Journal Club
Target Trial Emulation

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Review

Emulating a Randomised Controlled Trial With Observational Data: An Introduction to the Target Trial Framework

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REVIEW

Target Trial Emulation to Improve Causal Inference from Observational Data: What, Why, and How?

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Target trial emulation

Framework for designing and analyzing observational studies that aim to estimate the causal effect of intervention

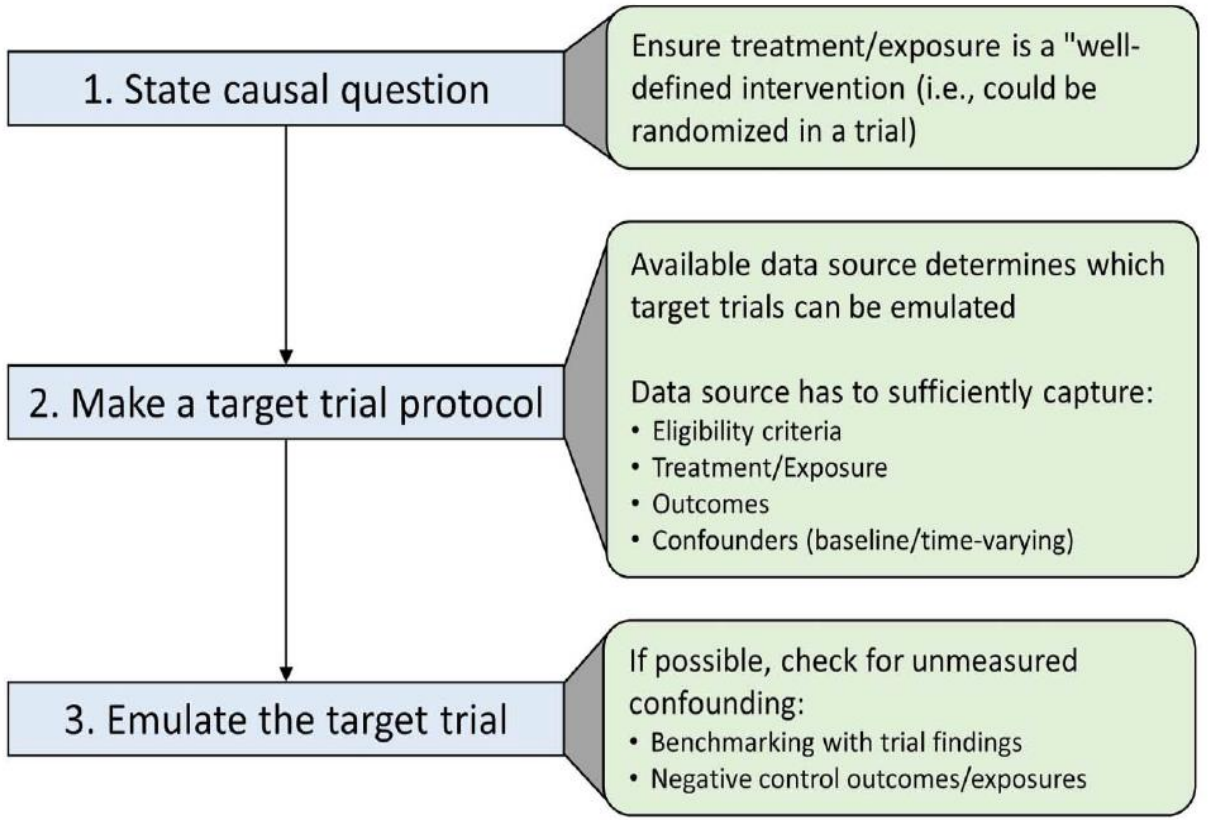


Figure 2. Workflow for conducting observational studies in the target trial emulation framework.

Identification principles of causal inference

- Exchangeability
  - Expectation that the outcome in treatment arm 1 would be the same as the comparator if the treatment assignments were reversed.
  - “Conditional exchangeability”
- Consistency
  - No variation in the treatment in each arm.
- Positivity
  - Each patient has the chance to undergo either treatment.

Key element of RCTs with observational equivalents in target trials

- Eligibility criteria
- Treatment assignment and randomization
- Specification of time zero
- Outcomes
- Follow-up
- Causal contrast
- Statistical analyses

Eligibility criteria

- Patient's eligibility for study inclusion need to be met before baseline.
- Number of encounters with the health care system before baseline may be part of the inclusion criteria.

  >>>> engage more regular follow up
- Common pitfall is to select eligible individuals based on postbaseline information collected during follow-up.
- Key baseline variables to assess eligibility and fulfill conditional exchangeability may be missing in observational study. >> depend on what data is available.

Treatment assignment
(randomization)

- Balance baseline confounding to ensure exchangeability and positivity identification principle are satisfied.

- Mimicking the concept of “treatment assignment”
  - Using first treatment initiated, i.e., new user
  - Randomization can be emulated with adjustment for baseline confounding

- *** Standard care arm, caution needs to be taken to define nonuser and time zero or the start of follow-up.

Treatment assignment

(randomization)

- Propensity score method used to reduce the systematic difference in baseline characteristics.

- Only for measured and known confounders can be provided the adjustment.

(Difference from randomization)

- Sensitivity analysis to evaluate the robustness of findings on unobserved confounder.

Time zero

- In an RCT : The time when
  - Eligibility criteria for inclusion is met.
  - Treatment is assigned
  - Follow up begins

- The timing of eligibility and initiated of prescribed or dispenced match.

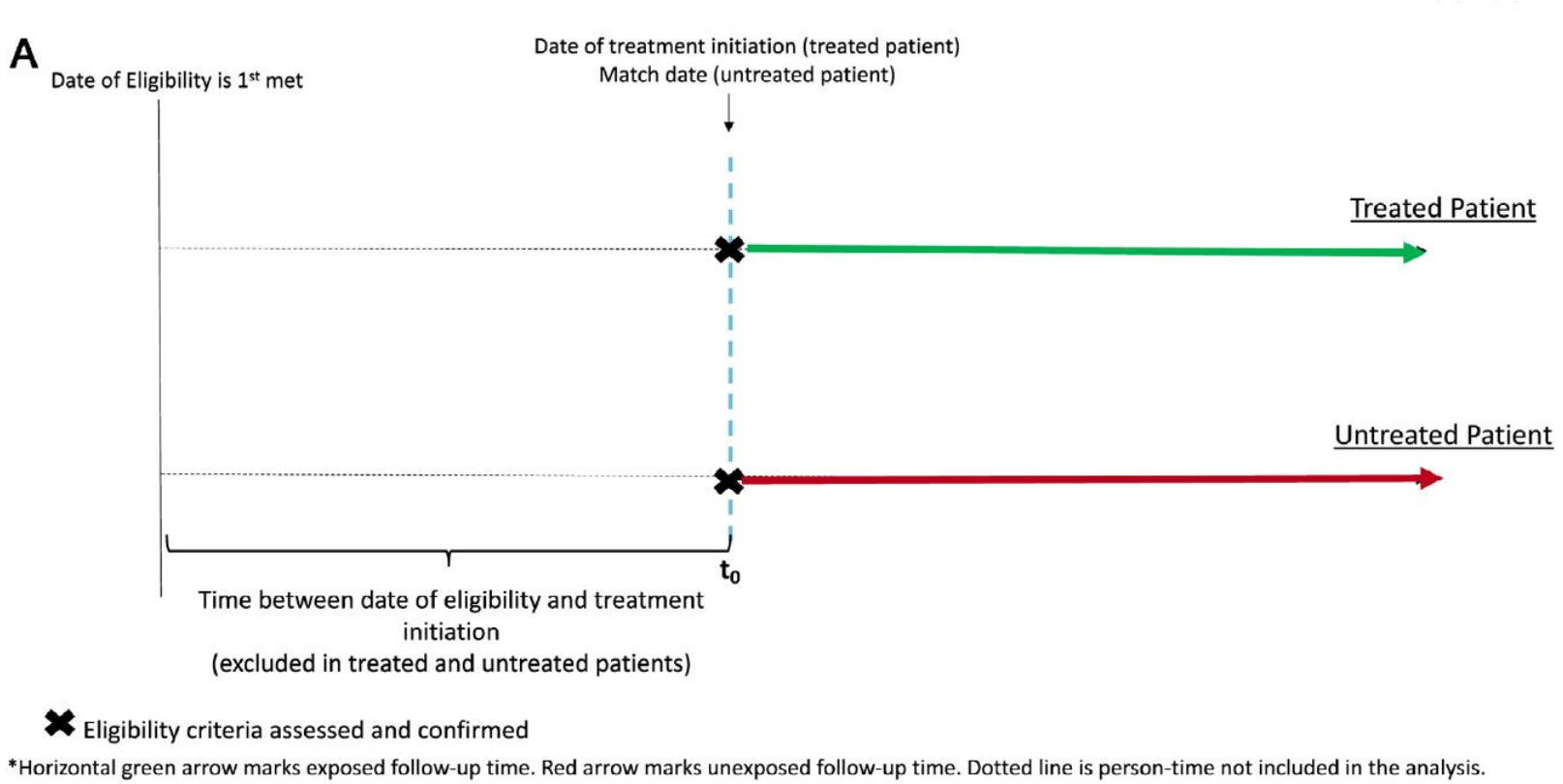
Accurately specifying time zero

- Patients may be eligible for along period of time; therefore, time zero would be the date that patient initiates therapy during the eligibility period.

- Both treatment arms: date of initiation for first treatment

- No therapy in control arm: multiple approaches to define time zero
  - Matching pretreatment person-time (preventing immortal time bias)
  - Series of nested trials

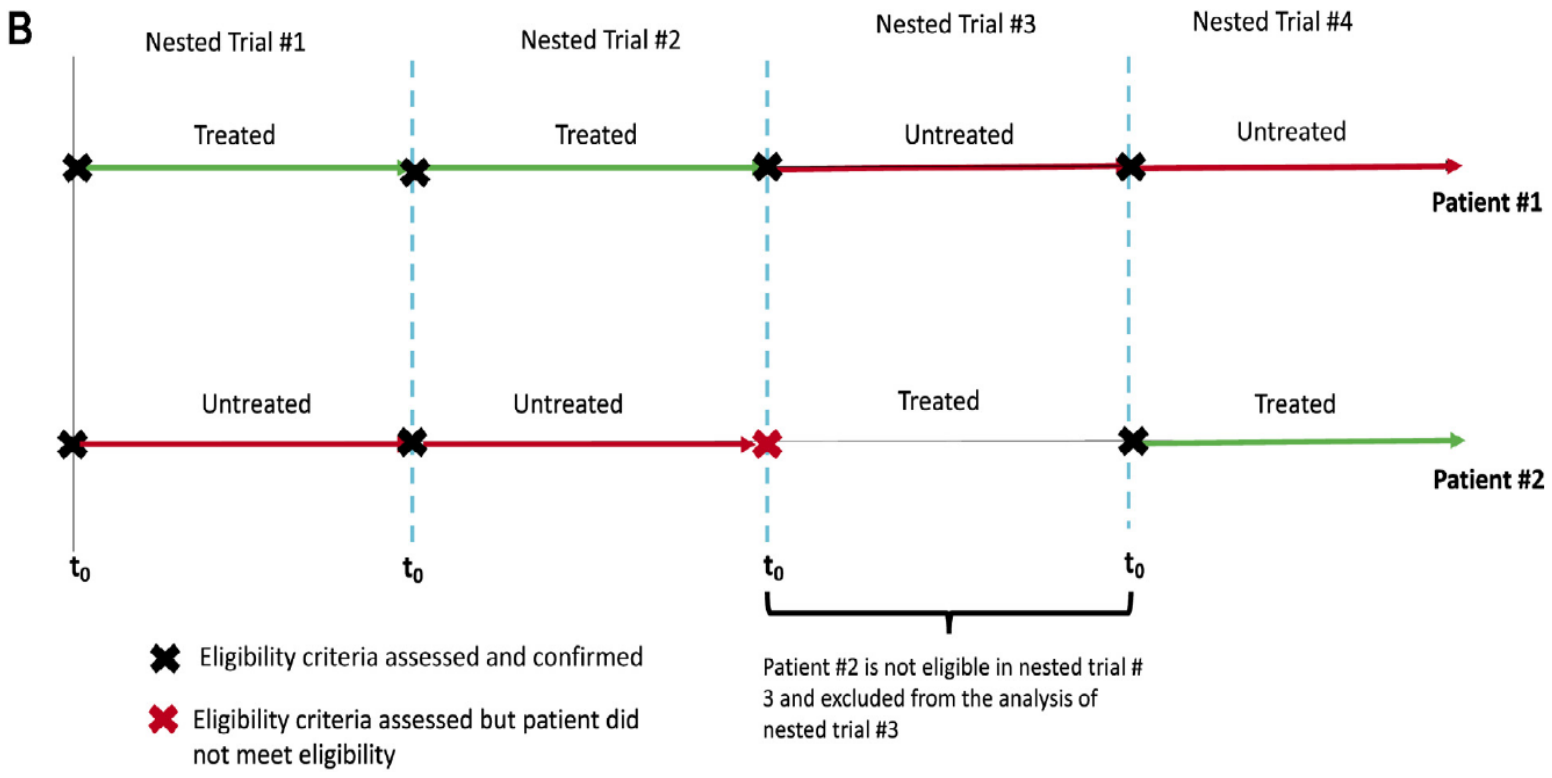
Matching pretreatment person-time



Same person-time duration from date of eligibility – date of initiation was matched.

Time zero = the date of Rx initiation in the treated patients, the matched date in the control patients.

Multiple nested trials



*Green arrows mark exposed person-time and red arrows mark unexposed person-time included in the analyses.

Interval: based on structure of data

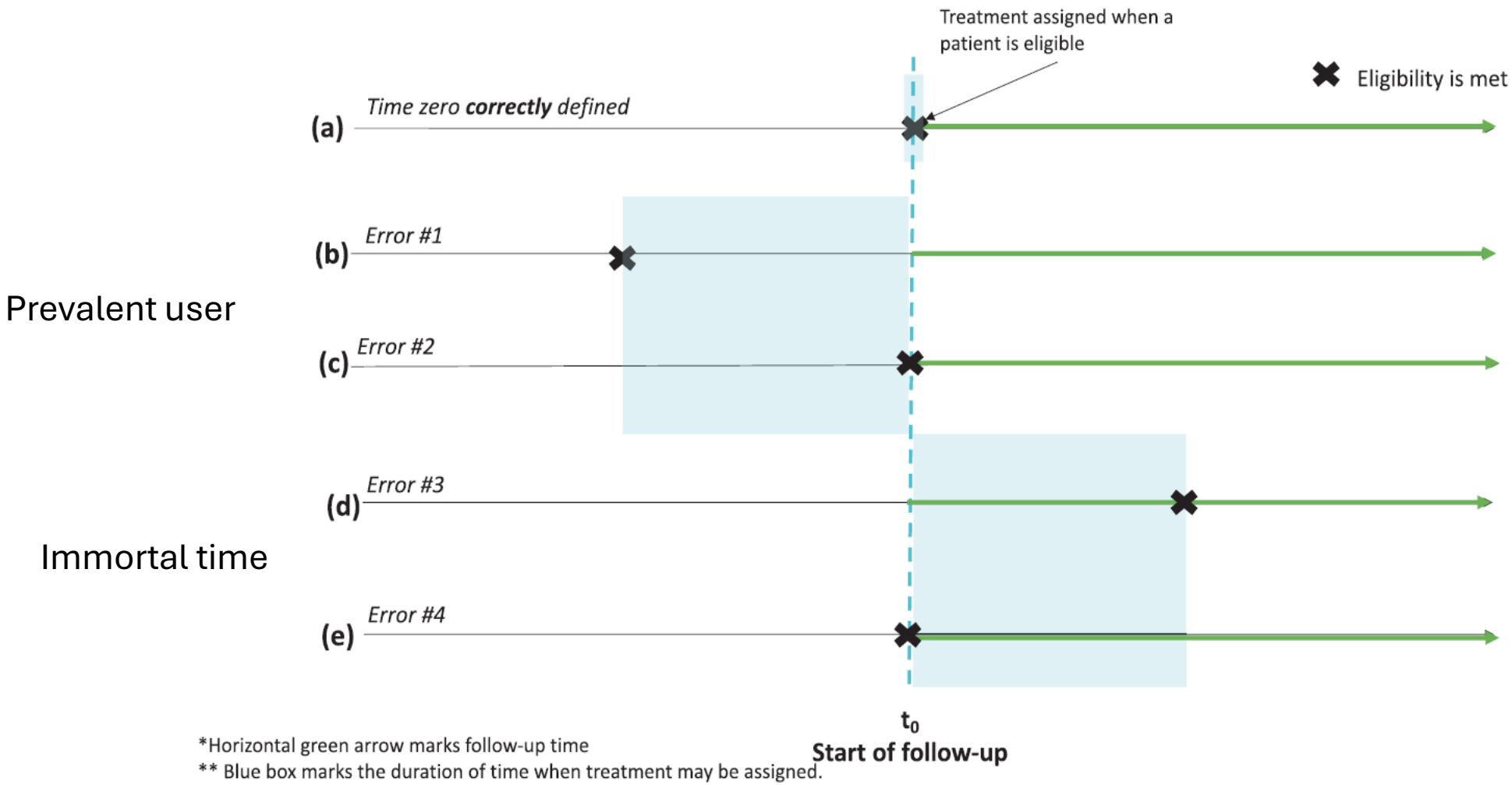
Eligibility is assessed at the beginning of each nested trial.

Treatment assignment for each trial is determined at the start of each nested trial.

The HR of each interval would be adjusted for covariates in previous intervals and pooled to the overall effect estimate. (time-varying confounder incorporated)

- Robust variance estimator; to account for lack of independence between the multiple nested trials.

Common errors of definition of time zero



Outcomes

- The primary and secondary outcomes need to be identified at the design stage of target trial, before the patients are enrolled.
  - Description of how and when

- Rely on the the database
  - Validated codes for outcome ascertainment and report the performance of positive predictive value, sensitivity and specificity

Follow up

- Follow-up begins at time zero and follows until an event is recorded or censored.
- When the distribution of these censoring events are independent and noninformative then analyses should yield unbiased average treatment effects, assuming that other biases are minimized.
- Informative loss to follow-up can be addressed through multiple imputation or inverse probability of censoring weighting.

Causal contrasts: ITT

ITT approach: preferred approach for RCT

- Observational study
  - Designation treatment assignment for the entire follow-up period can be based on
    - The first prescription
    - Treatment initiator (no prescribed medication available): first medication dispensed
  - Appropriate adjustment for baseline confounding to balance patient characteristics between treatment arms is needed.

Causal contrast: Per-protocol

- Effect of receiving treatment according to the trial protocol

- For sustained strategies in observational studies
  - Initiation of drug A and always using it during follow up, unless contraindication develop
  - Never initiating drug during follow up

- For unbiased estimation
  - High quality longitudinal data on confounders and treatment adherence to adjust for time-varying confounding
  - Appropriate method to handle time-varying confounding , such as inverse probability weighting

Statistical analysis

- Guided by ITT or per-protocol
- Methods were used to estimate ITT or per-protocol effect
  - Methods to adjust for confounding
  - Methods to deal with missing data
  - Methods to obtain effect estimates