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

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Abstract

This paper provides methodological guidance when emulating a target trial with 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. The target trial framework can eliminate common design biases that may arise when using observational data to investigate the effects of medical treatments. The framework consists of specifying the hypothetical pragmatic randomized trial (target trial) that would answer the causal question of interest, and then attempting to emulate it with observational data. A key principle in the process is that follow-up starts at the time that eligible individuals are assigned to a treatment strategy. Deviations from this principle may introduce immortal time or selection bias. This paper introduces a stepwise procedure that guides investigators interested in emulating a specified target trial. We illustrate the process with three target trials that compare different types of treatment strategies and show the connections with several existing study designs.

Summary points

- The target trial framework can eliminate common design biases that may arise when using observational data to investigate the effects of medical treatments by aligning eligibility criteria and treatment assignment at the start of follow-up.
- When using healthcare databases, 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 one of the treatment strategies.
- When individuals meet the eligibility criteria at multiple times or have data compatible with assignment to more than one treatment strategy, alignment can be achieved by repeated use of the same individual through sequential trial emulation or cloning.
- The target trial framework can be seen as the general version of many common study designs.

Introduction

Randomized trials with primary data collection are the preferred approach for causal inference. 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 of routinely collected healthcare data to answer causal questions. Causal inference from observational data can be viewed as an attempt to emulate a pragmatic randomized trial[1] —the target trial[2]— that would answer the causal question of interest.

Specifying the target trial protocol is a natural device to articulate a well-defined *causal question,* or *causal estimand*[2]. 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.

While the emulation cannot eliminate unmeasured confounding due to lack of randomization, it eliminates other biases that often arise in observational studies of medical treatments, such as immortal time and selection bias[3-5]. These biases result from an incorrect emulation that does not set the start of follow-up (time zero) as the time when an individual satisfies the eligibility criteria and is assigned to a treatment strategy. This lack of synchronization of eligibility and assignment at time zero is more frequent in settings in which individuals meet the eligibility criteria at multiple times or have data compatible with assignment to more than one treatment regime.

Here, we describe how to correctly synchronize eligibility and treatment assignment at time zero when emulating a target trial. We provide an illustration with three target trials of increasing complexity. We also describe how the target trial framework is the general version of many common study designs.

Specifying and emulating the target trial

Table 1 outlines the protocol of three target trials to estimate the effect of diabetes treatment on mortality among individuals with type 2 diabetes who have not been previously treated. These trials have been chosen to illustrate different settings regarding eligibility and treatment assignment.

Suppose we want to emulate the target trials outlined in **Table 1** using a large healthcare database that includes information on eligibility criteria and clinical characteristics, treatment prescriptions, and mortality in individuals with diabetes. The validity of the target trial emulation critically depends on having sufficient information on baseline confounders in the database. Otherwise, the target trial emulation would result in biased estimates of the effect of assignment to the treatment (the intention-to-treat effect). However, this paper focuses on common biases other than confounding. Therefore, for simplicity and to isolate the problem under study, we will temporarily assume that the database includes sufficient information on confounders.

A key decision in the emulation process is choosing a time interval (e.g., hours, days, weeks, months) that is 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 need to:

1. Determine at which intervals the individual meets the eligibility criteria.
2. Assign, at each eligible interval, the individual to the treatment strategies that are compatible with their observed information.
3. Set the start of follow-up (time zero) for each individual as the time when the individual meets the eligibility criteria and is assigned to one of the treatment strategies of interest.

Let us review this procedure for each of the target trials in **Table 1**, using the patient in **Figure 1** as an example.

Target trial 1: Eligibility met once, assignment to one strategy

The simplest emulation setting arises when a) individuals can only meet the eligibility criteria for the target trial once in their lifetime, and b) the observational data at the time of eligibility are compatible with assignment to only one of the treatment strategies. This is the situation in Target trial 1: Individuals can only be eligible during the month following their diabetes diagnosis and, during that month, it can be determined whether they do or do not start treatment.

The first step is to determine in which interval, if any, each individual is eligible. In **Figure 1**, the example person is only eligible during interval t_3 (the month following the diabetes diagnosis). The second step is to determine whether, at the eligible interval, the individual has data compatible with any of the treatment strategies. In **Figure 1**, the example person is not prescribed treatment

during the eligible interval t_3. Therefore, the person's data are compatible with the assignment to the treatment strategy "*Never start metformin (…)*". Follow-up is then started at t_3 (**Figure 2A**). Importantly, assignment to a treatment strategy must be determined based on information available at the eligible interval. Even though the person starts metformin at t_5, future information should not influence treatment assignment at t_3 to prevent immortal time[6].

Note that being eligible does not always imply that the person is included in the analysis. If we replace the treatment strategy "*Never start metformin (…)*" with "*Start SGLT-2 inhibitor (…)*, then the example patient in **Figure 1** has data incompatible with both treatment strategies under comparison, since he does not start metformin nor SGLT-2 inhibitor treatment during the eligible interval.

Target trial 2: Eligibility met multiple times, assignment to one strategy

Let us now consider the setting in which individuals can meet the eligibility criteria at multiple times. This is the case in Target trial 2: Individuals are eligible during the three months following their diabetes diagnosis. The example person in **Figure 1** is therefore eligible at intervals t_3 through t_5. Furthermore, he has data compatible with assignment to the treatment strategy "*Never start metformin (…)*" at t_3 and t_4, and with assignment to the strategy "*Start metformin (…)*" at t_5. 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[7,8] (**Supplemental Figure 1**). For instance, we could randomly select t_3 for the example person. A more statistically efficient option is to use all time zeros[2,9]. To do so, we

construct an expanded dataset to which each person contributes as many replicates as time zeros. As illustrated in **Figure 2B**, the example person would have three replicates which start follow-up at three different times. That is, we would emulate a sequence of target trials with different time zeros (sequential trial emulation)[10].

Meeting the eligibility criteria at multiple times does not necessarily result in multiple time zeros. For some target trials, individuals are eligible multiple times but are assigned to a treatment strategy only once. This occurs when emulating target trials with head-to-head comparisons of two or more treatments (as opposed to a comparison of treatment vs. no treatment). In such cases a sequential emulation approach is not required.

Target trial 3: Eligibility met once, assignment to multiple strategies

Let us now consider the setting in which a) individuals can only meet the eligibility criteria for the target trial once in their lifetime, and b) the observational data at the time of eligibility may be compatible with assignment to more than one of the treatment strategies. Condition b) occurs when the treatment strategies are not distinguishable at time zero, like in Target trial 3 with the strategies "*Start metformin within 3 months (…)*" and "*Never start metformin (…)*". Because of the 3-month grace period, an eligible individual who does not start metformin could be following either strategy. In **Figure 1**, the example person is eligible only during t_3 and does not start metformin during that interval. Therefore, the person's data are compatible with both strategies. Again, we cannot use information during t_5 to determine treatment assignment during t_3, since the use of future information introduces immortal time.

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 the individual to a single strategy. Another approach is assigning the individual to all compatible strategies. To do so, we construct an expanded dataset to which each person contributes as many clones as compatible strategies, which is visually shown in **Figure 2C**. Our example individual would be replaced by two clones starting follow-up at t_3. The first clone is assigned to the first treatment strategy, and the second clone to the second treatment strategy.

However, cloning makes it impossible to study the effect of treatment assignment (the intention-to-treat effect) because the same individuals may be assigned to both strategies. Therefore, when cloning, the effect of interest is typically the effect of adhering to the assigned treatment strategies during all or part of the follow-up (a per-protocol effect). This can be achieved by censoring the clones at deviation from the assigned treatment strategy and adjusting for time-varying confounders via inverse-probability weighting[11,12]. For the example patient, the second clone would be censored during t_5 since metformin is then initiated (**Figure 2C**), and the clone thus no longer adheres to the strategy "*Never start metformin (…)*". Censoring and inverse probability weighting can also be applied to the other target trials when interested in per protocol effects of sustained treatment strategies (**Figures 2A-B**).

Connections to previously proposed approaches

The explicit emulation of a specified target trial provides a general framework to address a large number of research questions. Many previously proposed designs are instances of target trial emulation. For example, the incident user design[13,14] was proposed to compare treatment initiation

vs. no initiation, the active comparator new user design[15,16] for head-to-head comparisons, the prevalent new user design[17,18] to compare treatment switching vs. not switching. The target trial framework covers a wide range of research questions, including those addressed by these study designs as well as others (e.g., our third target trial example).

Table 2 shows references from the literature with typical research questions. We converted these questions to simplified target trial protocols with specification of eligibility criteria and treatment strategies. These are then tied to the appropriate emulation approach using the flowchart outlined in **Figure 3**. These examples illustrate that seemingly small but key differences in eligibility criteria or treatment strategies require different procedures during emulation. Therefore, it is important to start with precisely specifying these aspects before following our emulation procedure.

Discussion

The target trial framework[2,19,20] is a unifying tool to design observational analyses that aim to estimate causal effects. The investigator's task is to first ask a causal question by specifying the target trial and then providing an answer by emulating the target trial with observational data. Following the procedure in this paper ensures proper alignment of eligibility and assignment of treatment strategies at the start of follow-up. This prevents design-induced biases such as immortal time and selection biases in observational studies.

However, synchronization of eligibility and assignment does not prevent the possibility of confounding if the groups of individuals assigned to each strategy differ in the distribution of prognostic factors. Therefore, the validity of the target trial emulation depends on sufficient

adjustment for these potential baseline confounders[21,22]. Moreover, details on estimating intention-to-treat or per protocol effects can be found elsewhere[23-25].

Our hope is that this guide will help clinical researchers to design methodologically sound observational studies that answer important causal questions in the absence of or to supplement randomized trial evidence.

Contributor and guarantor information

ELF conceived the paper, and drafted an initial version. 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.

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Table 1. Specification of the target trial protocols for three different target trials.

	Target trial 1	**Target trial 2**	**Target trial 3**
Eligibility criteria	– Diagnosis of type 2 diabetes *in the previous month* – No previous use of diabetes treatments	– Diagnosis of type 2 diabetes *in past 3 months* – No previous use of diabetes treatments	– Diagnosis of type 2 diabetes diagnosis *in the previous month* – No previous use of diabetes treatments
Treatment strategies	1. Start metformin and continue use unless contra-indications arise 2. Never start metformin unless indications arise	1. Start metformin and continue use unless contra-indications arise 2. Never start metformin unless indications arise	1. Start metformin within 3 months of diabetes diagnosis and continue use unless contra-indications arise 2. Never start metformin unless indications arise
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 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).		
Data analysis	Intention-to-treat analysis. Per protocol analysis.		

Table 2. Examples of target trials and their emulations.

References	Specification of elements of target trial protocol		Time zeros per person	Treatment assignment per time zero	Emulation approach
26-29	TS1	Start treatment A	One	One	
	TS2	Start treatment B			
	E	Not having received A or B previously			
30	TS1	Start and always use treatment A			
	TS2	Start and always use treatment B			
	E	Not having received A or B previously			
10,17,31	TS1	Start treatment A	Multiple	One	Sequential trial emulation
	TS2	Do not start treatment A			
	E	No prior use of treatment A			
31-34	TS1	Start and always use treatment A			
	TS2	Never start treatment A			
	E	No prior use of treatment A			
35,36	TS1	Start treatment A within *t* months after event Y	One	Multiple	Clone-censor-weight
	TS2	Do not start treatment A within *t* months after event Y			
	E	Moment event Y occurs (e.g. diagnosis)			
37-39	TS1	Stop treatment A within *t* months after event Y			
	TS2	Do not stop treatment A within *t* months after event Y			
	E	Moment event Y occurs (e.g. adverse event)			
40	TS1	Reach target within *t* months after start of treatment A			
	TS2	Do not reach target within *t* months after start of treatment A			
	E	Moment event Y occurs (e.g. diagnosis)			
41	TS1	Start treatment A and receive for t_1 months			
	TS2	Start treatment A and receive for t_2 months			
	E	Moment event Y occurs (e.g. diagnosis)			
42-49	TS1	Start treatment A when event Y_1 occurs	Multiple	Multiple	Sequential clone-censor-weight emulation
	TS2	Start treatment A when event Y_2 occurs			
	E	No prior use of treatment A			

TS1 = treatment strategy 1; TS2 = treatment strategy 2; E = eligibility criteria.

Figure 1. Visual depiction of the emulation procedure for the example person in each of the three target trials.

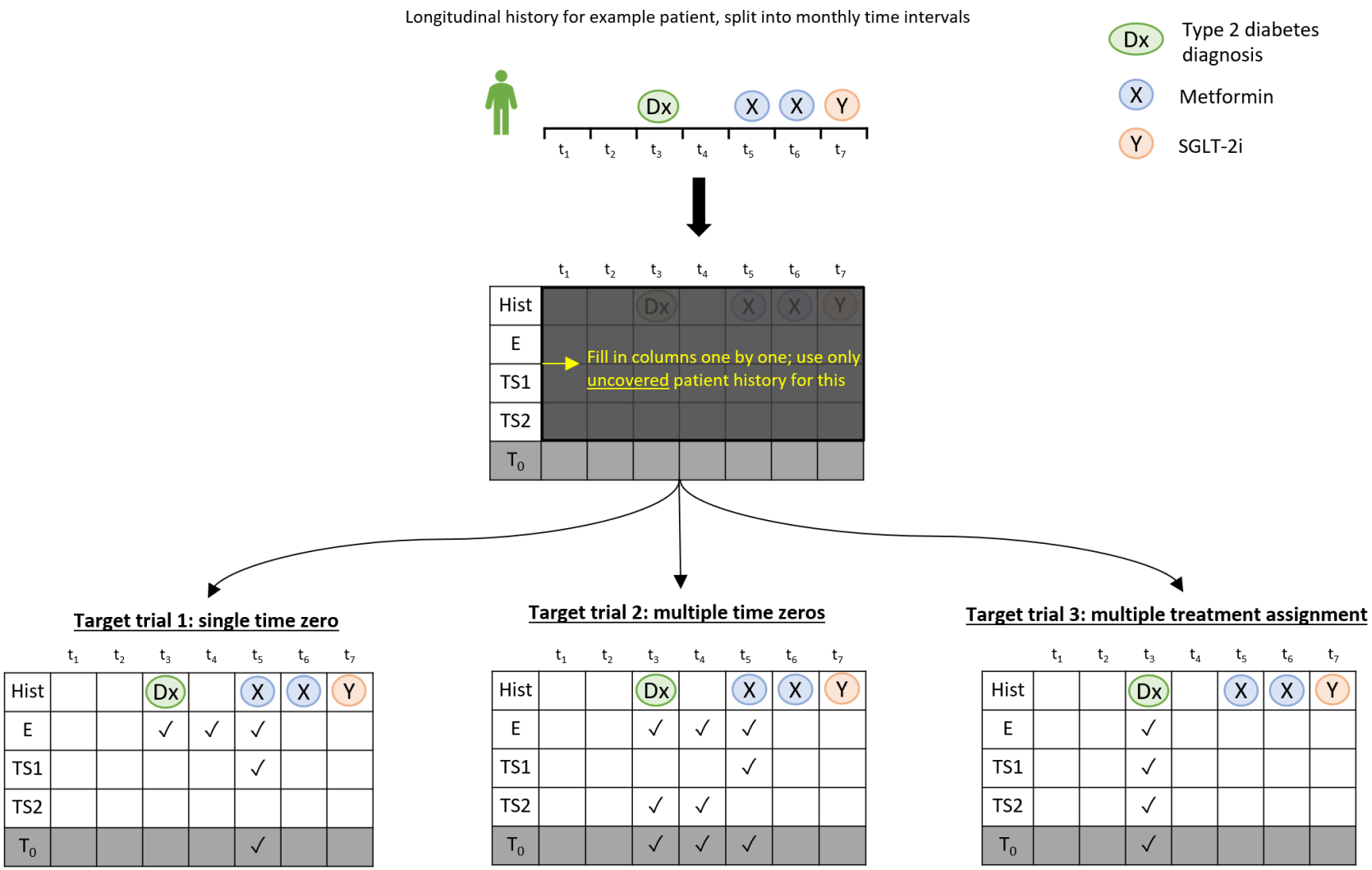
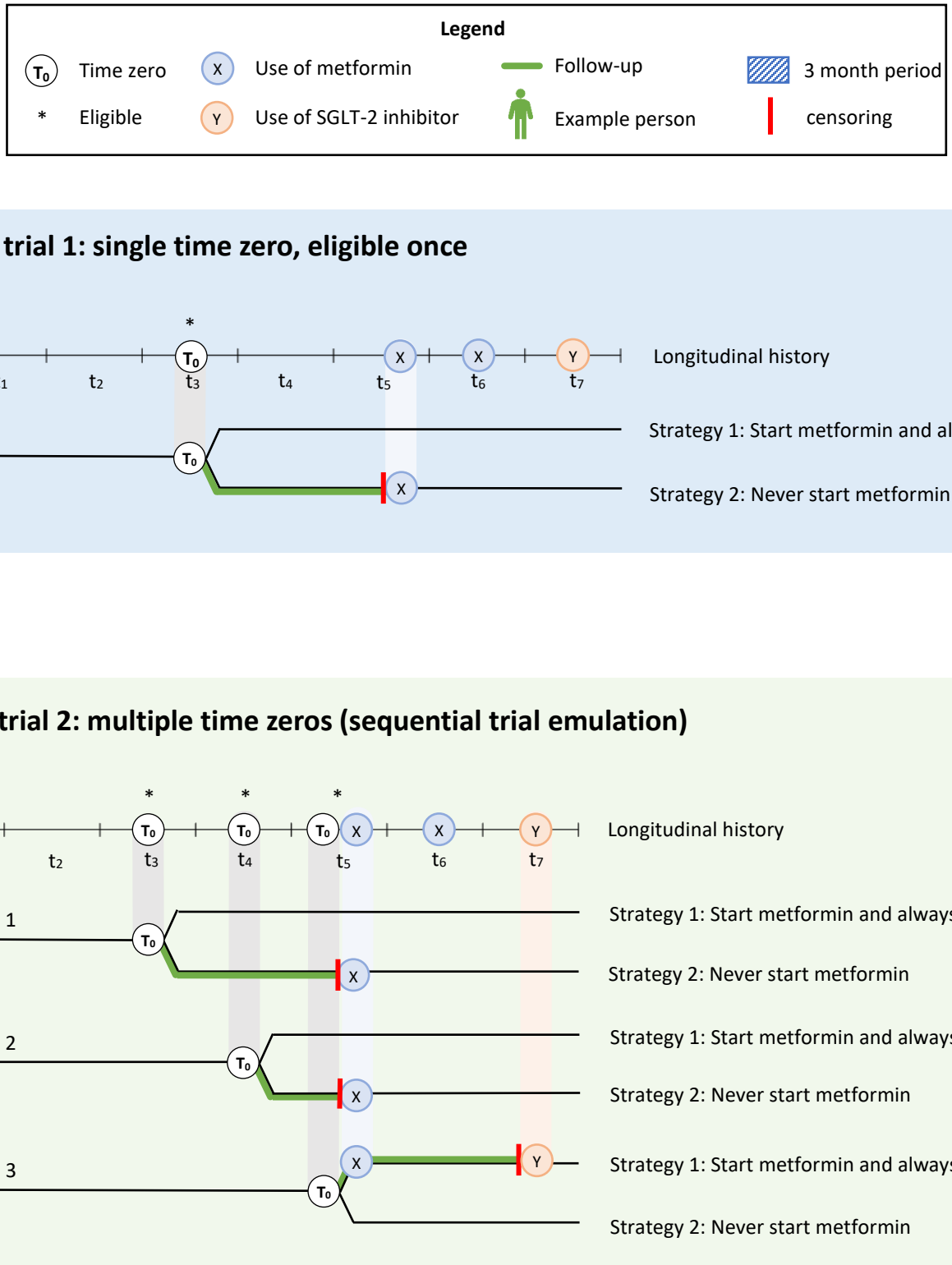


Figure legend: E = eligibility; Hist = longitudinal history of example individual; t_1-t_9 = time interval 1-9; TS1 = treatment strategy 1; TS2 = treatment strategy 2; T_0 = time zero. For each interval, we check whether the example patient meets all eligibility criteria, can be assigned to one of the treatment strategies, and set time zero as the time of treatment assignment. Importantly, one needs to fill in the columns one by one and ensure that only patient history up until the particular interval is used; the use of future information introduces immortal time.

Figure 2. Graphical depiction of emulation of the three target trials using the example person.



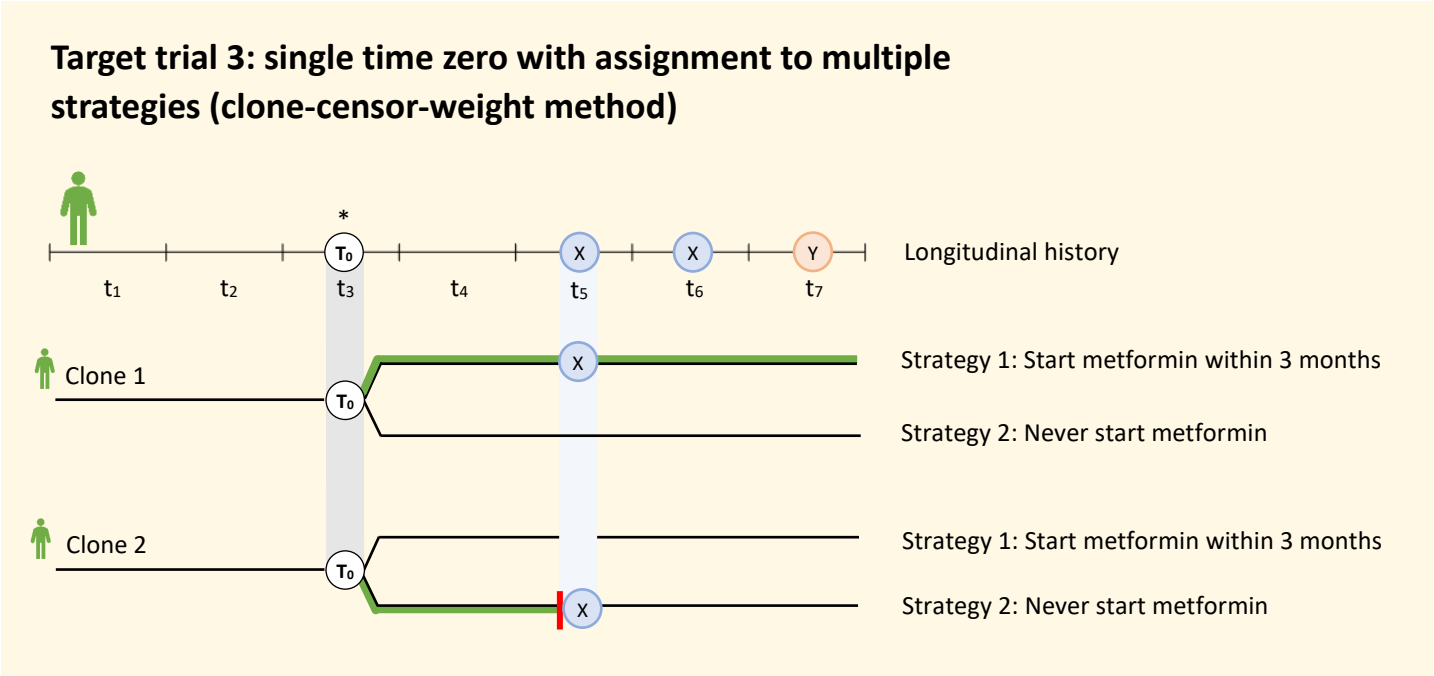


Figure legend: Note that the treatment strategies have been abbreviated for improved readability. Both sequential trials and cloning make repeated use of the same individual. However, whereas the start of follow-up occurs at different times for each of the replicates in sequential trials, it occurs at the same time for the clones in the clone-censor-weight design. In the examples, patients are censored (i.e. follow-up is stopped) when they no longer follow their assigned treatment strategy. When the interest is in the effect of treatment assignment (the intention to treat effect), patients should not be censored. Cloning (as in target trial 3) always needs to be combined with censoring.

Figure 3. Roadmap from target trial specification to its emulation, illustrated with the second target trial.

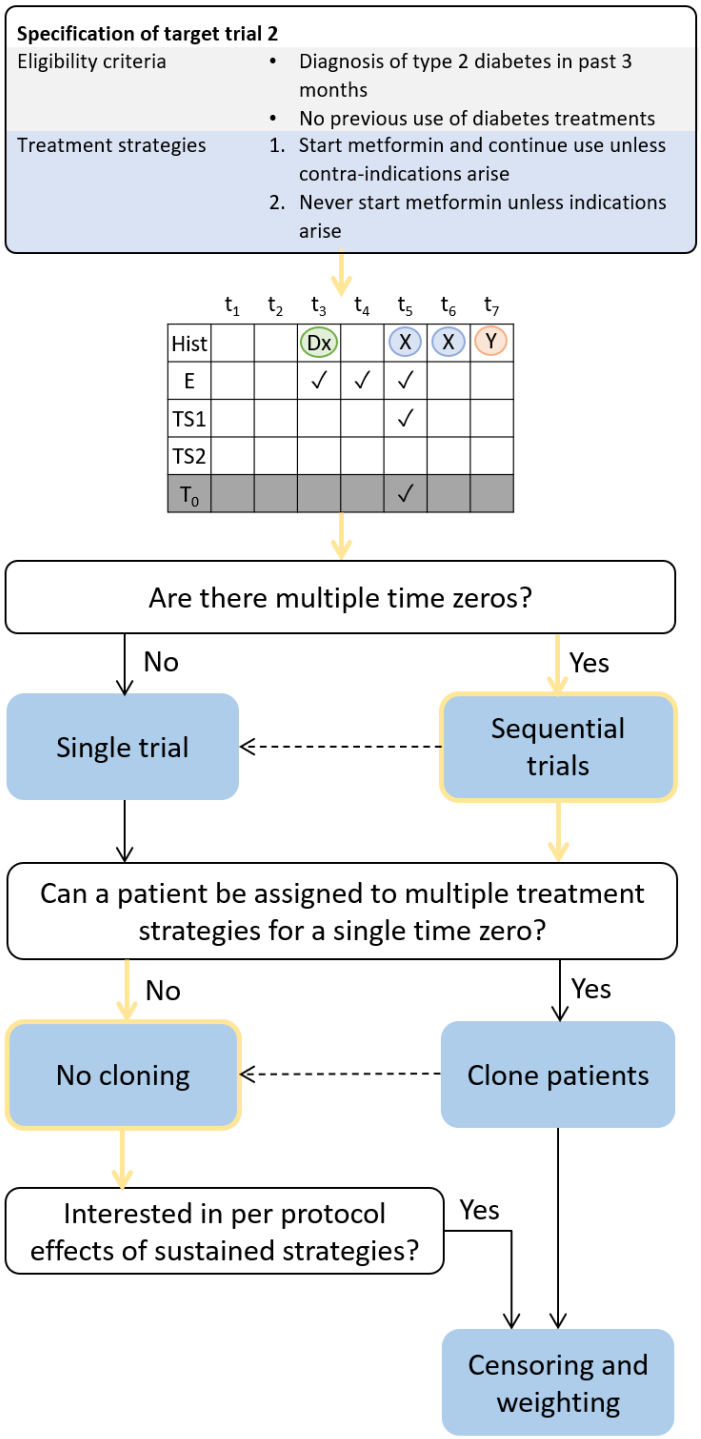
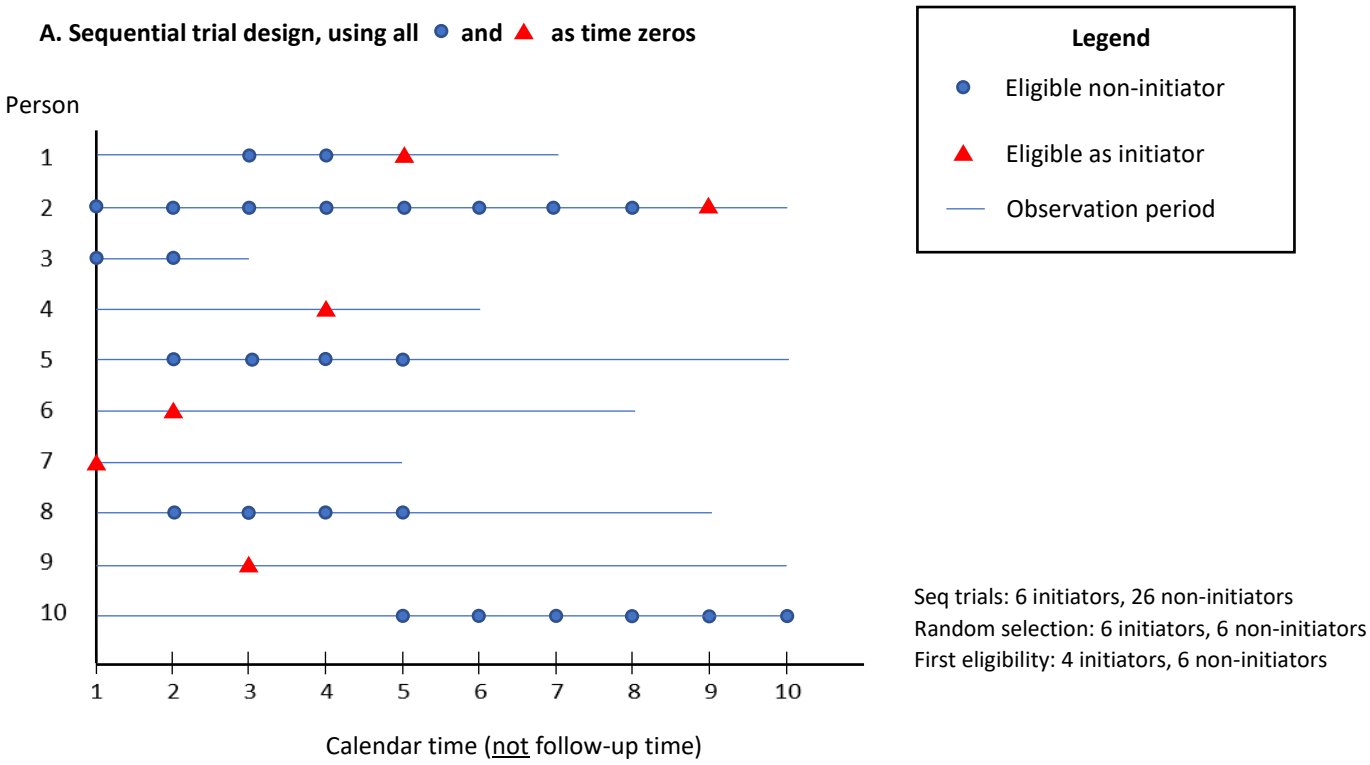
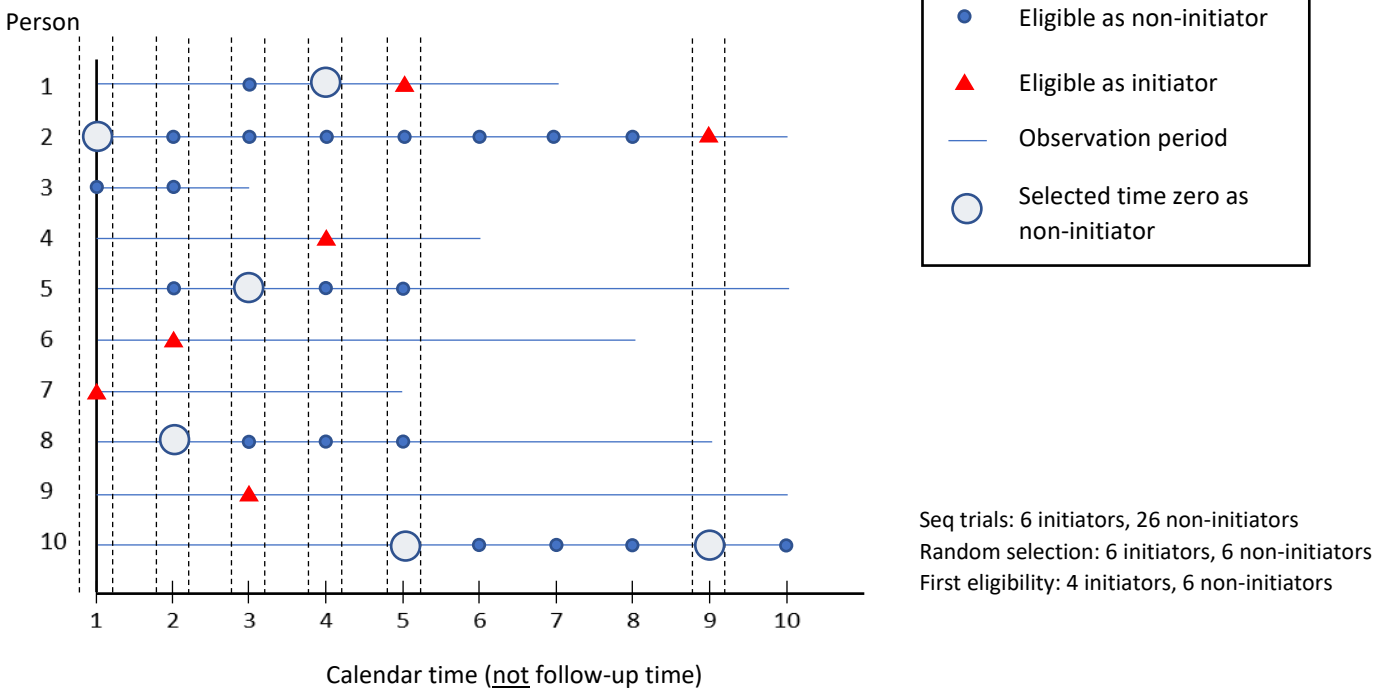


Figure legend: Dotted lines indicate that an investigator can make a choice during the emulation process: a single time zero per person can be chosen instead of using all time zeros, and persons can be randomly assigned to one of the strategies rather than using cloning.

Supplemental Figure 1. (A) Sequential trial design; (B) random selection of non-initiator every time an initiator is included; (C) including every individual at first eligibility.





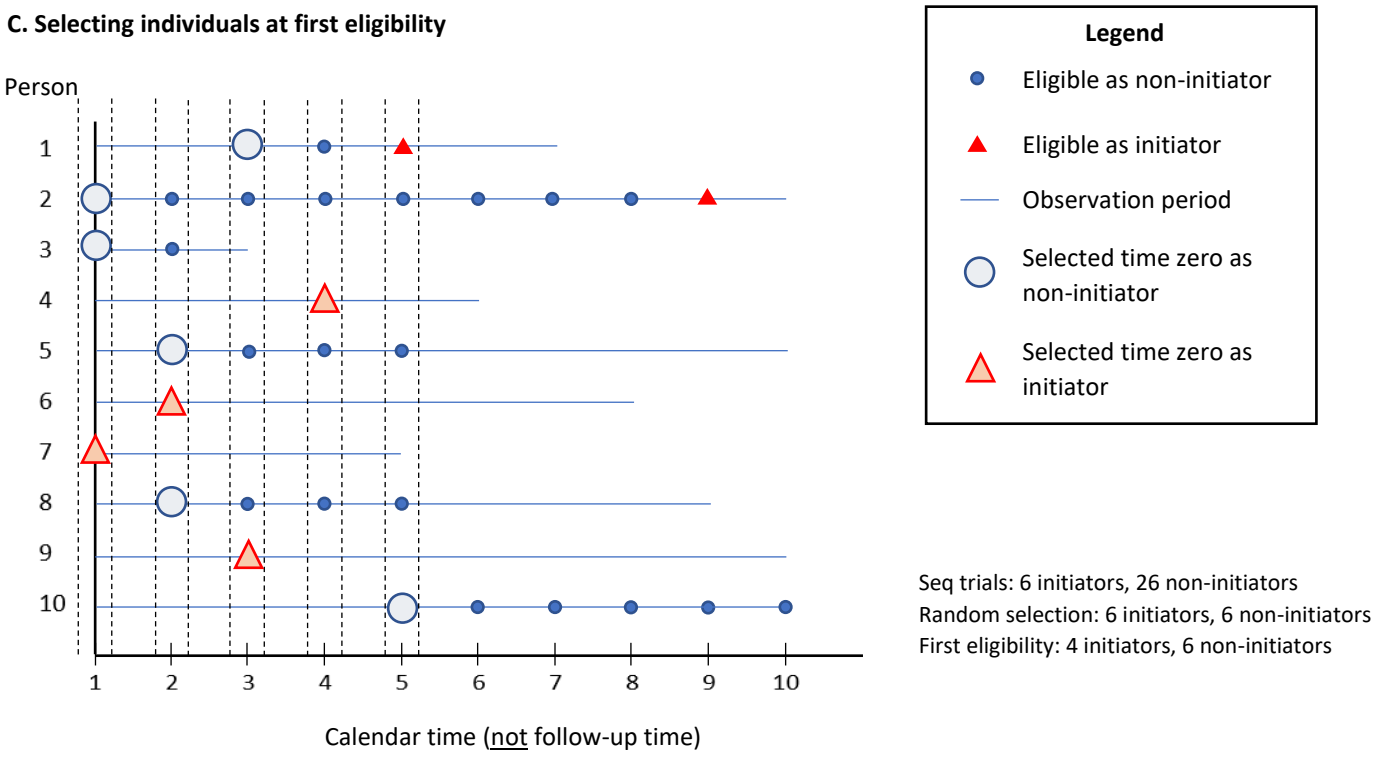


Figure legend:

- Note that initiators can be selected as non-initiator (person 4) before treatment initiation.
- In the figure, the ratio initiators to non-initiators is 1:1, but this matching ratio can be varied, e.g. 1:5 or 1:10.
- A particular non-initiator can be matched once or multiple times (i.e., with or without replacement).
- Additional matching criteria can be enforced, such as same age, sex or propensity score.

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. 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.
3. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* 2008;167:492-9. doi: 10.1093/aje/kwm324.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
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. 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.
12. 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.
13. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;158:915-20. doi: 10.1093/aje/kwg231.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.

19. Hernan MA. Methods of Public Health Research - Strengthening Causal Inference from Observational Data. *N Engl J Med* 2021;385:1345-48. doi: 10.1056/NEJMp2113319.
20. 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.
21. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ* 2019;367:l5657. doi: 10.1136/bmj.l5657.
22. Greifer N, Stuart EA. Matching Methods for Confounder Adjustment: An Addition to the Epidemiologist's Toolbox. *Epidemiol Rev* 2022;43:118-29. doi: 10.1093/epirev/mxab003.
23. Hernan MA, Hernandez-Diaz S. Beyond the intention-to-treat in comparative effectiveness research. *Clin Trials* 2012;9:48-55. doi: 10.1177/1740774511420743.
24. 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.
25. 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.
26. Fu EL, Clase CM, Evans M, et al. Comparative Effectiveness of Renin-Angiotensin System Inhibitors and Calcium Channel Blockers in Individuals With Advanced CKD: A Nationwide Observational Cohort Study. *Am J Kidney Dis* 2021;77:719-29 e1. doi: 10.1053/j.ajkd.2020.10.006.
27. Dickerman BA, Gerlovin H, Madenci AL, et al. Comparative Effectiveness of BNT162b2 and mRNA-1273 Vaccines in U.S. Veterans. *N Engl J Med* 2022;386:105-15. doi: 10.1056/NEJMoa2115463.
28. Poelemeijer YQM, Liem RSL, Vage V, et al. Gastric Bypass Versus Sleeve Gastrectomy: Patient Selection and Short-term Outcome of 47,101 Primary Operations From the Swedish, Norwegian, and Dutch National Quality Registries. *Ann Surg* 2020;272:326-33. doi: 10.1097/SLA.0000000000003279.
29. Desai RJ, Patorno E, Vaduganathan M, et al. Effectiveness of angiotensin-neprilysin inhibitor treatment versus renin-angiotensin system blockade in older adults with heart failure in clinical care. *Heart* 2021;107:1407-16. doi: 10.1136/heartjnl-2021-319405.
30. Xie Y, Bowe B, Gibson AK, et al. Comparative Effectiveness of Sodium-Glucose Cotransporter 2 Inhibitors vs Sulfonylureas in Patients With Type 2 Diabetes. *JAMA Intern Med* 2021;181:1043-53. doi: 10.1001/jamainternmed.2021.2488.
31. 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.
32. 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.
33. 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.
34. 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.
35. 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.
36. 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.

37. 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.
38. 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.
39. 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.
40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. 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.
46. Garcia-Albeniz X, Hsu J, Bretthauer M, Hernan MA. Effectiveness of Screening Colonoscopy to Prevent Colorectal Cancer Among Medicare Beneficiaries Aged 70 to 79 Years: A Prospective Observational Study. *Ann Intern Med* 2017;166:18-26. doi: 10.7326/M16-0758.
47. 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.
48. 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.
49. 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.