Starting right: aligning eligibility and treatment assignment at time zero when emulating a target trial

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This article provides methodological guidance when emulating a target trial with longitudinal observational data by showing how to align eligibility criteria and treatment assignment at the start of follow-up to prevent design induced biases, such as immortal time and selection bias.

Randomised trials with primary data collection are the preferred approach for estimating causal effects. However, trials are not always feasible, ethical, or timely, and the number of clinically relevant questions far outnumbers the randomised trials that can be conducted. Therefore, many researchers turn to observational datasets to answer causal questions.

Causal inference from observational data can be viewed as an attempt to emulate a pragmatic randomised trial—the target trial—that would answer the causal question of interest.[1] Specifying the protocol of this target trial is a natural device to articulate a well defined causal question and specify the target quantity of interest (causal estimand). The components of the target trial protocol that define the causal estimand are eligibility criteria, treatment strategies, treatment assignment, outcomes of interest, start and end of follow-up, and causal contrast. A precise specification of the target trial will then guide the approach for its emulation.

The emulation will fail if the data are inadequate (eg, imperfect information on key confounders or outcomes) or if the data are inadequately used (ie, incorrect design of the observational analysis). While target trial emulation cannot remove bias from inadequate data, it eliminates common biases induced by an incorrect design, such as misclassification or selection bias that may result in immortal time (a period of follow-up included in the analysis during which an individual, by definition, cannot develop an event of interest).[2-4] These design biases can be avoided by synchronising eligibility and treatment assignment at the start of follow-up (time zero). Design biases are more frequent in settings in which individuals meet the eligibility criteria at multiple times or when treatment strategies remain indistinguishable for some time.[4]

Here, we review general procedures to achieve alignment of eligibility and treatment assignment when using healthcare databases to emulate a target trial. We illustrate these procedures with three target trials of increasing complexity, discuss their implications for the choice of causal contrast, and provide a decision diagram to help investigators choose an approach for the data analysis.

SUMMARY POINTS

By aligning eligibility and treatment assignment at the start of follow-up (time zero), an explicit target trial emulation eliminates common design biases when analysing observational databases to investigate the effects of medical treatments

The target trial emulation starts by discretising a person's data into intervals and checking, for each interval, if the individual meets the eligibility criteria and can be assigned to (classified into) a treatment strategy

When individuals meet the eligibility criteria at multiple times or have data compatible with assignment to more than one treatment strategy, design biases can be prevented by repeated use of the same individual through sequential trial emulation or cloning, respectively

The target trial: eligibility and assignment to treatment strategies

Table 1 outlines the protocols for three target trials to estimate the effect of treatment on mortality among eligible individuals who have not been previously treated. As an example, we consider the effect of metformin among individuals with type 2 diabetes, but the principles explained here are generally applicable. The target trials differ in eligibility criteria and treatment strategies. In target trial 1, individuals in the observational dataset can only meet eligibility once and can be assigned to one treatment strategy. In target trial 2, individuals can meet the eligibility criteria at different times but at each time have data compatible with only one treatment strategy. In target trial 3, individuals can only meet the eligibility criteria once and can have data compatible with more than one treatment strategy.

Suppose that we want to emulate the target trials outlined in table 1 using a large longitudinal healthcare database that includes information on eligibility criteria and clinical characteristics, filled prescriptions, and mortality.

The first step in the emulation process is structuring the data for each individual in time intervals (eg, hours, days, weeks, months). The interval width needs to be sufficiently short to capture changes in eligibility criteria, treatments, and outcomes. For instance, if studying a therapy in the intensive care unit, we might require hourly data intervals; if studying the effects of a diabetes medication on long term outcomes, using weekly or monthly intervals would typically suffice. Then, for each individual in the dataset, we:

- Determine at which intervals the individual meets the eligibility criteria.
- At each eligible interval, assign (ie, classify) the individual to the treatment strategies that are compatible with the individual's data until that interval.

Table 1 | Causal estimand: simplified protocols of three target trials aiming to investigate the causal effect of metformin on all cause mortality

	Target trial 1	Target trial 2	Target trial 3
Eligibility criteria	Diagnosis of type 2 diabetes in previous month; no previous use of diabetes drug treatments	Diagnosis of type 2 diabetes in past 3 months; no previous use of diabetes drug treatments	Diagnosis of type 2 diabetes in previous month; no previous use of diabetes drug treatments
Treatment strategies	1. Start metformin and continue use unless contraindications arise	1. Start metformin and continue use unless contraindications arise	1. Start metformin within 3 months and continue use unless contraindications arise
	2. Never start metformin unless an absolute indication arises	2. Never start metformin unless an absolute indication arises	2. Never start metformin unless an absolute indication arises
Treatment assignment	Eligible individuals are randomly assigned to a strategy and are aware of the treatment strategy they are assigned to		
Outcomes	All cause mortality		
Start and end of follow-up	For each eligible individual, follow-up starts at the time of assignment to a treatment strategy and ends at the earliest of death, loss to follow-up, or administrative end of follow-up		
Causal contrast	Intention-to-treat effect (effect of assignment to the treatment strategy); per protocol effect (effect of adhering to the assigned treatment strategy)		

- Start the follow-up (set time zero) at an interval when the individual meets the eligibility criteria and is assigned to a treatment strategy.

We review this procedure for each of the target trials in table 1, using the hypothetical individual in figure 1 as an example. When emulating these trials, we assign individuals into treatment strategies according to their filled prescription history.

Target trial 1: Eligibility met once, treatment strategies distinguishable at eligibility

In target trial 1, individuals can only be eligible during the month following their diabetes diagnosis and, during that month, are assigned to exactly one of the two strategies based on whether they filled a prescription for metformin during that time.

Figure 1 illustrates this scenario for the example person, who is only eligible during interval m=2 (the month following the diabetes diagnosis) and does not fill a prescription during the eligible interval. The example person's data during m=2 are compatible with assignment to the treatment strategy "Never start metformin unless an absolute indication arises" (in the remainder of this article, we will abbreviate this strategy to "Never start metformin . . . " for readability). Follow-up is therefore started at m=2 (fig 2). Importantly, assignment to a treatment strategy must be determined based on information available at the eligible interval. Even though the person starts metformin at m=4, future information should not influence treatment assignment at m=2 to avoid introducing immortal time.[4]

Target trial 2: Eligibility met multiple intervals, treatment strategies distinguishable at eligibility

In target trial 2, individuals are eligible during each of the three months following their diabetes diagnosis. The example person in figure 1 is then eligible at intervals m=2, 3, 4, with data compatible with assignment to the treatment strategy "Never start metformin . . . " at m=2 and m=3, and with assignment

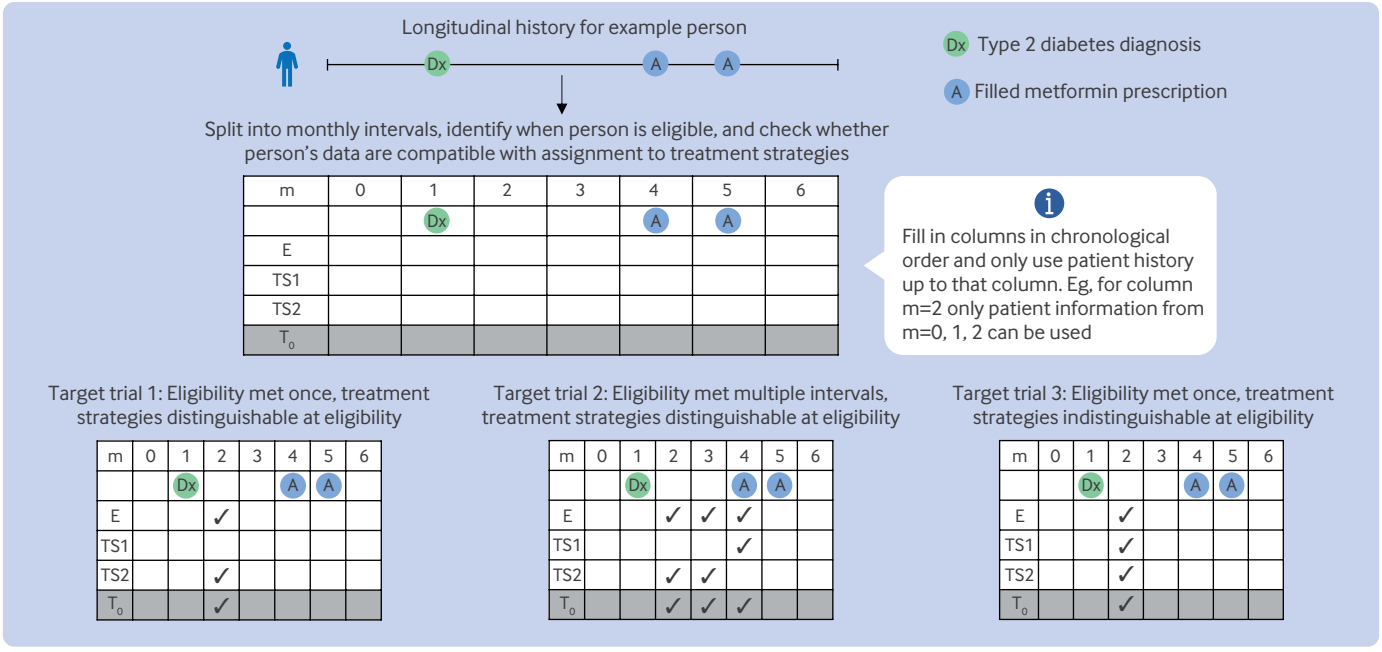

Fig 1 | Aligning eligibility and treatment assignment at time zero of three target trials for an example person. E=eligibility; m=month; TS1=assignment to treatment strategy 1; TS2=assignment to treatment strategy 2; T_0=time zero

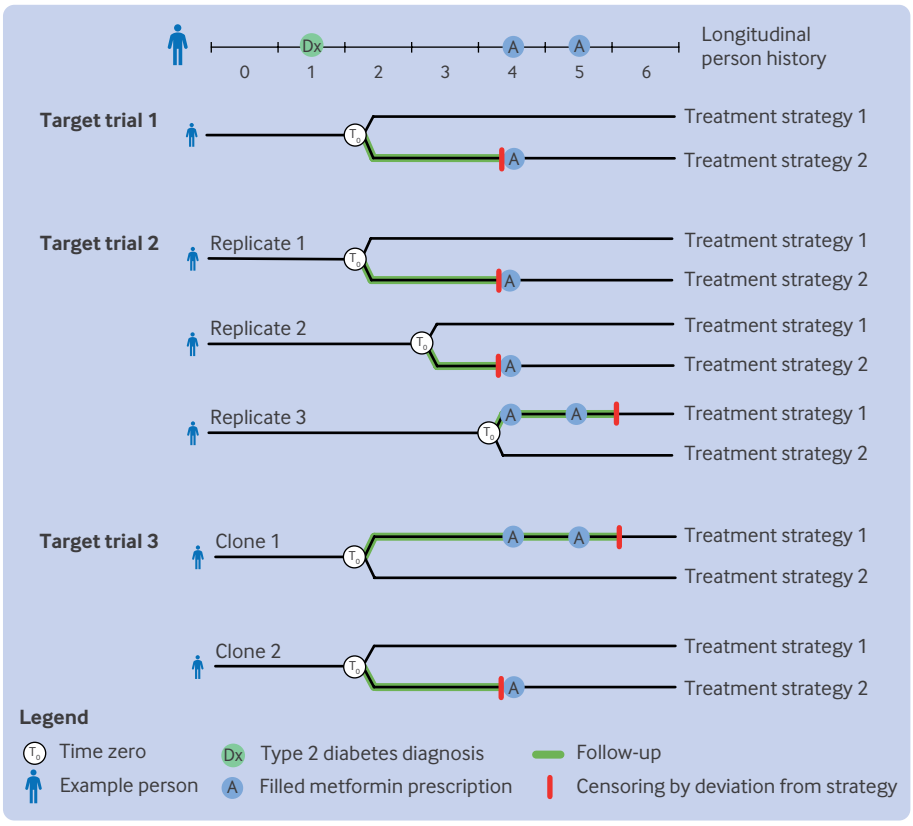

Fig 2 | Emulation of target trials 1-3 to estimate a per protocol effect via censoring using the example person in figure 1. Follow-up starts at different times for each of the replicates in the emulation of target trial 2, and at the same time for the clones in the emulation of target trial 3. Individuals, replicates, and clones are censored (ie, follow-up is stopped) when they no longer follow their assigned treatment strategy

to the strategy "Start metformin . . . " at m=4. Thus, time zero can possibly be set at three different times.

If a person has multiple intervals that could be used as time zero, one option is to choose one of those times at random.[5 6] For instance, we could randomly select m=2 for the example person. A more statistically efficient option is to use all times zero.[7 8] To do so, we construct an expanded dataset to which each person contributes as many replicates as eligible times zero. As illustrated in figure 2, the example person would have three replicates that start follow-up at three different times: that is, we emulate a sequence of target trials with different starting points.[9 10] We can then pool the data from all the sequential trials for a joint analysis with appropriate variance estimation to account for the repeated use of the same individual (eg, by using robust variance estimation or bootstrapping). Sequential trial emulation has been applied to various clinical domains.[11-15]

For some target trials, individuals are eligible multiple times but are assigned to a treatment strategy only once, which can occur in a target trial with a head-to-head comparison of two treatments (as opposed to a comparison of treatment *v* no treatment). As an illustration, suppose we replaced the treatment strategy "Never start metformin . . . " with "Start SGLT [sodium-glucose cotransporter]-2 inhibitor . . . " in target trial 2. The example person is now eligible at m=2, 3, 4, but is only assigned to a treatment strategy at m=4, which then serves as time zero. Because each individual will have at most a single time zero, sequential trial emulation is not required. Furthermore, some eligible individuals may never initiate any treatment and therefore cannot be assigned to any treatment strategy of interest, which results in their exclusion from the head-to-head comparison. In this setting, investigators may want to clarify whether their target population is that comprised by all eligible individuals or that comprised by those who start a new treatment. If it is the first option, investigators could consider a generalisability analysis such that the effect estimated among eligible individuals who start a treatment is recalculated for the target population.[16] If the second option, they may be more specific by adding the eligibility criterion "physician's determination that treatment should be initiated," which can be mapped to a drug prescription.

Target trial 3: Eligibility met once, treatment strategies indistinguishable at eligibility

In target trial 3, the strategies "Start metformin within 3 months . . . " and "Never start metformin . . . " imply that an eligible individual who does not immediately start metformin has data compatible with assignment

to both strategies (fig 1). The example person is eligible during m=2 and does not start metformin during that interval. This person has data compatible with the strategy "Start metformin within 3 months . . . " at m=2 because the grace period of three months allows for delayed initiation. Simultaneously, the example person's data are also compatible with assignment to the "Never start metformin . . ." strategy. Thus, the treatment strategies are indistinguishable for this example person at m=2. Remember that we cannot use information during m=4 to determine treatment assignment at m=2, because the use of future information may introduce immortal time.[4]

When a person's data are compatible with assignment to more than one treatment strategy, one valid (but statistically inefficient) approach is to randomly assign these individuals to a single strategy. Another approach is assigning the individual to all compatible strategies by using cloning, whereby we make as many copies (clones) of an individual's data as the number of compatible strategies.[17] In figure 2, the example person is represented by two clones starting follow-up at m=2. The first clone is assigned to the first treatment strategy, and the second clone to the second treatment strategy. The statistical analysis should then account for the repeated use of the same individual (eg, by using robust variance estimation or bootstrapping).[18 19]

Besides strategies with a grace period, other examples of indistinguishable strategies are strategies that compare different treatment durations[18] and dynamic strategies that mandate a treatment change when the individual develops some condition (eg, start metformin when HbA1c (glycated haemoglobin) first rises above 6.5%).[17] Cloning has been applied to a wide range of clinical questions.[20-33] When a person has multiple possible times zero and have data compatible with assignment to multiple strategies, sequential trial emulation can be combined with cloning.[34]

Causal contrasts in the target trial

Typical causal contrasts of interest in the target trial are the intention-to-treat effect and the per protocol effect.[35] In a randomised trial, the intention-to-treat effect (the effect of assignment) is estimated via an intention-to-treat analysis that compares outcomes between groups assigned to different treatment strategies at time zero. A similar analysis (with adjustment for baseline confounders) can be conducted in the observational data after assigning individuals to treatment strategies. In our example, we classified individuals into treatment strategies according to filled prescriptions.

In a randomised trial, the per protocol effect is the effect of adhering to the assigned treatment strategies as indicated in the protocol. The per protocol effect can be estimated via a per protocol analysis[35] that censors individuals (ie, stops their follow-up) when they stop adhering to the protocol. A similar analysis can be conducted in the observational data. For the example person in target trial 1, the person would be censored at m=4 when metformin was started (fig 2), and the person no longer adheres to the "Never start metformin . . . " strategy.

However, in both randomised trials and observational studies, censoring introduces selection bias if the censoring is related to risk factors for the outcome. This bias could, for example, occur if individuals who deviate from their assigned strategy have more comorbid conditions than those

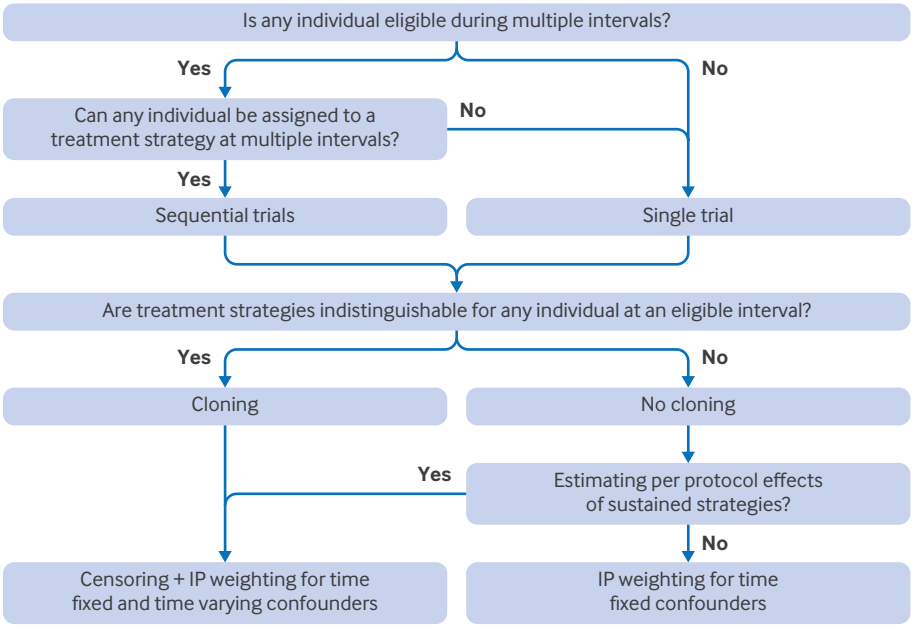

Fig 3 | Decision diagram for target trial emulation when sequential trials are used to handle multiple eligibility times, cloning is used to handle indistinguishable strategies, and inverse probability (IP) weighting is used to adjust for time fixed and time varying confounders

who do not deviate from their strategy. The per protocol analysis should account for this informative censoring by adjusting for baseline and time varying prognostic factors associated with adherence (eg, via inverse probability weighting).[36-38] An alternative is estimating the per protocol effect using the plug-in g-formula.[39] Regardless of the adjustment approach, the identification and measurement of the time varying prognostic factors may be difficult.

Thus, in both randomised trials and their emulations, investigators may choose to estimate the effect of assignment or the per protocol effect, or both. An exception is when, as in target trial 3 above, clones of the same individual are assigned to different treatment strategies. In this case, the effect of treatment assignment is not relevant because the groups are identical at time zero, and the effect of interest is typically a per protocol effect.

Discussion

In the target trial framework, investigators ask a causal question by specifying the target trial and then generate an answer by attempting to emulate the target trial using observational data. Following the procedures reviewed in this article ensures that the emulation correctly aligns eligibility and assignment to the treatment strategies at the start of follow-up, which prevents common design biases.[9 40] Figure 3 presents a decision diagram with the analytical approaches discussed in this article. The target trial framework unifies several observational designs to estimate causal effects, such as incident user designs for the effect of treatment initiation,[41 42] prevalent new user designs[43 44] for the effect of treatment switching, and active comparator new user designs[45 46] for head-to-head comparisons. The different eligibility criteria and treatment strategies of the target trial need to be explicitly specified so that an appropriate emulation approach can be chosen.

Although aligning eligibility and treatment assignment at time zero avoids design biases, it does not protect against data inadequacies such as unmeasured confounding, measurement error, and missing data. Dealing with these potential sources of bias typically requires high quality data on treatment, confounders, and outcomes. Furthermore, a failure to identify[47 48] and correctly adjust for important confounders, because of inappropriate adjustment methods or misspecified models, may result in substantial bias in the effect estimates.

In conclusion, we reviewed procedures to design sound analyses for causal inference from observational data, and we discussed them in the context of causal questions commonly encountered by researchers interested in the effects of medical treatments.

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