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Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses

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Abstract

Many analyses of observational data are attempts to emulate a target trial. The emulation of the target trial may fail when researchers deviate from simple principles that guide the design and analysis of randomized experiments. We review a framework to describe and prevent biases, including immortal time bias, that result from a failure to align start of follow-up, specification of eligibility, and treatment assignment. We review some analytic approaches to avoid these problems in comparative effectiveness or safety research.

Keywords: Observational; studies; Comparative effectiveness research; Target trial; Time zero; Immortal time bias; Selection bias

1. Introduction

Many analyses of observational data are attempts to emulate a hypothetical pragmatic randomized trial, which we refer to as the target trial [1]. There are many reasons why an observational analysis may fail to correctly emulate its target trial. Most prominently, the observational data may contain insufficient information on confounders to approximately emulate randomization [2].

However, even in the absence of residual confounding, the emulation of the target trial may fail when researchers deviate from simple principles that guide the design and analysis of randomized experiments. One of those principles is the specification of time zero of follow-up as the time when the eligibility criteria are met and a treatment strategy is assigned.

This article reviews a framework to describe and prevent biases, including immortal time bias [3–5], that result from a failure to align start of follow-up, eligibility, and treatment assignment. We review some analytic approaches to avoid this problem in observational analyses that estimate comparative effectiveness or safety. This article focuses on relatively simple treatment strategies. However, the perils of unhitching eligibility or treatment assignment from time zero are compounded for complex strategies that are sustained over time or that involve joint interventions on several components.

2. Emulating the target trial

Consider a nonblinded randomized trial to estimate the effect of daily aspirin on mortality among individuals who have survived first surgery to treat colon cancer. Participants with no prior use of daily aspirin, no contraindications to aspirin, and a colon cancer diagnosis are randomly assigned, 1 month after surgery, to either immediate initiation of daily aspirin or to no aspirin use. Time

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zero of follow-up (or baseline) for each individual is the time when she meets the eligibility criteria and she is assigned to either treatment strategy, that is, the time of randomization. Participants are then followed from time zero until the end of follow-up at 5 years or until death, whichever occurs earlier. The intention-to-treat mortality risk ratio is the ratio of the 5-year mortality risks in the groups assigned to the aspirin and no aspirin strategies. For simplicity, suppose there are no losses to follow-up, which would require adjustment for potential selection bias [6].

Now suppose we try to emulate the above target trial using high-quality electronic medical records from five million individuals. First, we identify the individuals in the observational database at the time they meet the eligibility criteria. Second, we assign eligible individuals to the daily aspirin strategy if they are prescribed aspirin therapy (when using prescription data) or if they initiate aspirin therapy (when using dispensing data) at the time of eligibility and to the no aspirin strategy otherwise. Time zero for each individual is the time when she meets the eligibility criteria and she is assigned to either treatment strategy. Individuals are then followed from time zero until the end of follow-up at 5 years or until death, whichever occurs earlier.

We can now calculate the ratio of the 5-year mortality risks in the groups assigned to the aspirin and no aspirin strategies. This risk ratio is analogous to the intention-to-treat risk ratio in the target trial (if using prescription data) or in a similar target trial with 100% adherence for initiation of the treatment strategies (if using dispensing data). In what follows we use the term "treatment initiation" to refer to either medication prescription or dispensing, depending on the data source. Importantly, all individuals eligible at time zero and all deaths after time zero are included in the calculation of the risk ratio or of any other effect measure we might have chosen. Again, let us assume no losses to follow-up occur.

Emulating the random assignment of the treatment strategies is critical. To do so, we adjust the risk ratio for prognostic factors that also predict aspirin initiation at time zero, such as baseline age and history of coronary heart disease. If all such confounders were adequately adjusted for, then the adjusted mortality risk ratio for the aspirin vs. no aspirin strategies estimated from the observational data approximates the intention-to-treat risk ratio that would have been estimated in a target trial. Many adjustment methods are available, including matching, standardization, and stratification/regression with or without propensity scores, inverse probability (IP) weighting and g-estimation [7].

Of course, success in adjusting for all confounding is never certain, which casts a doubt over causal inferences from observational data. But, in this article, imagine we do have sufficient data on baseline confounders to reasonably emulate the randomized assignment. Even in that ideal scenario, our observational analysis may fail to emulate the target trial if some simple tenets of study design are not followed.

3. Four target trial emulation failures

The target trial emulation can fail when the time zero, the specification of the eligibility criteria, and the treatment assignment are not synchronized. Below we review some of these emulation failures (see also the Fig. 1) and the biases they introduce.

3.1. Emulation failure 1: time zero is set after both eligibility and strategy assignment

Suppose we correctly emulated the target trial described above using observational data, but we then decided to

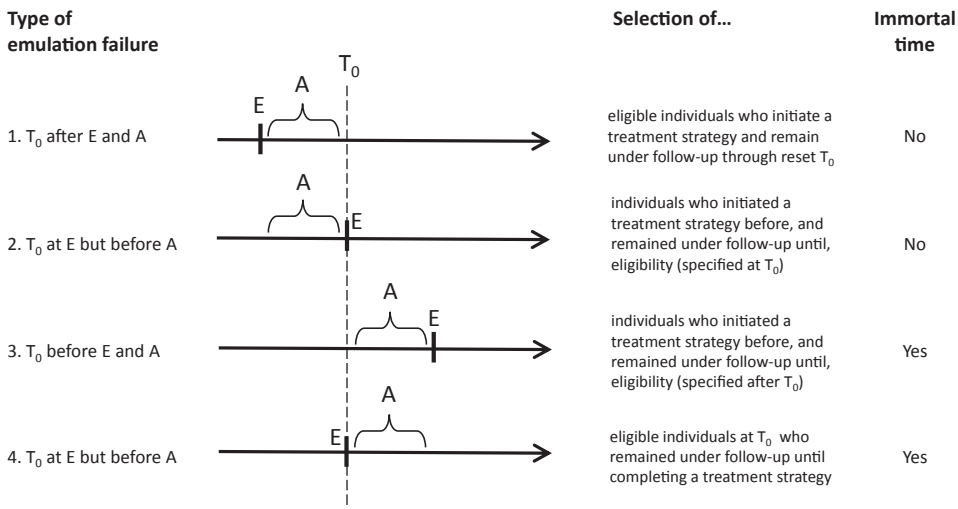

Fig. 1. Four examples of failures of emulation of a target trial using observational data. T_0, time zero; E, eligibility; A, period during which treatment strategies are assigned.