

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

Edouard L. Fu^{1,2}, Michael O. Harhay³, Sebastian Schneeweiss², Rishi J. Desai^{2,*}, Miguel A. Hernán^{4,*}

¹ Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

² Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

³ Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

⁴ CAUSALab and Departments of Epidemiology and Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA

* Contributed equally

Word count: 2222

Number of tables: 1

Number of figures: 3

Corresponding author

Edouard L. Fu

Assistant Professor

Department of Clinical Epidemiology, Leiden University Medical Center

Albinusdreef 2, 2333 ZA Leiden

E-mail: e.l.fu@lumc.nl, Phone: +316 17385859

Abstract

This paper 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.

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.

Introduction

Randomized 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 by far outnumbers the randomized 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 randomized trial—the target trial—that would answer the causal question of interest¹. 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 (e.g., imperfect information on key confounders or outcomes) or if the data are inadequately used (i.e., 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 time²⁻⁴. These design biases can be avoided by synchronizing 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 time⁴.

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.

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 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 (e.g., 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:

1. Determine at which intervals the individual meets the eligibility criteria.
2. At each eligible interval, assign (i.e., classify) the individual to the treatment strategies that are compatible with the individual's data until that interval.
3. Start the follow-up (set time zero) at an interval when the individual meets the eligibility criteria and is assigned to a treatment strategy.

Let us 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 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 through $m=2$ are compatible with assignment to the treatment strategy “*Never start metformin unless an absolute indication arises*” (in the remainder of the paper we will abbreviate this strategy to “*Never start metformin (...)*” to improve readability). Follow-up is therefore started at $m=2$ (**Figure 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 time⁴.

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 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 which 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 (e.g., by using robust variance estimation or bootstrapping). Sequential trial emulation has been applied to various clinical domains¹¹⁻¹⁵.

For some target trials, individuals are eligible multiple times but are assigned to a treatment strategy only once. This can occur in a target trial with a head-to-head comparison of two treatments (as opposed to a comparison of treatment vs. no treatment). As an illustration, suppose we replaced the treatment strategy “*Never start metformin (...)*” with “*Start SGLT-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. As 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 the former, they could consider a generalizability analysis such that the effect estimated among eligible individuals who start a treatment is recalculated for the target population¹⁶. If the latter, 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. This situation is illustrated in **Figure 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 $m=2$ since the 3-month grace period allows for delayed initiation. Simultaneously, the example person’s data are also compatible with assignment to “*Never start metformin (...)*”. 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 $m=2$, as the use of future information may introduce immortal time⁴.

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”. With cloning, we make as many copies (clones) of an individual’s data as the number of compatible strategies¹⁷. 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 (e.g., 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 durations¹⁸ and dynamic strategies that mandate a treatment change when the individual develops some condition (e.g. start metformin when HbA1c first rises above 6.5%)¹⁷. Cloning has been applied to a wide range of clinical questions²⁰⁻³³. When persons have multiple possible times zero and have data compatible with assignment to multiple strategies, sequential trial emulation can be combined with cloning³⁴.

The target trial: Causal contrasts

Typical causal contrasts of interest in the target trial are the intention-to-treat effect and the per-protocol effect³⁵.

In a randomized 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 randomized 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 analysis³⁵ that censors individuals (i.e. 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 (**Figure 2**), and the person no longer adheres to the strategy “*Never start metformin (...)*”.

However, in both randomized trials and observational studies, censoring introduces selection bias if the censoring is related to risk factors for the outcome. This could for example occur if persons who deviate from their assigned strategy have more comorbid conditions than those 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, e.g. via inverse-probability weighting (IP weighting)³⁶⁻³⁸. An alternative is estimating the per-protocol effect using the plug-in g-formula³⁹. Regardless of the adjustment approach, the identification and measurement of the time-varying prognostic factors may be difficult.

Thus, in both randomized 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 paper 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 analytic approaches discussed in this paper. 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 design”^{43,44} for the effect of treatment switching, and “active comparator new user design”^{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. Addressing 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 discussed them in the context of causal questions commonly encountered by researchers interested in the effects of medical treatments.

Contributor and guarantor information

ELF and MAH conceived the paper, and produced the first full draft. RJD and MAH revised this version with feedback over multiple iterations. MOH and SS provided further written feedback on these versions. ELF is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing interests declaration

No conflicts of interest are reported.

Funding

Dr. Fu is supported by a VENI grant (09150162310058) from the Dutch Research Council (NWO), a Junior Kolff Grant from the Dutch Kidney Foundation (22OK2026) and a Junior Principal Investigator grant from Leiden University Medical Center. Dr. Harhay is supported by NIH grant R01HL168202. Dr. Schneeweiss is supported by NIH grants R01-HL141505 and NIAMS R01-AR080194. Dr. Hernán is supported by NIH grant R37 AI102634.

Acknowledgments

The authors thank Anne C. Kemmeren for constructive comments on the manuscript and help with developing the figures.

Copyright/license for publication

The corresponding author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms,

formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Patient and Public Involvement statement

No patients were involved in this research methods paper. A number of members of the public with no or little experience in causal inference were presented the three-step process to refine its clarity for a general audience.

Table 1. Causal estimand: Outline of the protocols of three target trials of metformin and all-cause mortality.

	Target trial 1	Target trial 2	Target trial 3
Eligibility criteria	<ul style="list-style-type: none"> – Diagnosis of type 2 diabetes <i>in the previous month</i> – No previous use of diabetes medications 	<ul style="list-style-type: none"> – Diagnosis of type 2 diabetes <i>in past 3 months</i> – No previous use of diabetes medications 	<ul style="list-style-type: none"> – Diagnosis of type 2 diabetes <i>in the previous month</i> – No previous use of diabetes medications
Treatment strategies	<ol style="list-style-type: none"> 1. Start metformin and continue use unless contra-indications arise 2. Never start metformin unless an absolute indication arises 	<ol style="list-style-type: none"> 1. Start metformin and continue use unless contra-indications arise 2. Never start metformin unless an absolute indication arises 	<ol style="list-style-type: none"> 1. Start metformin within 3 months and continue use unless contra-indications arise 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).		

Figure 1. Aligning eligibility and treatment assignment at time zero of three target trials for an example person.

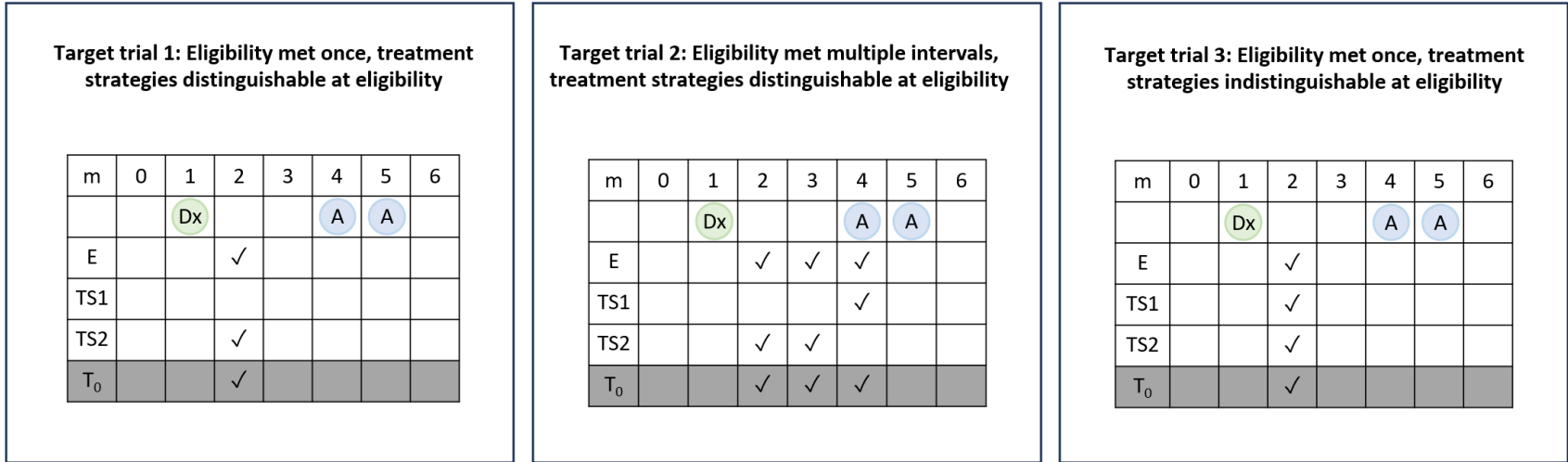
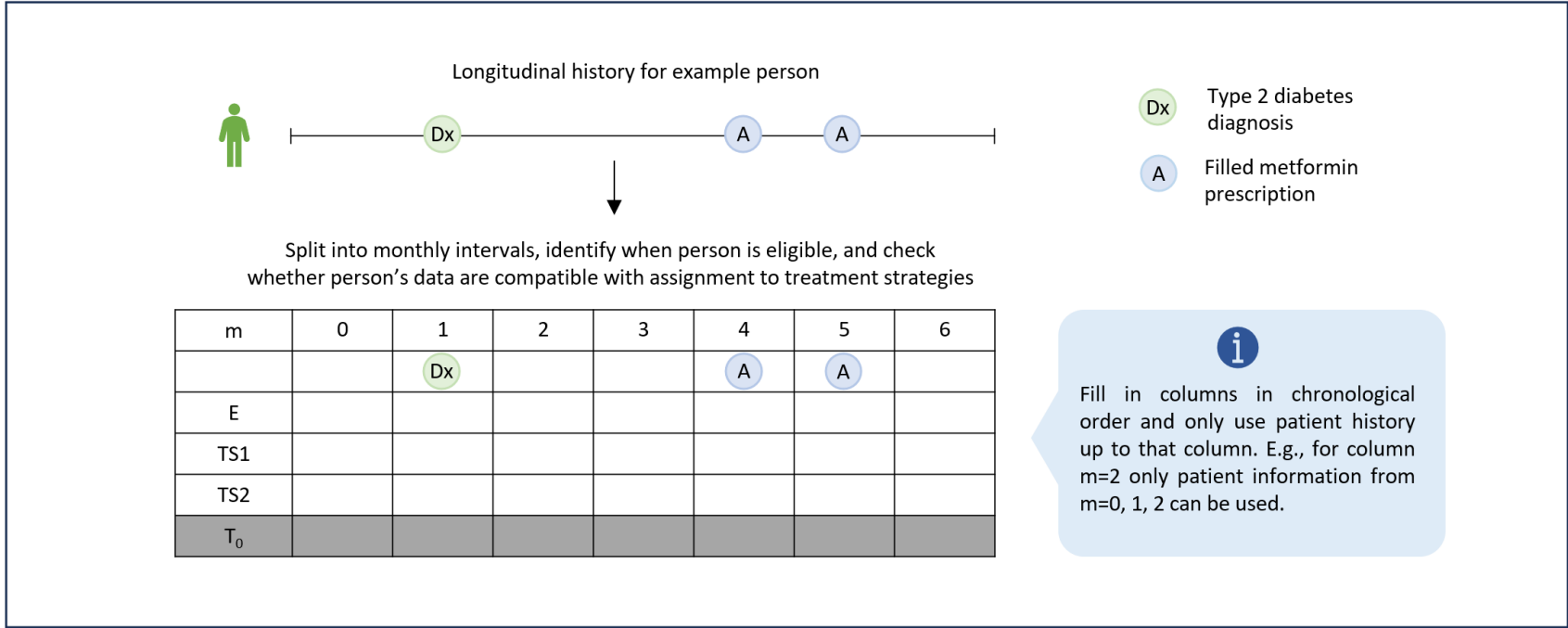


Figure legend: E = eligibility; m = month; TS1 = assignment to treatment strategy 1; TS2 = assignment to treatment strategy 2; T₀ = time zero.

Figure 2. Emulation of the three target trials to estimate a per-protocol effect via censoring using the example person.

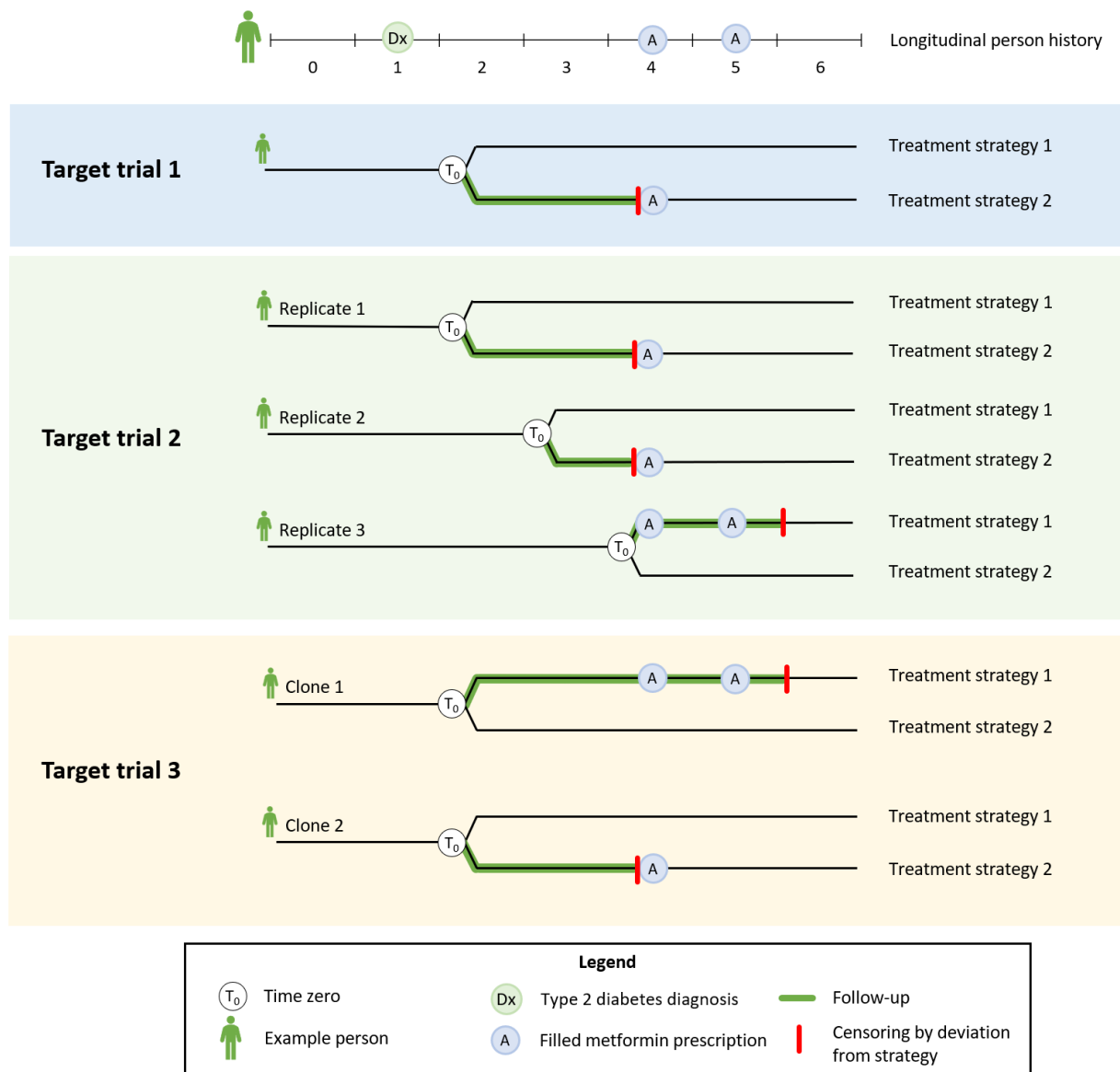
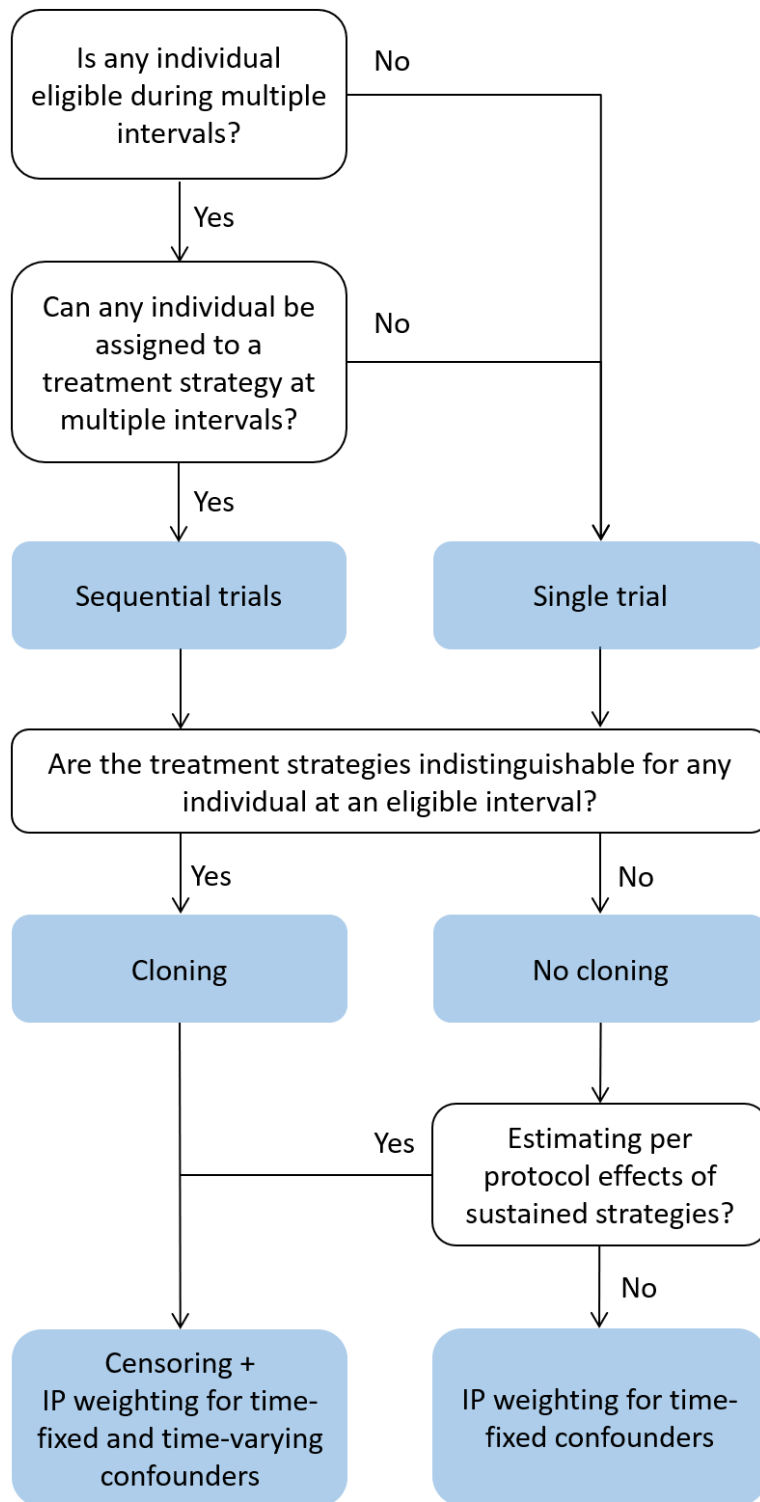


Figure legend: Follow-up starts at different times for each of the replicates in the emulation of target trial 2, and at the same time for the clones in the emulation of target trial 3. Individuals, replicates, and clones are censored (i.e. follow-up is stopped) when they no longer follow their assigned treatment strategy.

Figure 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 IP weighting is used to adjust for time-fixed and time-varying confounders.



References

1. Hernán MA, Dahabreh IJ, Dickerman BA, Swanson SA. The Target Trial Framework for Causal Inference From Observational Data: Why and When Is It Helpful? *Ann Intern Med* 2025 doi: 10.7326/annals-24-01871.
2. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* 2008;167:492-9. doi: 10.1093/aje/kwm324.
3. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ* 2010;340:b5087. doi: 10.1136/bmj.b5087.
4. Hernán MA, Sterne JAC, Higgins JPT, Shrier I, Hernández-Díaz S. A Structural Description of Biases That Generate Immortal Time. *Epidemiology* 2025;36:107-14. doi: 10.1097/ede.0000000000001808.
5. Noel JA, Bota SE, Petrcich W, et al. Risk of Hospitalization for Serious Adverse Gastrointestinal Events Associated With Sodium Polystyrene Sulfonate Use in Patients of Advanced Age. *JAMA Intern Med* 2019;179:1025-33. doi: 10.1001/jamainternmed.2019.0631.
6. Lenain R, Boucquemont J, Leffondre K, et al. Clinical Trial Emulation by Matching Time-dependent Propensity Scores: The Example of Estimating Impact of Kidney Transplantation. *Epidemiology* 2021;32:220-29. doi: 10.1097/EDE.0000000000001308.
7. Garcia-Albeniz X, Hsu J, Hernan MA. The value of explicitly emulating a target trial when using real world evidence: an application to colorectal cancer screening. *Eur J Epidemiol* 2017;32:495-500. doi: 10.1007/s10654-017-0287-2.
8. Hernan MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol* 2016;183:758-64. doi: 10.1093/aje/kwv254.
9. Hernan MA, Sauer BC, Hernandez-Diaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol* 2016;79:70-75. doi: 10.1016/j.jclinepi.2016.04.014.
10. Danaei G, Rodriguez LA, Cantero OF, Logan R, Hernan MA. Observational data for comparative effectiveness research: an emulation of randomised trials of statins and primary prevention of coronary heart disease. *Stat Methods Med Res* 2013;22:70-96. doi: 10.1177/0962280211403603.
11. Danaei G, Garcia Rodriguez LA, Fernandez Cantero O, Hernan MA. Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival. *Diabetes Care* 2013;36:1236-40. doi: 10.2337/dc12-1756.
12. Dickerman BA, Garcia-Albeniz X, Logan RW, Denaxas S, Hernan MA. Avoidable flaws in observational analyses: an application to statins and cancer. *Nat Med* 2019;25:1601-06. doi: 10.1038/s41591-019-0597-x.
13. Kainz A, Kammer M, Reindl-Schwaighofer R, et al. Waiting Time for Second Kidney Transplantation and Mortality. *Clin J Am Soc Nephrol* 2022;17:90-97. doi: 10.2215/CJN.07620621.
14. Madenci AL, Kurgansky KE, Dickerman BA, et al. Estimating the Effect of Bariatric Surgery on Cardiovascular Events Using Observational Data? *Epidemiology* 2024;35:721-29. doi: 10.1097/EDE.0000000000001765.
15. Schmidt M, Sorensen HT, Pedersen L. Diclofenac use and cardiovascular risks: series of nationwide cohort studies. *BMJ* 2018;362:k3426. doi: 10.1136/bmj.k3426.
16. Dahabreh IJ, Robertson SE, Tchetgen EJ, Stuart EA, Hernan MA. Generalizing causal inferences from individuals in randomized trials to all trial-eligible individuals. *Biometrics* 2019;75:685-94. doi: 10.1111/biom.13009.

17. Cain LE, Robins JM, Lanoy E, et al. When to start treatment? A systematic approach to the comparison of dynamic regimes using observational data. *Int J Biostat* 2010;6:Article 18. doi: 10.2202/1557-4679.1212.
18. Hernan MA. How to estimate the effect of treatment duration on survival outcomes using observational data. *BMJ* 2018;360:k182. doi: 10.1136/bmj.k182.
19. Orellana L, Rotnitzky A, Robins JM. Dynamic regime marginal structural mean models for estimation of optimal dynamic treatment regimes, Part I: main content. *Int J Biostat* 2010;6:Article 8.
20. Emilsson L, Garcia-Albeniz X, Logan RW, et al. Examining Bias in Studies of Statin Treatment and Survival in Patients With Cancer. *JAMA Oncol* 2018;4:63-70. doi: 10.1001/jamaoncol.2017.2752.
21. Petito LC, Garcia-Albeniz X, Logan RW, et al. Estimates of Overall Survival in Patients With Cancer Receiving Different Treatment Regimens: Emulating Hypothetical Target Trials in the Surveillance, Epidemiology, and End Results (SEER)-Medicare Linked Database. *JAMA Netw Open* 2020;3:e200452. doi: 10.1001/jamanetworkopen.2020.0452.
22. Maringe C, Benitez Majano S, Exarchakou A, et al. Reflection on modern methods: trial emulation in the presence of immortal-time bias. Assessing the benefit of major surgery for elderly lung cancer patients using observational data. *Int J Epidemiol* 2020;49:1719-29. doi: 10.1093/ije/dyaa057.
23. Fu EL, Evans M, Clase CM, et al. Stopping Renin-Angiotensin System Inhibitors in Patients with Advanced CKD and Risk of Adverse Outcomes: A Nationwide Study. *J Am Soc Nephrol* 2021;32:424-35. doi: 10.1681/ASN.2020050682.
24. Xu Y, Fu EL, Trevisan M, et al. Stopping renin-angiotensin system inhibitors after hyperkalemia and risk of adverse outcomes. *Am Heart J* 2022;243:177-86. doi: 10.1016/j.ahj.2021.09.014.
25. Trevisan M, Fu EL, Xu Y, et al. Stopping mineralocorticoid receptor antagonists after hyperkalaemia: trial emulation in data from routine care. *Eur J Heart Fail* 2021;23:1698-707. doi: 10.1002/ejhf.2287.
26. Wei J, Choi HK, Neogi T, et al. Allopurinol Initiation and All-Cause Mortality Among Patients With Gout and Concurrent Chronic Kidney Disease : A Population-Based Cohort Study. *Ann Intern Med* 2022 doi: 10.7326/M21-2347.
27. Boyne DJ, Cheung WY, Hilsden RJ, et al. Association of a Shortened Duration of Adjuvant Chemotherapy With Overall Survival Among Individuals With Stage III Colon Cancer. *JAMA Netw Open* 2021;4:e213587. doi: 10.1001/jamanetworkopen.2021.3587.
28. Cain LE, Logan R, Robins JM, et al. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational study. *Ann Intern Med* 2011;154:509-15. doi: 10.7326/0003-4819-154-8-201104190-00001.
29. Caniglia EC, Sabin C, Robins JM, et al. When to Monitor CD4 Cell Count and HIV RNA to Reduce Mortality and AIDS-Defining Illness in Virologically Suppressed HIV-Positive Persons on Antiretroviral Therapy in High-Income Countries: A Prospective Observational Study. *J Acquir Immune Defic Syndr* 2016;72:214-21. doi: 10.1097/QAI.0000000000000956.
30. Fu EL, Evans M, Carrero JJ, et al. Timing of dialysis initiation to reduce mortality and cardiovascular events in advanced chronic kidney disease: nationwide cohort study. *BMJ* 2021;375:e066306. doi: 10.1136/bmj-2021-066306.
31. Garcia-Albeniz X, Chan JM, Paciorek A, et al. Immediate versus deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study. *Eur J Cancer* 2015;51:817-24. doi: 10.1016/j.ejca.2015.03.003.
32. Li X, Cole SR, Kshirsagar AV, et al. Safety of Dynamic Intravenous Iron Administration Strategies in Hemodialysis Patients. *Clin J Am Soc Nephrol* 2019;14:728-37. doi: 10.2215/CJN.03970318.

33. Lyu H, Yoshida K, Zhao SS, et al. Delayed Denosumab Injections and Fracture Risk Among Patients With Osteoporosis : A Population-Based Cohort Study. *Ann Intern Med* 2020;173:516-26. doi: 10.7326/M20-0882.
34. Garcia-Albeniz X, Hernan MA, Logan RW, et al. Continuation of Annual Screening Mammography and Breast Cancer Mortality in Women Older Than 70 Years. *Ann Intern Med* 2020;172:381-89. doi: 10.7326/M18-1199.
35. Hernan MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. *N Engl J Med* 2017;377:1391-98. doi: 10.1056/NEJMsm1605385.
36. Murray EJ, Caniglia EC, Petito LC. Causal survival analysis: A guide to estimating intention-to-treat and per-protocol effects from randomized clinical trials with non-adherence. *Research Methods in Medicine & Health Sciences* 2021;2:39-49. doi: 10.1177/2632084320961043.
37. Toh S, Hernan MA. Causal inference from longitudinal studies with baseline randomization. *Int J Biostat* 2008;4:Article 22. doi: 10.2202/1557-4679.1117.
38. Toh S, Hernandez-Diaz S, Logan R, Robins JM, Hernan MA. Estimating absolute risks in the presence of nonadherence: an application to a follow-up study with baseline randomization. *Epidemiology* 2010;21:528-39. doi: 10.1097/EDE.0b013e3181df1b69.
39. Robins JM. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. *Mathematical Modelling* 1986;7:1393-512.
40. Fu EL. Target Trial Emulation to Improve Causal Inference from Observational Data: What, Why, and How? *J Am Soc Nephrol* 2023 doi: 10.1681/ASN.0000000000000152.
41. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;158:915-20. doi: 10.1093/aje/kwg231.
42. Johnson ES, Bartman BA, Briesacher BA, et al. The incident user design in comparative effectiveness research. *Pharmacoepidemiol Drug Saf* 2013;22:1-6. doi: 10.1002/pds.3334.
43. Suissa S, Moodie EE, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. *Pharmacoepidemiol Drug Saf* 2017;26:459-68. doi: 10.1002/pds.4107.
44. Suissa S, Dell'Aniello S, Renoux C. The Prevalent New-user Design for Studies With no Active Comparator: The Example of Statins and Cancer. *Epidemiology* 2023;34:681-89. doi: 10.1097/EDE.0000000000001628.
45. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol* 2015;11:437-41. doi: 10.1038/nrrheum.2015.30.
46. Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep* 2015;2:221-28. doi: 10.1007/s40471-015-0053-5.
47. Feeney T, Hartwig FP, Davies NM. How to use directed acyclic graphs: guide for clinical researchers. *BMJ* 2025;388:e078226. doi: 10.1136/bmj-2023-078226.
48. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999;10:37-48.