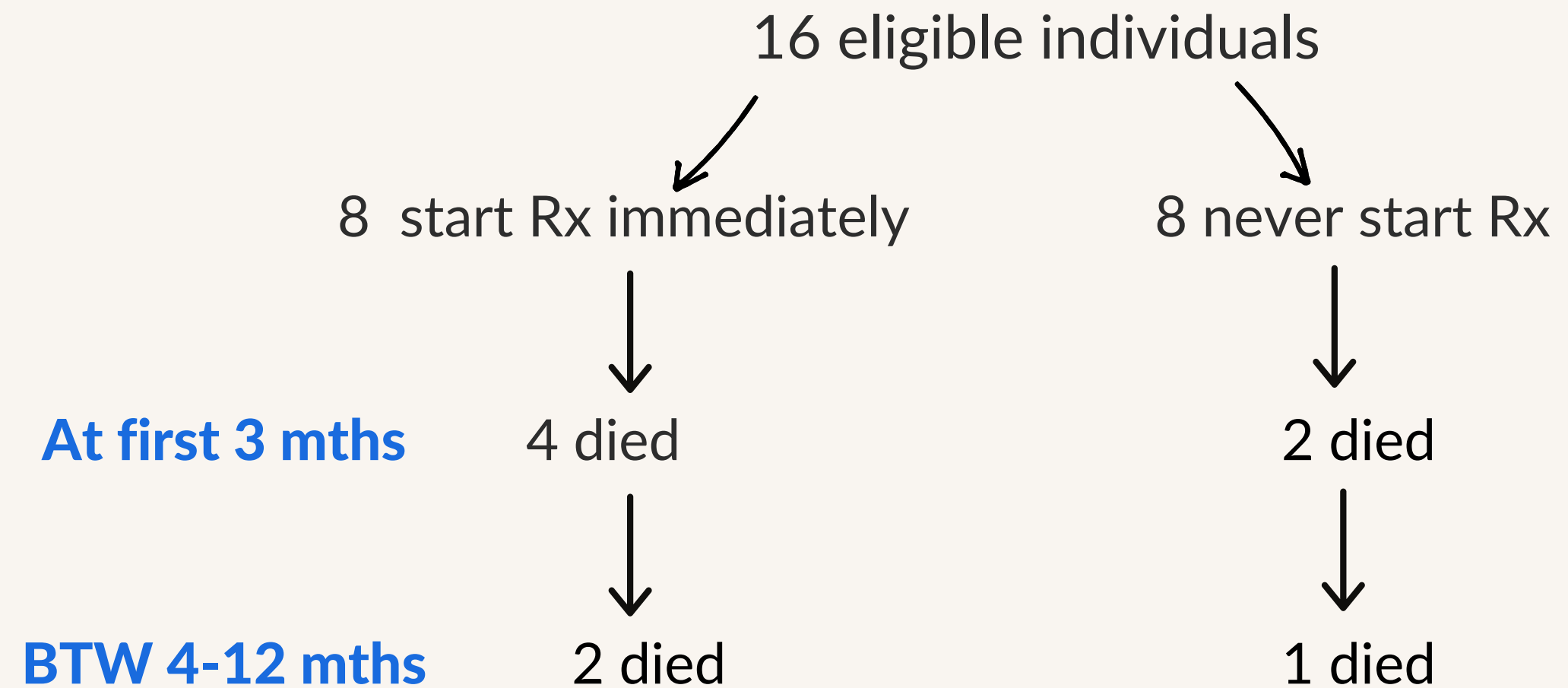
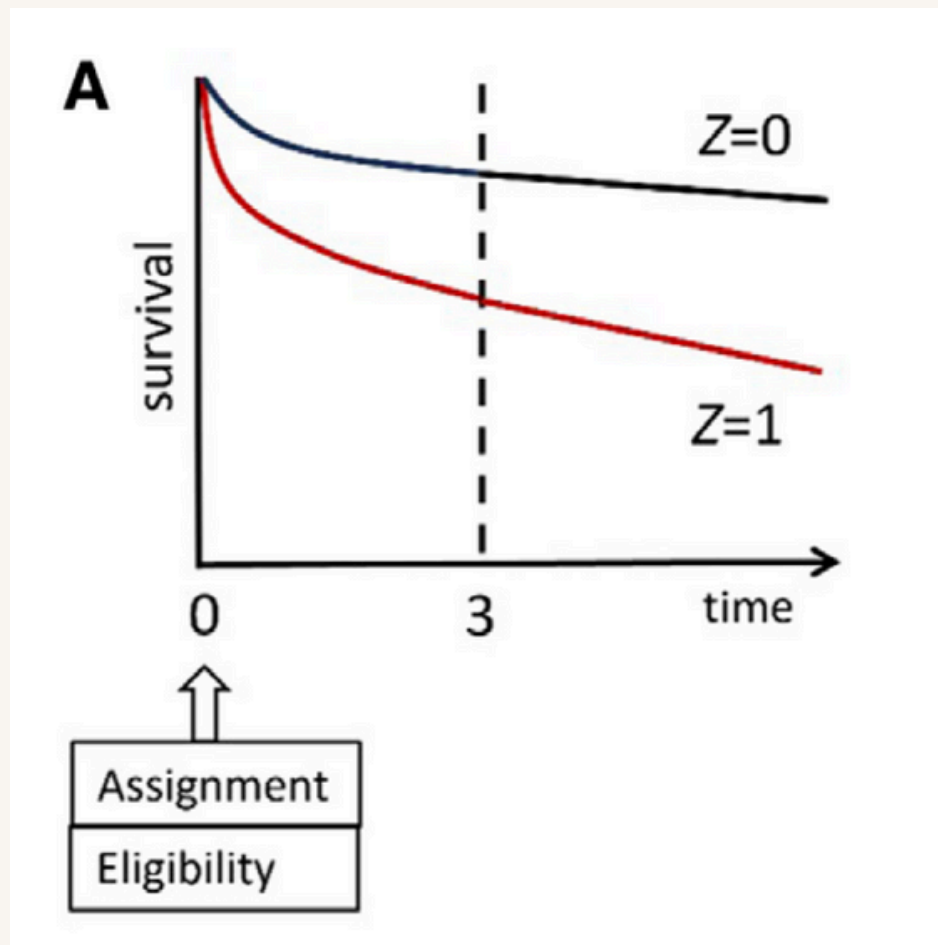
When misclassifying individuals into a treatment group that differs from the one they should have been assigned to.



Immortal time due to Selection

“Post-assignment Eligibility”

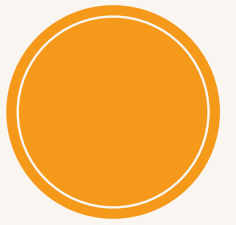
Randomized trial



RCT: patients are assigned Rx only after eligibility has been met.

Immortal time due to Selection

“Post-assignment Eligibility”



Large observational cohort:
emulated target trial

individuals who met trial’s eligibility
criteria

started Rx at time zero

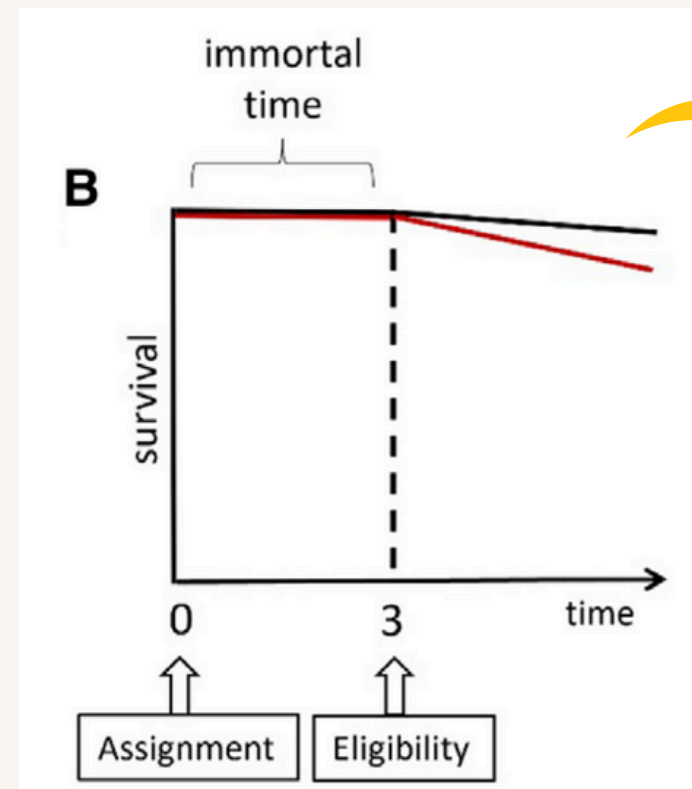
no Rx at time zero

At first 3 mths

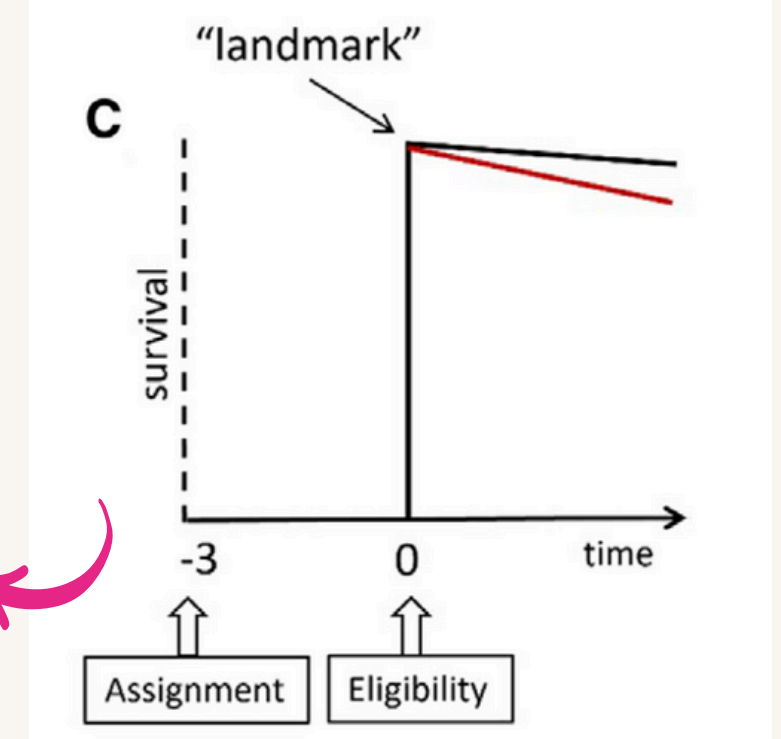
Record outcomes
at 12 mths

Comparing the risks

Restrict the analysis to
individuals who have completed 3 mths FU



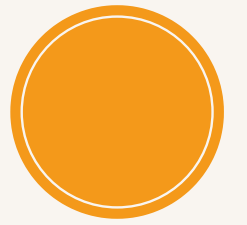
When immortal time is included in
calculation: “Immortal time bias”.
Enroll individuals who have started Rx
before and analysis start at the time of Rx
initiation



: “Prevalent user bias”
Not include immortal time in calculation
Differential depletion of susceptibles

Immortal time due to Selection

“Post-assignment Eligibility”

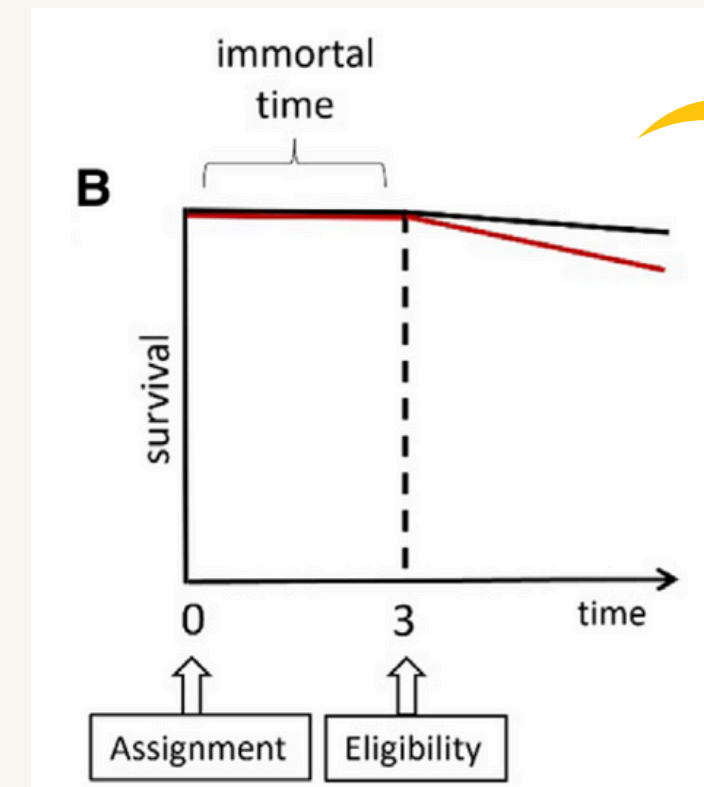


Large observational cohort:
emulated target trial

What to do

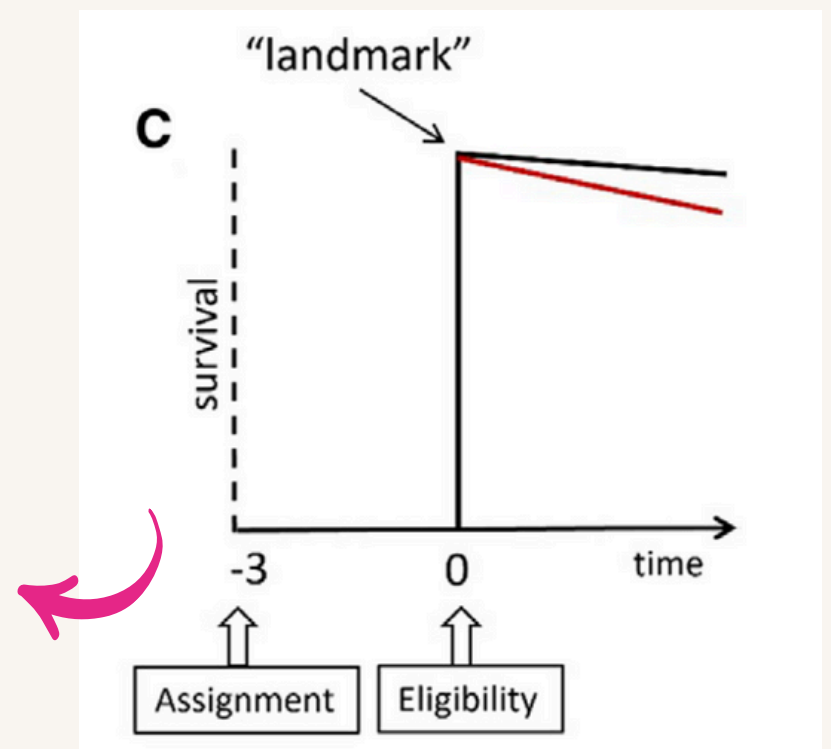
- All eligibility criteria are defined at time zero so no selection occurs after treatment assignment.
- Explicitly emulating target trial based on data for all eligible individuals from the time of treatment assignment

Restrict the analysis to individuals who have completed 3 mths FU



When immortal time is included in calculation: “Immortal time bias”.
Enroll individuals who have started Rx before and analysis start at the time of Rx initiation

: “Prevalent user bias”
Differential depletion of susceptibles

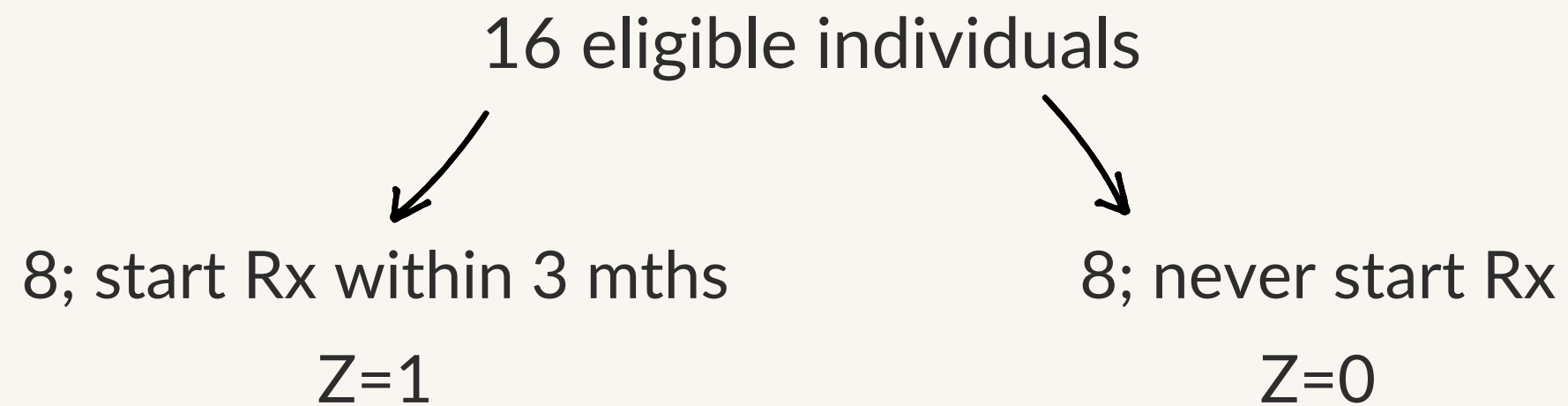


Immortal time due to Misclassification

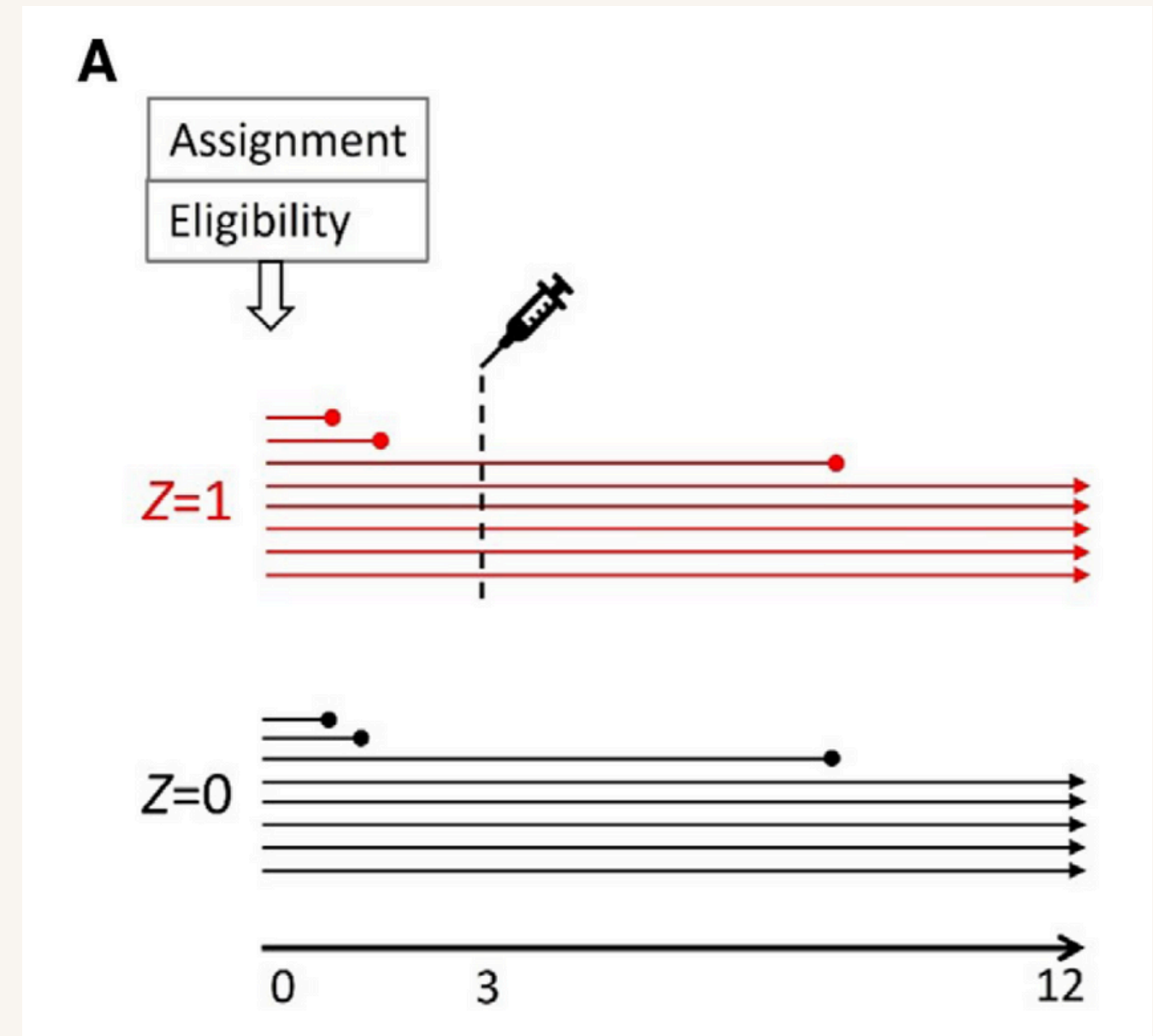


When some strategies under study cannot be distinguished at time zero

New randomized trial with full adherence

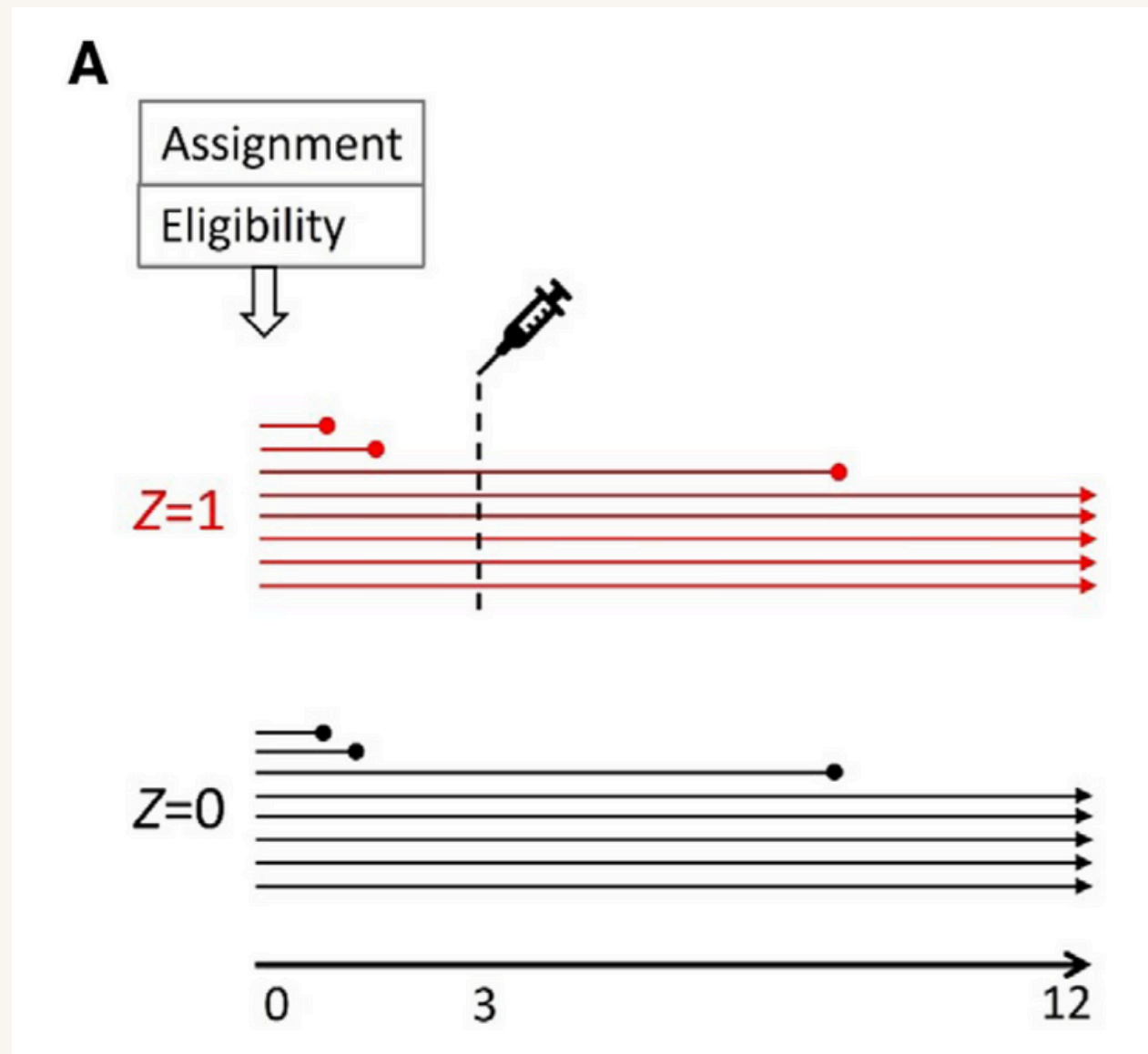


Z=1 has a 3 month 'grace period' within which treatment should be started.

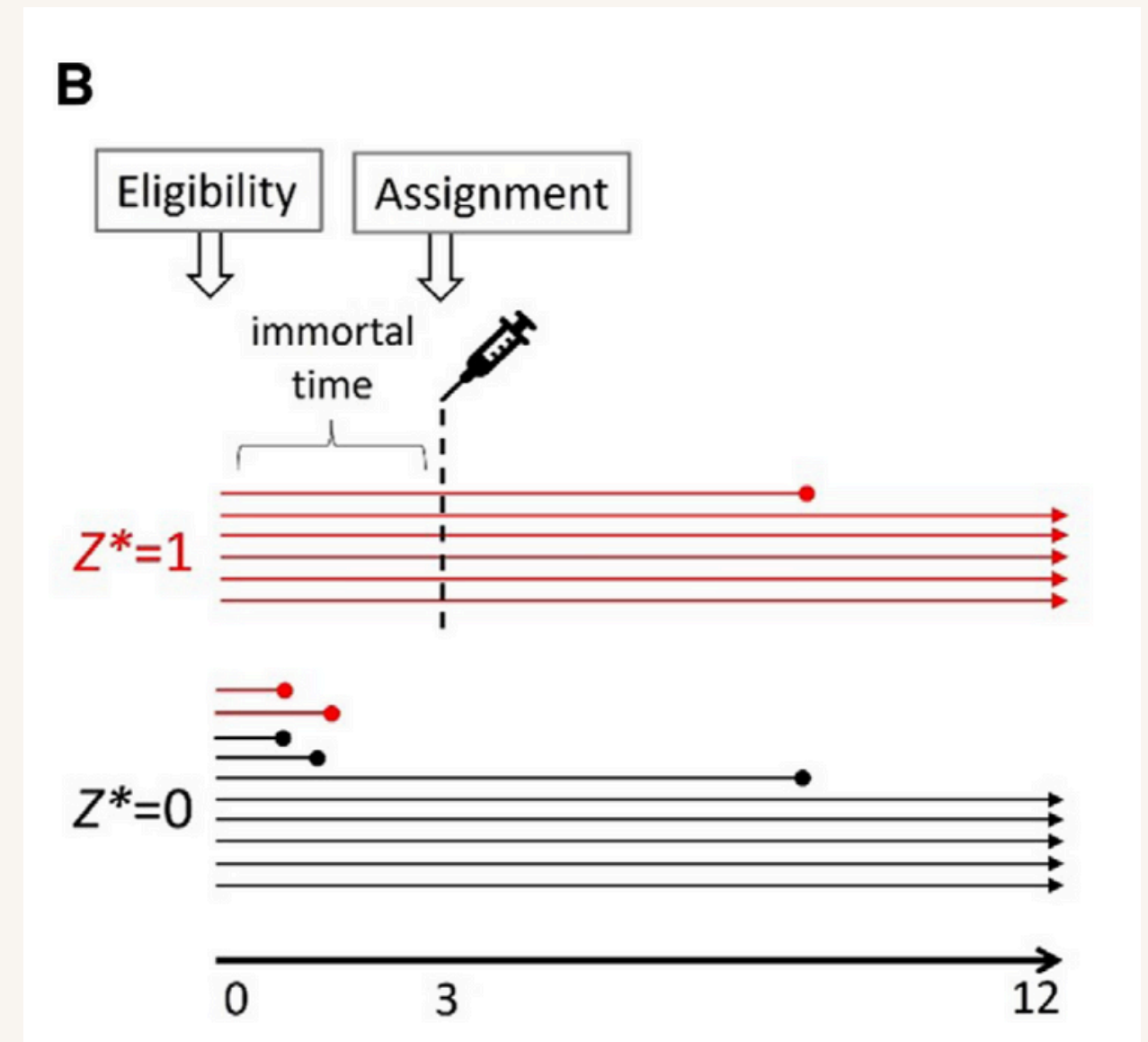


Immortal time due to Misclassification

Observational study include information on treatment Am and outcome Ym overtime



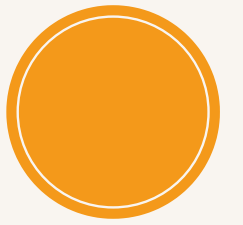
The patients who died during grace period were classified to $Z^*=0$.



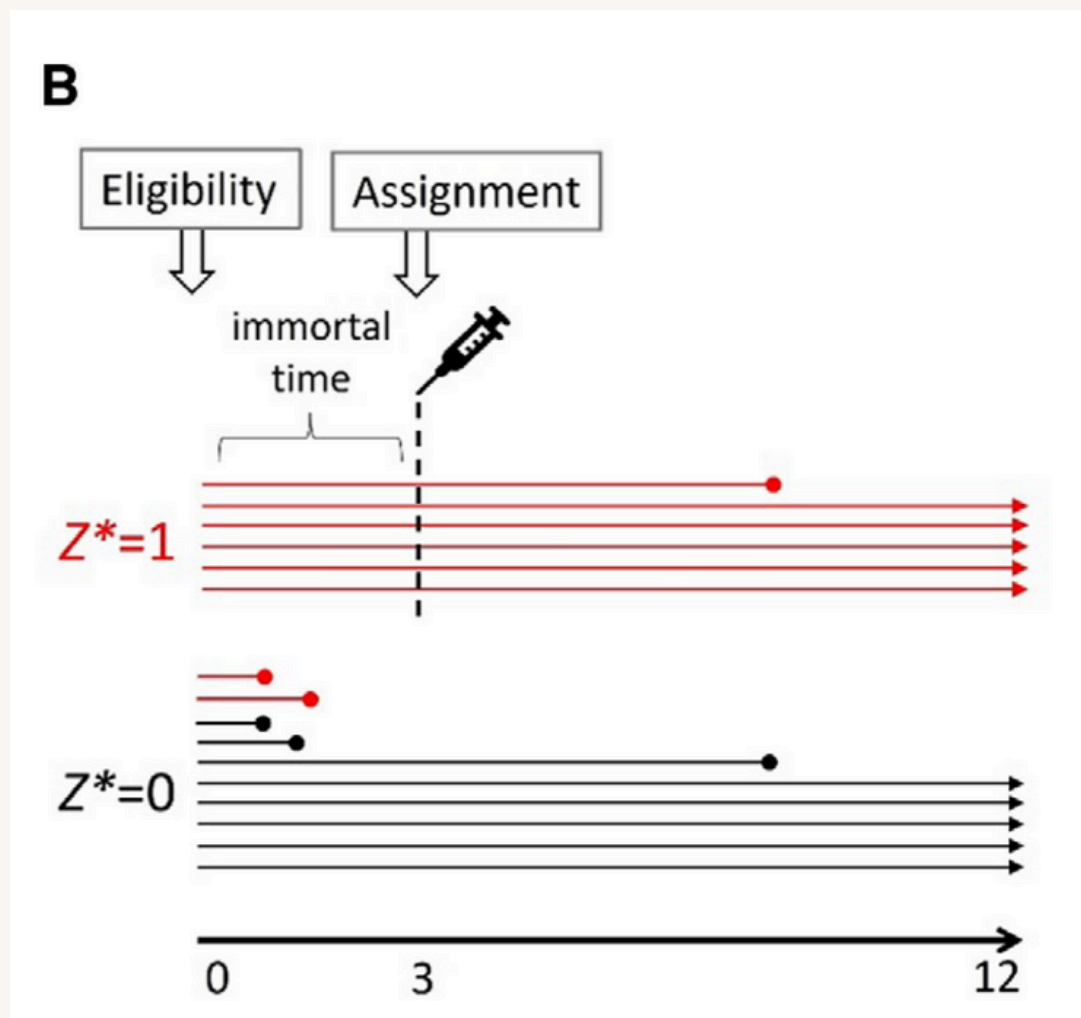
What if, assign to $Z^*=1$ if the individual received treatment within 3 months (i.e., $A_m=1$ for m (month)=0,1, or 2)

“bias in assignment of subjects”

Immortal time due to Misclassification



This form of misclassification of assignment is relevant for any strategies that are not distinguishable at time zero (e.g., strategies with grace or waiting periods, strategies of different durations of treatment).



What to do

Several approaches to prevent the emergence of this type of immortal time.

1. Changing the causal question: strategies that are distinguishable at time zero
2. Cloning followed by censoring
3. g-formula

Cloning followed by censoring



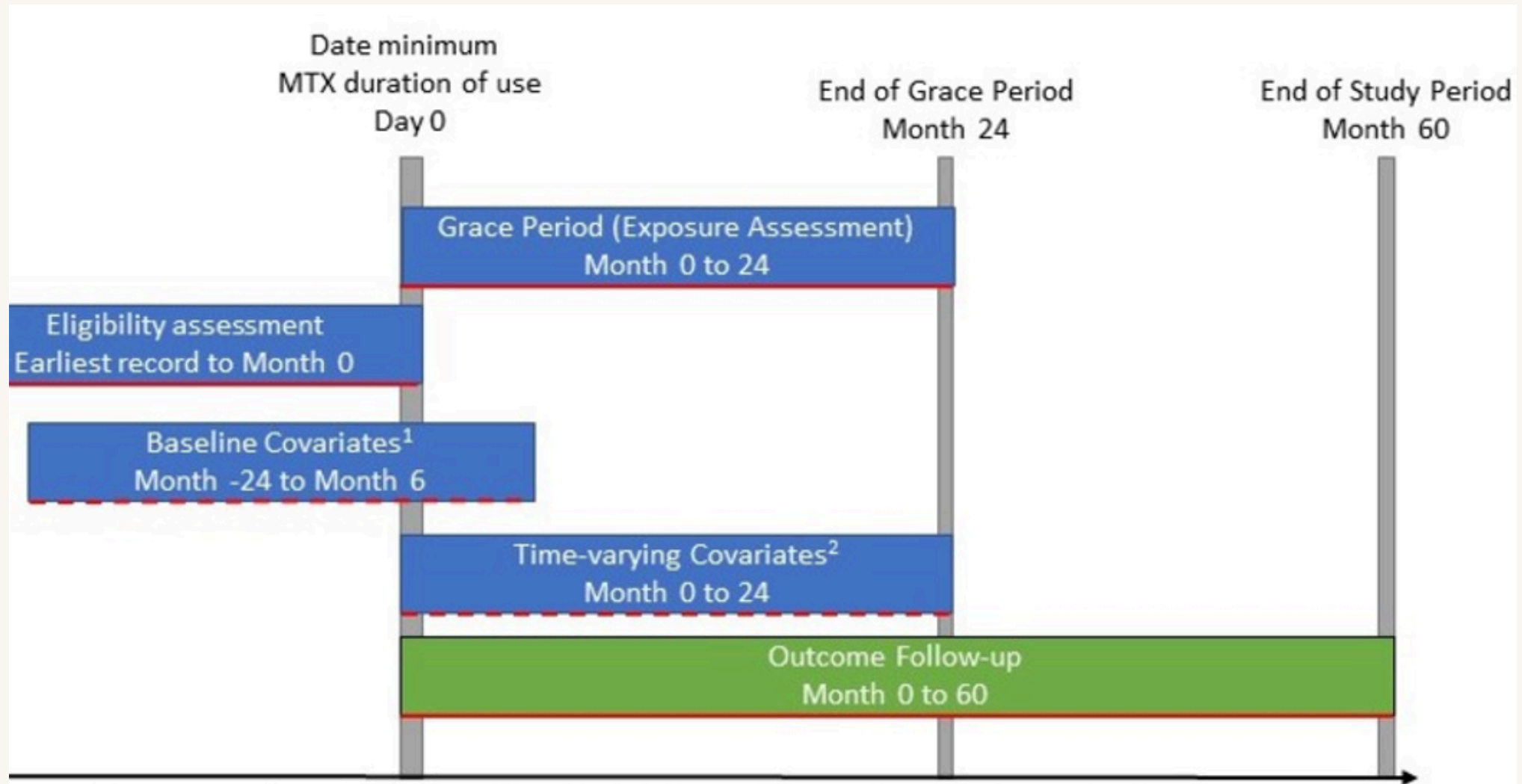
At time zero, some individuals have data compatible with more than one strategy.

We can create as many “clones” of each individual as treatment strategies the individual’s data are compatible with at baseline.

Each clone is assigned to a single strategy and censored if and when the clone deviates from it (i.e., stops having data compatible with it).

Adjustment via inverse-probability weighting is required.

Computation of the variance for cloning estimators is accounted.



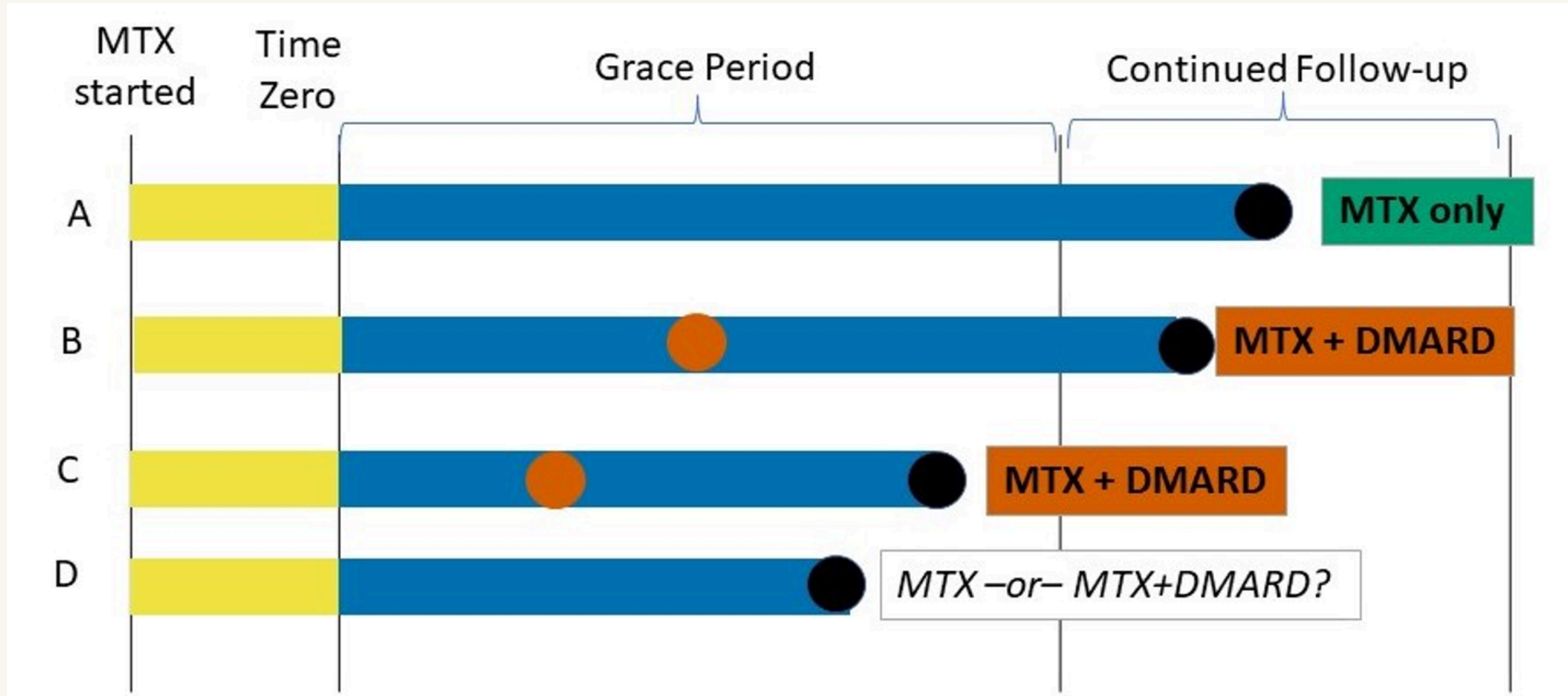
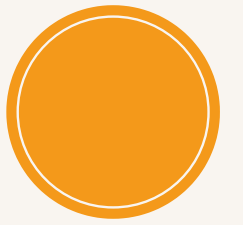
Data sources: pharmacy, diagnosis codes, death, healthcare utilization, laboratory tests

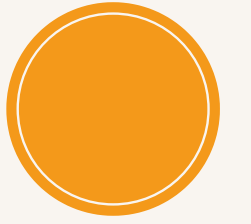
Legend:

- Outcome, treatment status, enrollment and comorbidities were completely observed and not imputed.
- - - Some missing baseline and time-varying covariates were incompletely and irregularly observed. For clinical baseline covariates that can be repeatedly measured, the one closest to time zero with prioritization of values measured before time zero over those measured after . If still missing, data was imputed. For time-varying clinical covariates, we performed last-observation carried forward.

Note that missing data from possible out-of-system diagnosis or healthcare visits is possible for all variables.

Misclassification





Thank you