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Target trial emulation: applying principles of randomised trials to observational studies

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The randomised trial is the preferred study design for evaluating the effectiveness and safety of interventions. Yet such trials can be prohibitively expensive, unethical, or take too long. When it is not possible to carry out a randomised trial, observational data can be used to answer similar questions. Here, we describe the process of using observational data to emulate a target trial, which applies the study design principles of randomised trials to observational studies that aim to estimate the causal effect of an intervention. The target trial provides a formal framework to help avoid self-inflicted biases common to observational studies.

The need for target trial emulation

Observational studies can provide evidence on the effectiveness of interventions when randomised trials are not feasible because they are expensive, unethical, or take too long. Causal inference using observational data is, however, challenging; not only are observational studies prone to confounding bias due to the lack of randomisation, but incorrect study design choices (such as the specification of the start of follow-up) can also cause self-inflicted biases.[1] Such study design flaws can be overcome by first designing a hypothetical randomised trial—the target trial—that would answer the question of interest, then emulating this target trial using the available observational data and appropriate methodology.[2 3]

How to design a target trial

The first step is to specify the protocol of the trial that ideally would have been conducted, within the constraints of the available observational data. Several elements are considered at this stage [2 4 5]: eligibility criteria, treatment strategies, assignment procedures, outcome(s), follow-up, causal contrasts of interest (eg, the intention-to-treat effect), and statistical analysis plan. The target trial must be a pragmatic trial because observational data cannot be used to emulate a placebo controlled trial. **Box 1** describes each component of the target trial protocol.

Box 1

Components of target trial protocol

Eligibility criteria

In randomised trials, eligibility is based on the characteristics of the participants at enrolment. Researchers must therefore ensure that eligibility criteria of the target trial are explicitly stated and are only based on values that are available at baseline, never after.

Treatment strategies

Formulation of the treatment strategies should include the specific treatments a participant could be assigned to in the target trial, and, if a sustained strategy, the length of time participants should adhere to this strategy, and any legitimate reasons why they could discontinue or switch from the assigned treatments. An example would be the initiation of 10 mg/day atorvastatin at baseline and continuation for five years or until the development of a contraindication versus no initiation of any statin at baseline or within the next five years, until the development of an indication for statins.

Assignment procedures

In the target trial that would ideally be undertaken, eligible, enrolled participants would be randomised to a treatment strategy. However, observational data reflect treatments that have already been given in routine clinical practice and as such, the emulation must assign individuals to the treatment strategy with which their data are compatible, and adjust for baseline covariates to control for confounding. An untestable assumption is that treatment is randomly assigned

within levels of the baseline covariates identified as potential confounders. The minimum set of covariates required to adjust for confounding should be chosen using a causal directed acyclic graph.[2]

Outcome(s)

The definition of the outcome must be clearly stated (eg, using ICD-10 (international classification of diseases, 10th revision) diagnostic codes), along with the validity and reliability of the measurement algorithm or tools used.

Follow-up

Start of follow-up should coincide with three conditions: when eligibility criteria are met, treatment strategies are assigned, and study outcomes begin to be counted. In a randomised trial, these three conditions often coincide by design, but it is easy to deviate from this rule when designing an observational study, which can result in biases such as selection of prevalent users or immortal time bias.[6] Follow-up then usually continues until the earliest of: occurrence of an outcome, censoring, death, competing events (depending on the effect being estimated), or end of follow-up (administrative or otherwise).[7]

Causal contrast of interest

In randomised trials, the main causal contrast is often the intention-to-treat effect (ie, effect of treatment assignment). An observational analogue of the intention-to-treat effect can be targeted if data on treatment assignment are available (eg, prescription) and participants are analysed according to the treatment strategy with which their data are compatible at baseline. However, it is also possible to target the per protocol effect (ie, the effect that would have been observed under full adherence to the assigned treatment strategy (see below)).

Statistical methods

When carrying out an intention-to-treat analysis using observational data, standard statistical methods can be used to adjust for baseline covariates. When carrying out a per protocol analysis in either randomised trials or observational studies, participants should be censored when they deviate from their assigned treatment strategy. G methods, which enable the identification and estimation of the effects of generalised treatment plans under less restrictive assumptions than standard regression methods, must then be used to adjust for prognostic factors (before and after baseline) associated with adherence. [2 8 9] Planned subgroup and sensitivity analyses should also be specified.

In their paper in *The BMJ*,[10] Urner and colleagues present an emulated pragmatic randomised controlled trial to estimate the effect of treatment with extracorporeal membrane oxygenation compared with conventional mechanical ventilation on hospital mortality within 60 days of admission to the intensive care unit in patients with covid-19 associated respiratory failure. By using the target trial framework, the authors avoided biases common to the design of such observational studies and estimated a per protocol effect using appropriate statistical methods (cloning, censoring, and weighting). In this setting, the use of traditional statistical methods (not G methods) could have introduced additional biases—for example, by falsely adjusting for consequences of treatment.[11]

When and why should target trial emulation be used

The target trial framework should be used to estimate the causal effect of interventions from observational data. Explicitly defining the protocol of the target trial, before emulating it using observational data, helps avoid many common design pitfalls. For example, observational studies that include prevalent users of a treatment are prone to selection bias.[8] This bias happens when an active arm includes participants who had already initiated treatment before the start of follow-up. These participants must have survived and remained event-free (if no history of the outcome event is specified in the eligibility criteria) while receiving treatment until the start of follow-up. Thus, participants that initiate treatment and survive this arbitrary period of time are often artificially healthy. This selection bias cannot happen in a randomised trial because individuals must be alive, event-free, and not taking the treatment of interest, when assessed for eligibility.

Conclusion

Observational studies are susceptible to confounding, regardless of the study design. However, the emulation of a target trial using observational data will yield the same effect estimate as that of a randomised trial if the emulation is successful.

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