Leiden University
Medical Center

Starting right

Aligning eligibility and treatment assignment at time zero when emulating a target trial

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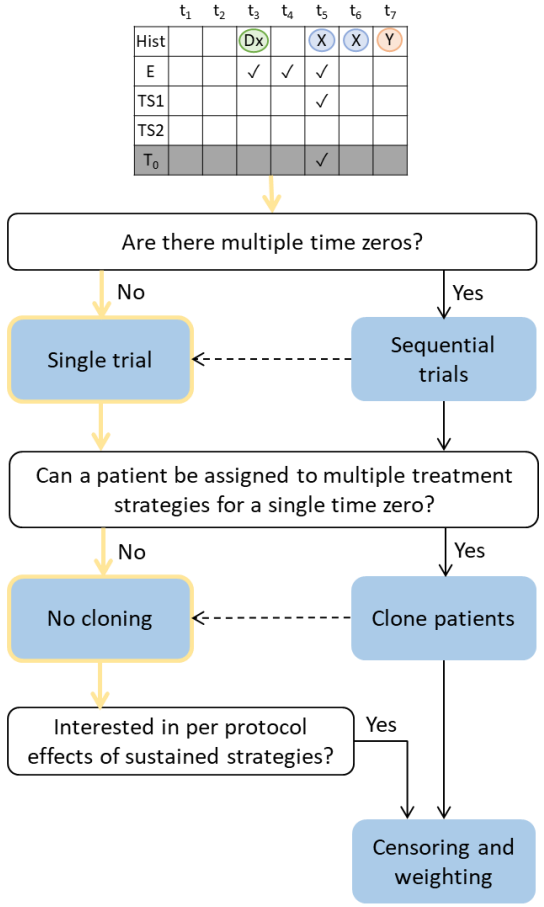
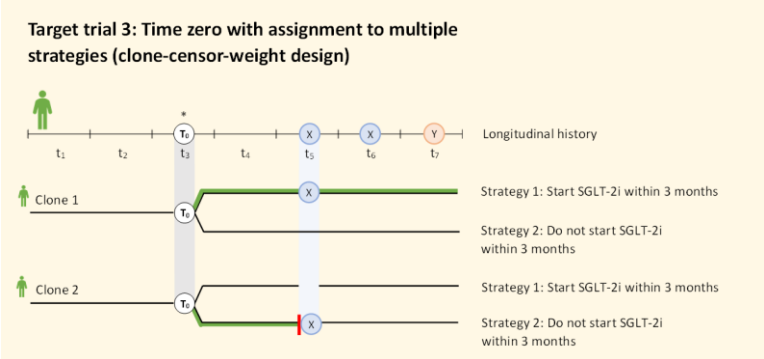
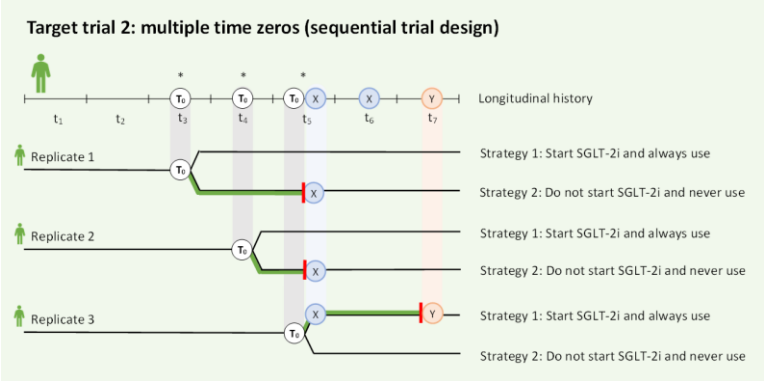
Talk based on

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

Edouard L. Fu[1,2], Michael O. Harhay[3], Sebastian Schneeweiss[1], Rishi J. Desai[1,*], Miguel A. Hernán[4,*]







What will we discuss today?

1. How to align eligibility and treatment assignment at time zero when emulating a target trial using a simple 3-step procedure

2. Why misalignment introduces immortal time bias or selection bias

3. How this procedure connects with clone-censor-weight, sequential trials and other designs such as active comparator new user designs

- This is going to be an interactive lecture

- Go to **classpoint.app** and fill in the classcode at the top right corner of this slide

Basic knowledge of target trial emulation

American Journal of Epidemiology

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Practice of Epidemiology

Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

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REVIEW www.jasn.org

JASN Journal of the American Society of Nephrology

Target Trial Emulation to Improve Causal Inference from Observational Data: What, Why, and How?

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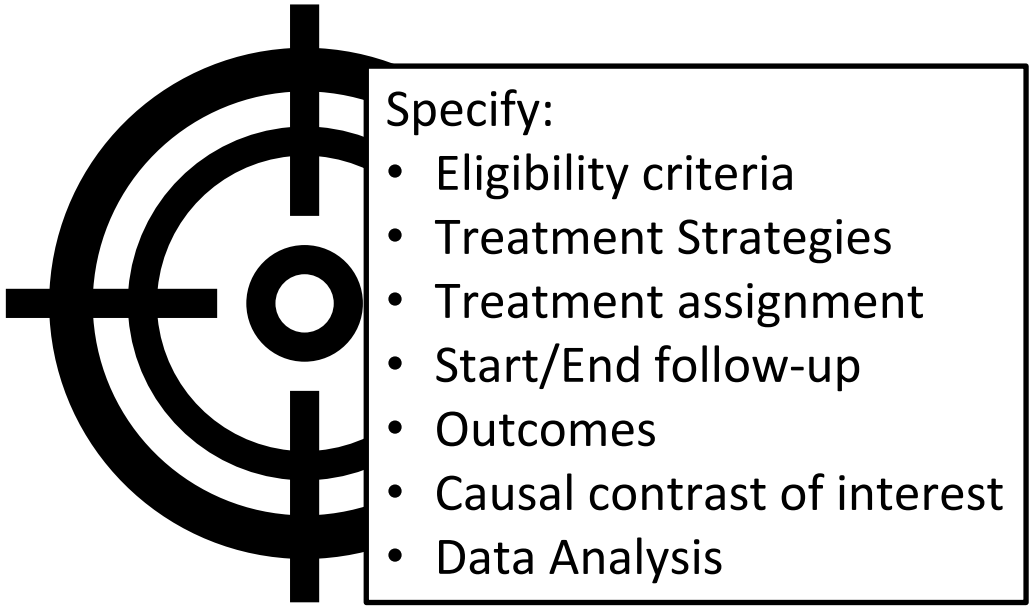
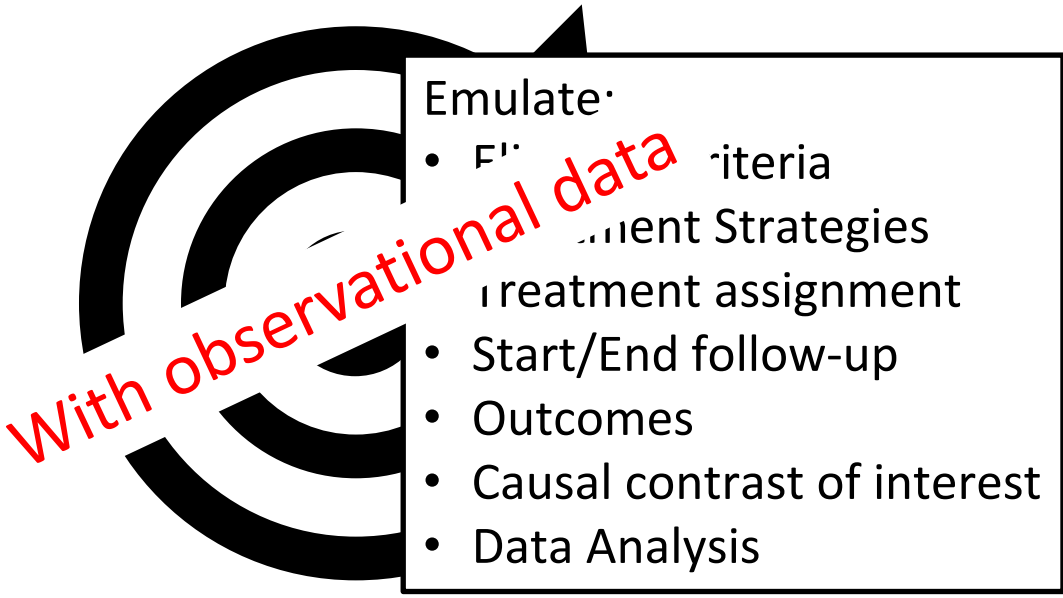
Target trial emulation framework



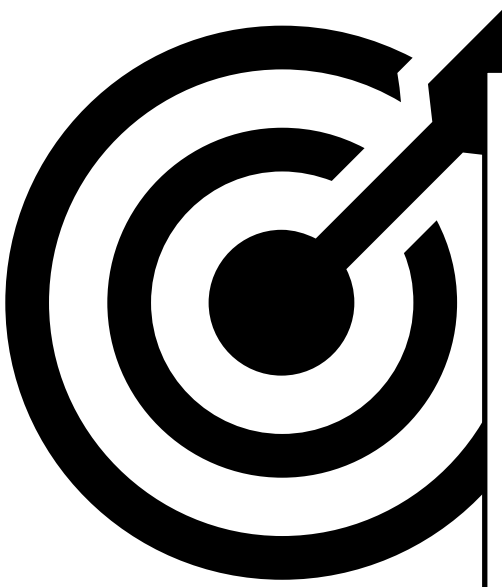
Target trial specification



Target trial emulation

Hernán et al. AJE 2016

Target trial emulation



Emulate:

- Eligibility criteria
- Treatment Strategies
- Treatment assignment
- Start/End follow-up
- Outcomes
- Causal contrast of interest
- Data Analysis

1. Make treatment groups correctly
2. Adjust for baseline & time-varying confounding
3. Estimate your treatment effect of interest

Target trial **emulation**

What target trial emulation is and what it is not

- Framework for designing & analyzing observational studies
- Specification step & emulation step
- Can be applied to every causal question on interventions

- A specific design (“sequential trials”, “clone-censor-weight”)

Specification of the target trial: the importance of being precise

Three hypothetical target trial specifications

What is the causal effect of metformin on all-cause mortality?

	Specification column		
	Target trial 1	**Target trial 2**	**Target trial 3**
Eligibility criteria	• Diagnosis of T2DM in past 3 months • No previous use of metformin or SGLT-2i	• Diagnosis of T2DM in past 3 months • No previous use of metformin	• Moment of type 2 diabetes diagnosis • No previous use of metformin
Treatment strategies	1. Start metformin and always use 2. Start SGLT-2i and always use	1. Start metformin and always use 2. Never start metformin	1. Start metformin within 3 months of diabetes diagnosis 2. Never start metformin

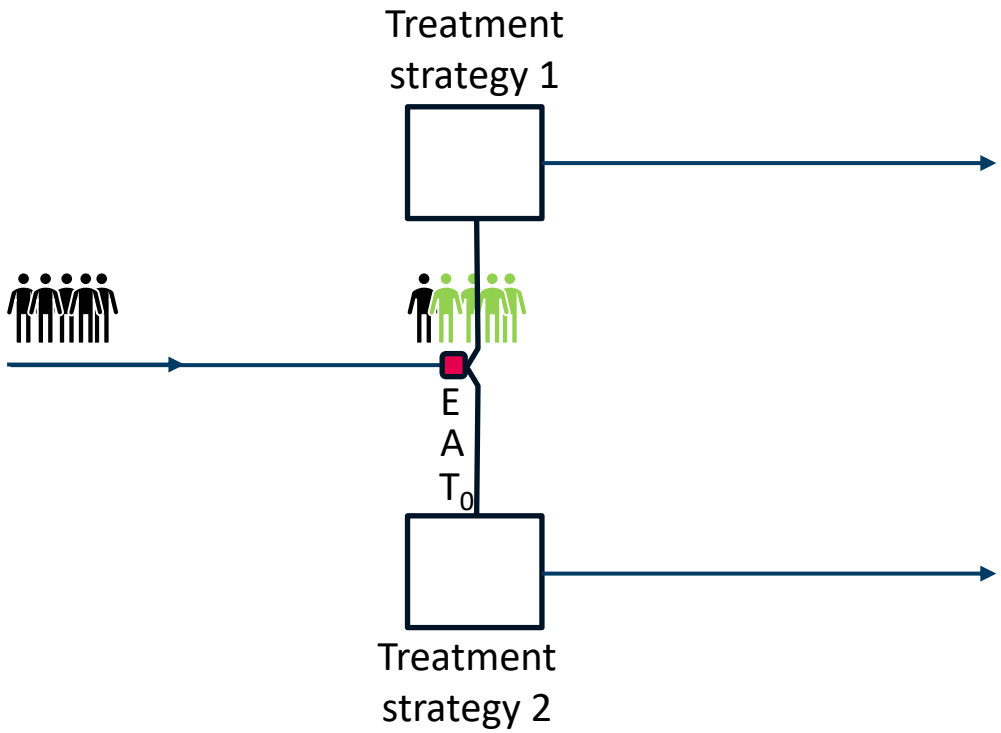
Other components are equivalent for each TT

	Specification column		
	Target trial 1	**Target trial 2**	**Target trial 3**
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 or estimand	Intention-to-treat effect (effect of treatment assignment). Per protocol effect (effect of following the assigned treatment strategy).		
Data analysis	Intention-to-treat analysis. Non-naïve per protocol analysis: individuals are artificially censored if they deviate from their assigned treatment strategy, and inverse probability weighting is used to adjust for informative censoring.		

Emulating the target trial: making treatment groups

Fundamental design principle

What happens in an RCT?



3 components must align:

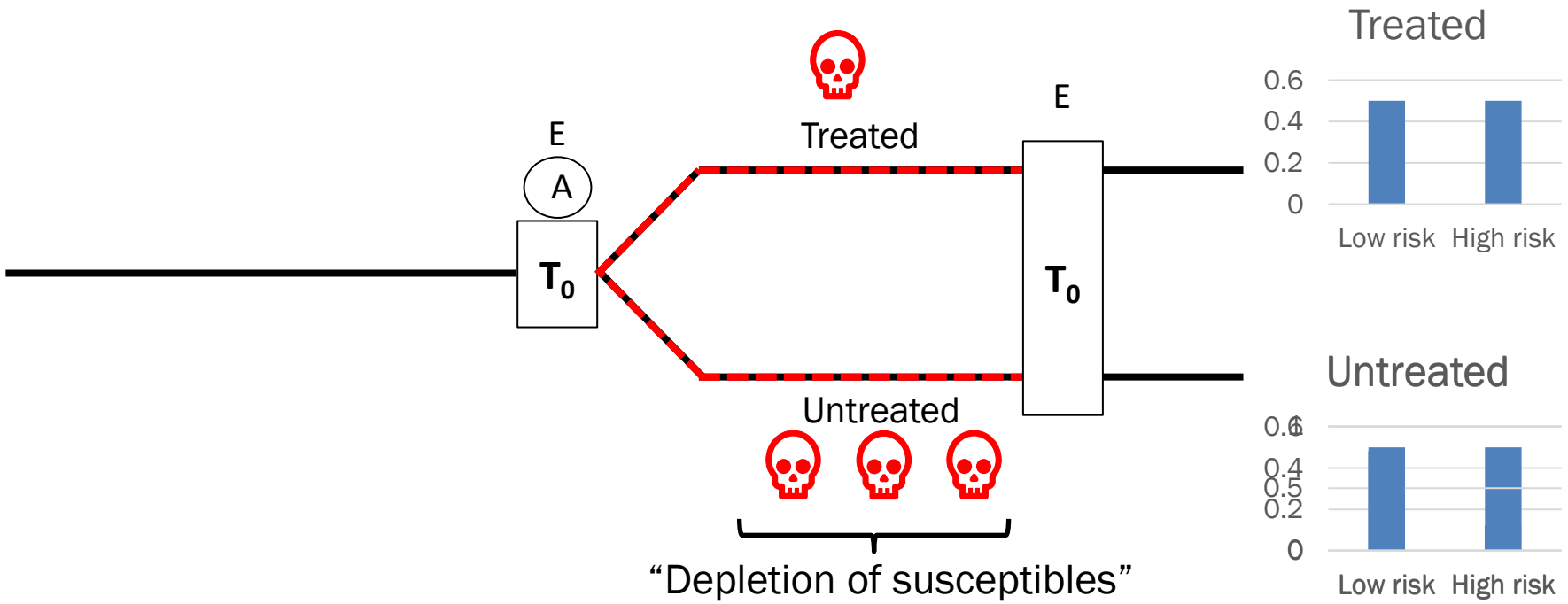
- Eligibility criteria are met (E)
- Assignment of treatment strategy (A)
- Start of follow-up (= **time zero**, T_0)

No alignment of these 3 components introduces bias

>50% of studies assessing the effects of medications with observational data do not follow this principle (Bykov et al. CPT 2022)

Immortal time bias or depletion of susceptibles bias (form of selection bias/collider stratification bias)

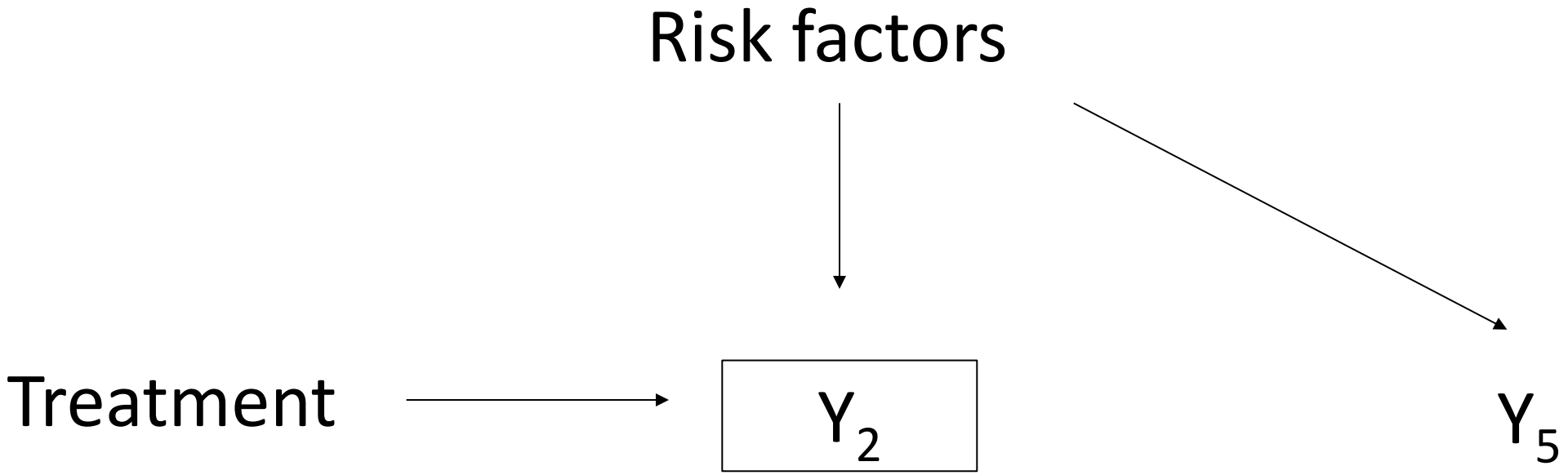
What happens if we start follow-up after treatment assignment?



If treatment is truly protective…

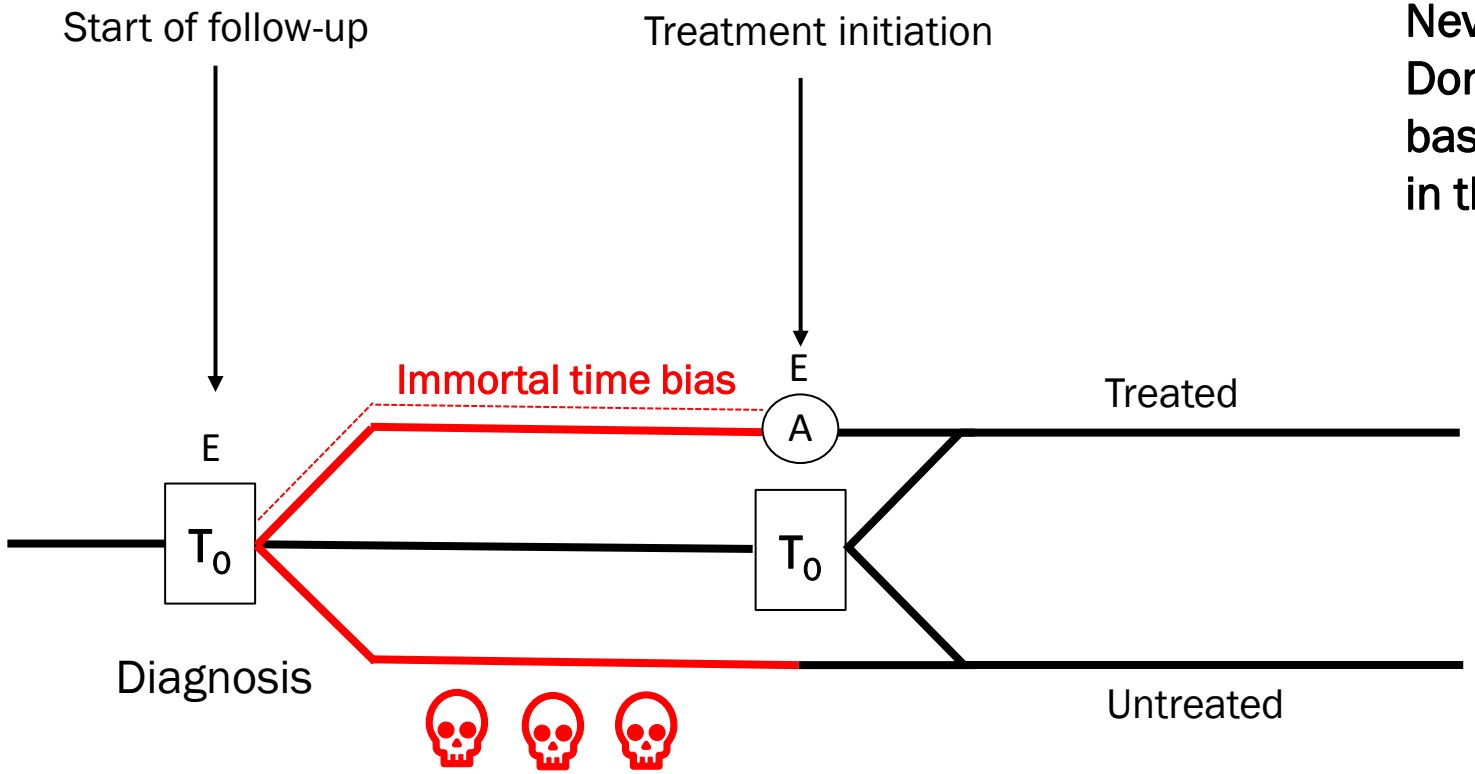
"Depletion of susceptibles bias" occurs whenever the start of follow-up is *after* treatment initiation (medication studies use "prevalent user bias"), and is a form of selection bias

Prevalent user bias = selection bias



What happens if we start follow-up *before* treatment assignment?

Observational cohort study



Never "peek into the future":
Don't classify patients into treatment arms based on treatment they receive in the future!

Immortal time bias occurs whenever the start of follow-up is *before* treatment initiation

How to make treatment groups correctly?

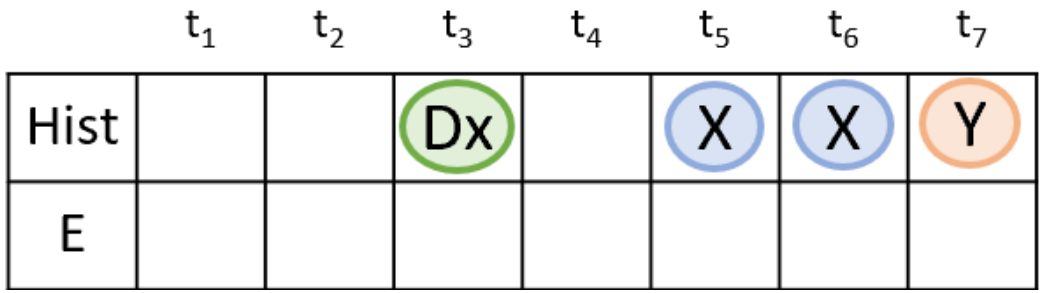
For each individual in the dataset, we need to:

1. Determine when individual meets eligibility criteria
2. At time of eligibility, assign individual to treatment strategies that are compatible with individual's data *without using future information*
3. Set start of follow-up (time zero) as time of treatment assignment

Target trial 1

1. Determine when the individual meets the eligibility criteria

Component	Target trial 1 specification
Eligibility	• Diagnosis of T2DM in past 3 months • No previous use of metformin or SGLT-2i
Treatment strategies	1. Start metformin and always use 2. Start SGLT-2i and always use



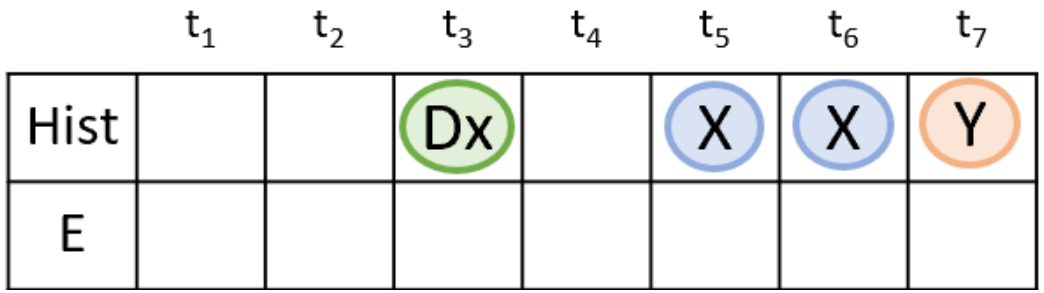
Dx T2DM diagnosis

X Filled prescription for metformin

Y Filled prescription for SGLT-2i

1. Determine when the individual meets the eligibility criteria

Component	Target trial 1 specification
Eligibility	• Diagnosis of T2DM in past 3 months • No previous use of metformin or SGLT-2i
Treatment strategies	1. Start metformin and always use 2. Start SGLT-2i and always use



A **B** **C** **D** **E** **F**

During which interval(s) is the patient eligible?

Multiple Choice

Dx T2DM diagnosis

X Filled prescription for metformin

Y Filled prescription for SGLT-2i

1. Determine when the individual meets the eligibility criteria

Component	Target trial 1 specification
Eligibility	• Diagnosis of T2DM in past 3 months • No previous use of metformin or SGLT-2i
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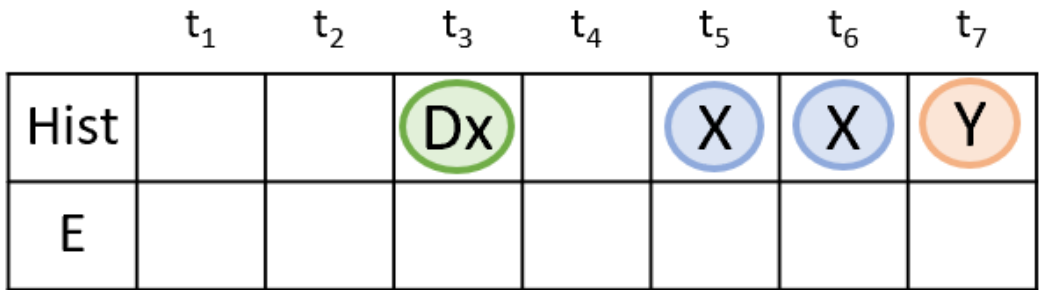


A B C D E F

During which interval(s) is the patient eligible?

Multiple Choice

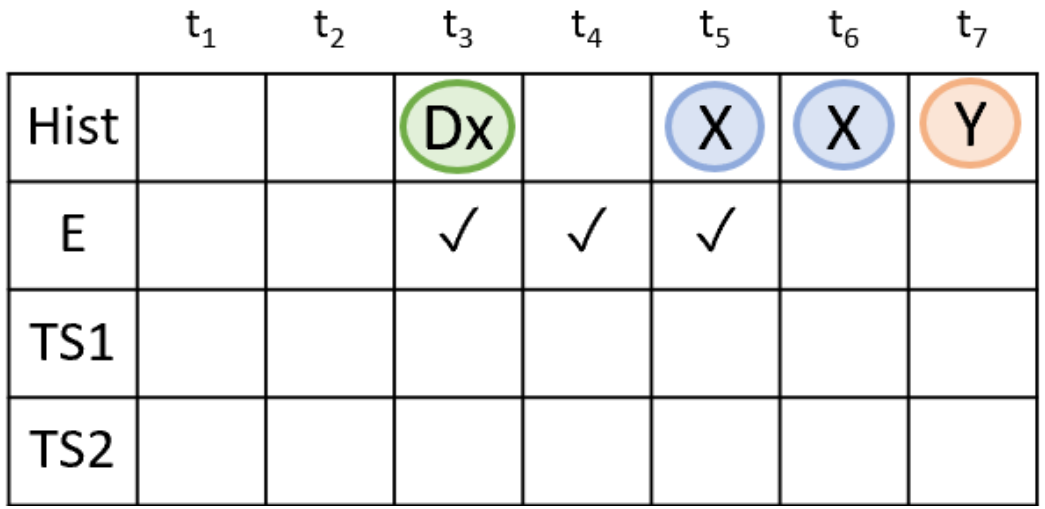
Dx T2DM diagnosis

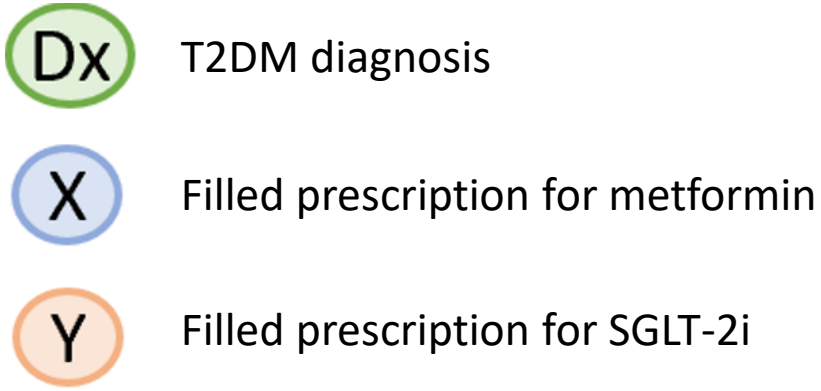
X Filled prescription for metformin

Y Filled prescription for SGLT-2i

2. At the time of eligibility, assign the individual to the treatment strategies that are compatible with the individual's data

Component	Target trial 1 specification
Eligibility	• Diagnosis of T2DM in past 3 months • No previous use of metformin or SGLT-2i
Treatment strategies	1. Start metformin and always use 2. Start SGLT-2i and always use





2. At the time of eligibility, assign the individual to the treatment strategies that are compatible with the individual's data

Component	Target trial 1 specification
Eligibility	• Diagnosis of T2DM in past 3 months • No previous use of metformin or SGLT-2i
Treatment strategies	1. Start metformin and always use 2. Start SGLT-2i and always use

	t_1	t_2	t_3	t_4	t_5	t_6	t_7
Hist			Dx		X	X	Y
E			✓	✓	✓		
TS1			**A**	**B**	**C**		
TS2			**D**	**E**	**F**		

Dx T2DM diagnosis

X Filled prescription for metformin

Y Filled prescription for SGLT-2i

To which strategy can the patient be assigned (choose A-F)?

Multiple Choice

2. At the time of eligibility, assign the individual to the treatment strategies that are compatible with the individual's data

Component	Target trial 1 specification
Eligibility	• Diagnosis of T2DM in past 3 months • No previous use of metformin or SGLT-2i
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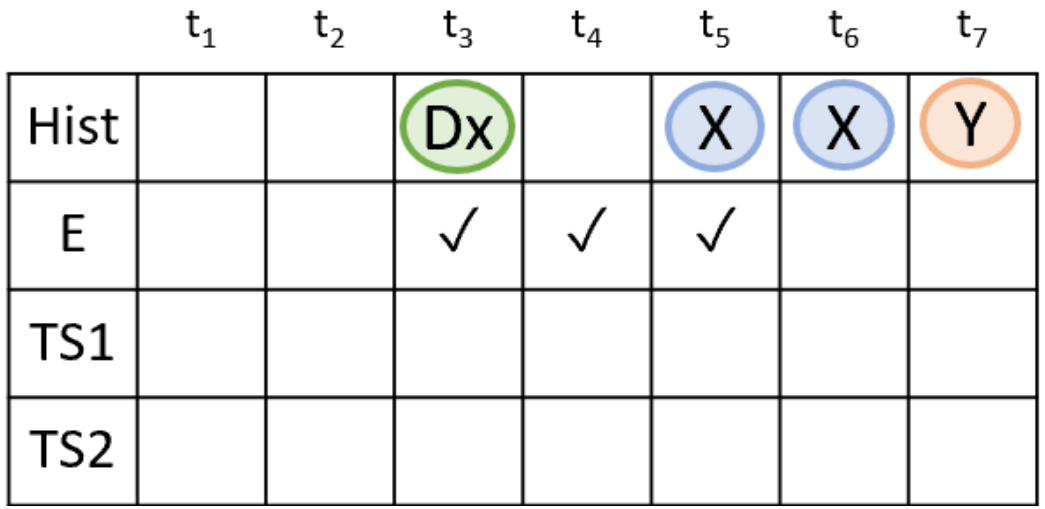


Dx T2DM diagnosis

X Filled prescription for metformin

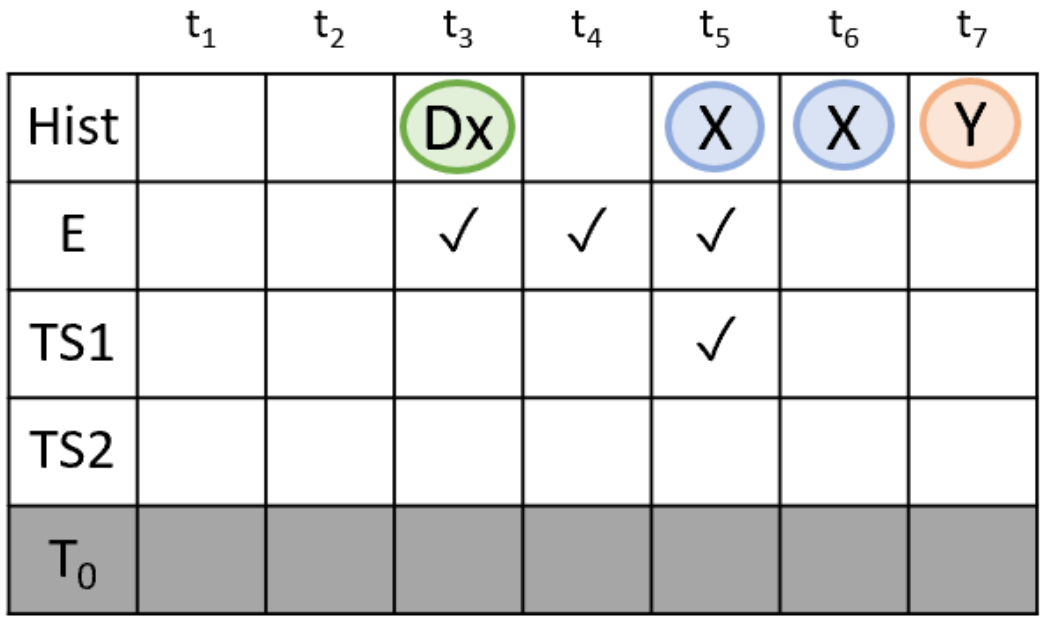
Y Filled prescription for SGLT-2i

To which strategy can the patient be assigned (choose A-F)?

Multiple Choice

3. Set the start of follow-up (time zero) as the time of treatment assignment

Component	Target trial 1 specification
Eligibility	• Diagnosis of T2DM in past 3 months • No previous use of metformin or SGLT-2i
Treatment strategies	1. Start metformin and always use 2. Start SGLT-2i and always use

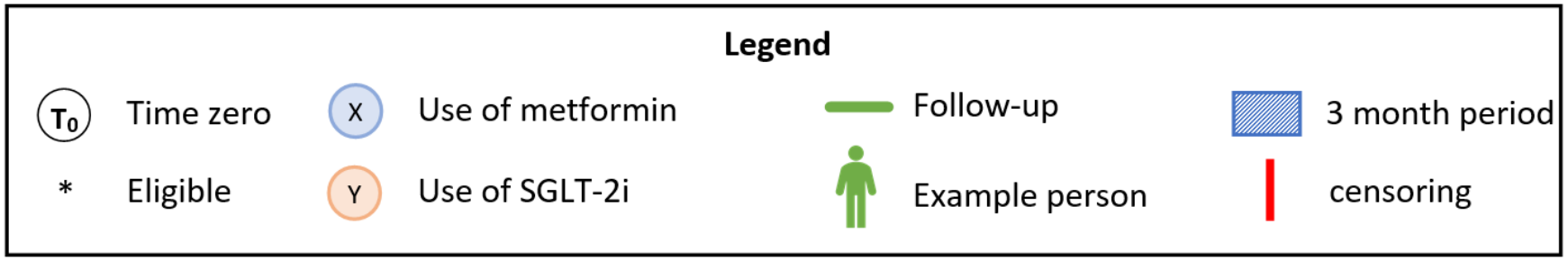


Dx T2DM diagnosis

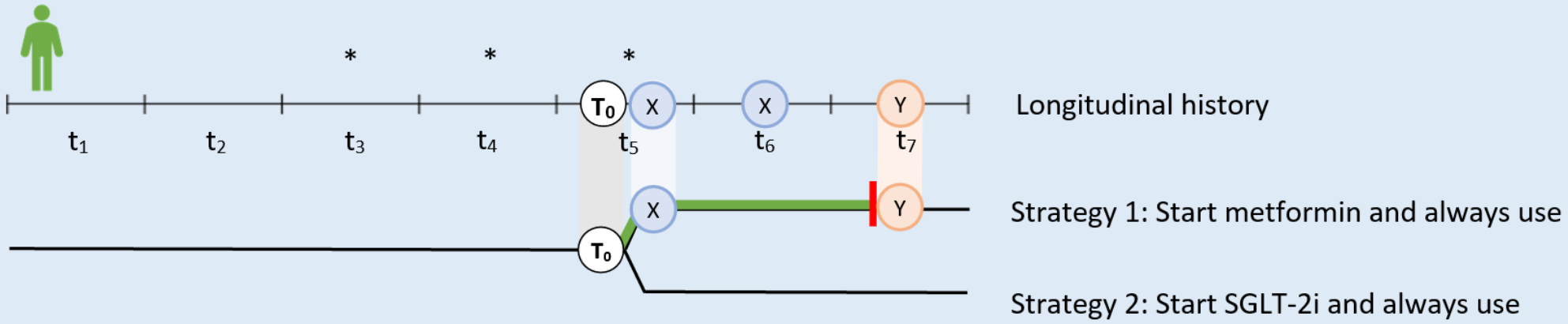
X Filled prescription for metformin

Y Filled prescription for SGLT-2i

Example person is assigned to first strategy



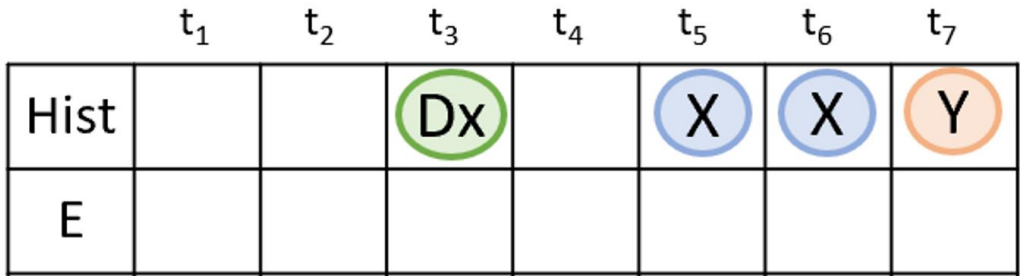
Target trial 1: single time zero, eligible multiple times

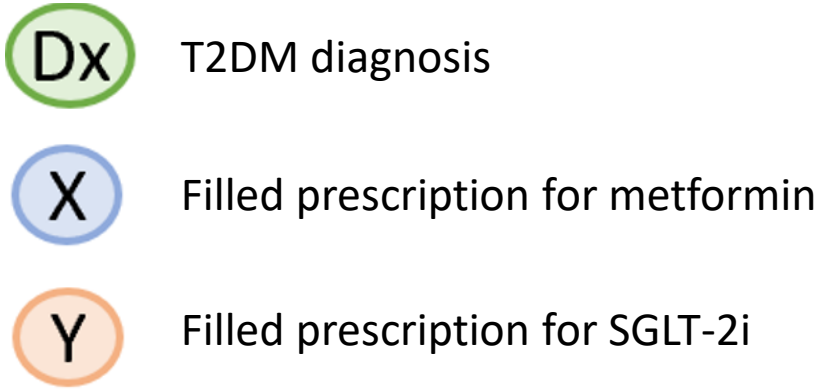


Target trial 2

1. Determine when the individual meets the eligibility criteria

Component	Target trial 2 specification
Eligibility	• Diagnosis of T2DM in past 3 months • No previous use of metformin
Treatment strategies	1. Start metformin and always use 2. Never start metformin





2. At the time of eligibility, assign the individual to the treatment strategies that are compatible with the individual's data

Component	Target trial 2 specification
Eligibility	• Diagnosis of T2DM in past 3 months • No previous use of metformin
Treatment strategies	1. Start metformin and always use 2. Never start metformin

	t_1	t_2	t_3	t_4	t_5	t_6	t_7
Hist			Dx		X	X	Y
E			✓	✓	✓		
TS1			**A**	**B**	**C**		
TS2			**D**	**E**	**F**		

Dx T2DM diagnosis

X Filled prescription for metformin

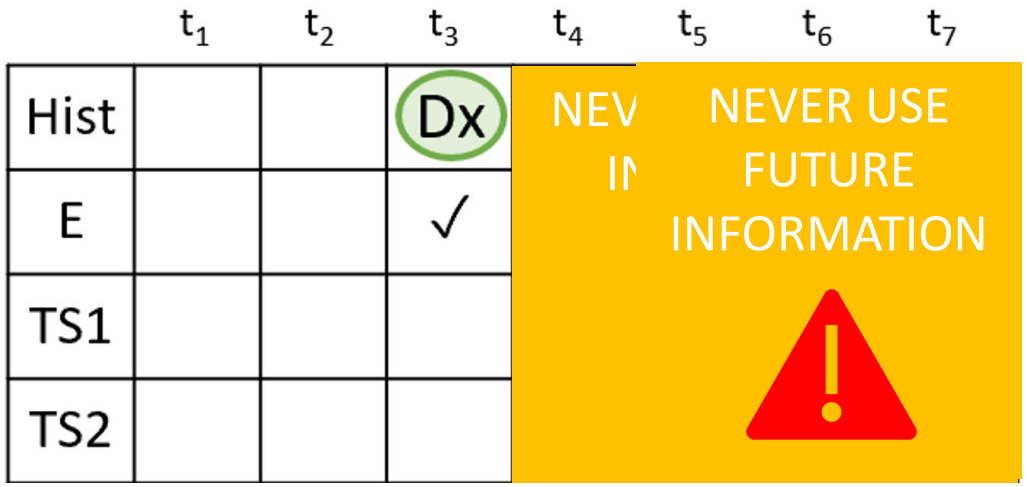
Y Filled prescription for SGLT-2i

To which strategy can the patient be assigned (choose A-F)?

Multiple Choice

2. At the time of eligibility, assign the individual to the treatment strategies that are compatible with the individual's data

Component	Target trial 2 specification
Eligibility	• Diagnosis of T2DM in past 3 months • No previous use of metformin
Treatment strategies	1. Start metformin and always use 2. Never start metformin



Dx T2DM diagnosis

X Filled prescription for metformin

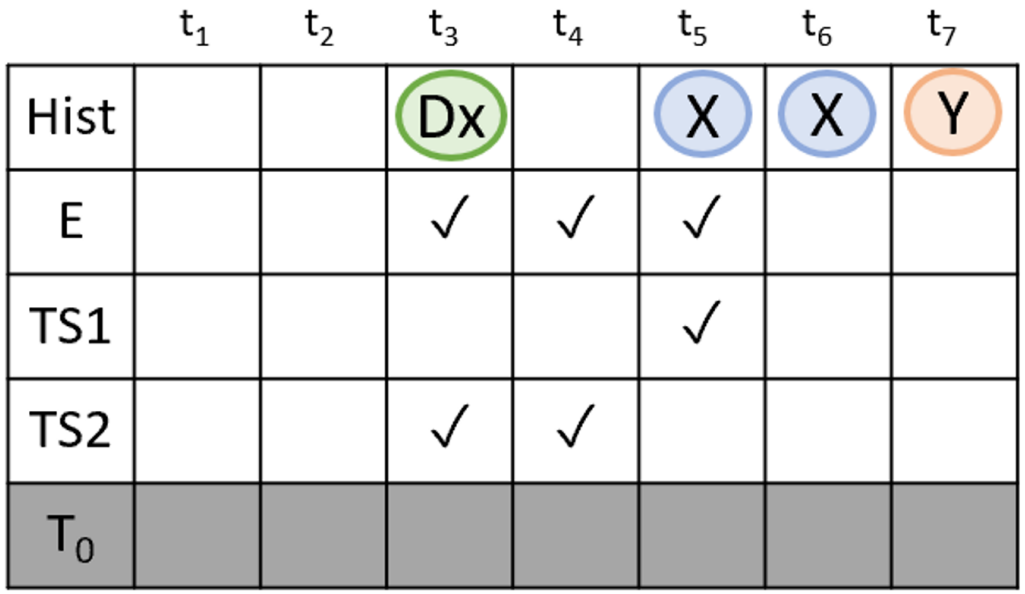
Y Filled prescription for SGLT-2i

To which strategy can the patient be assigned (choose A-F)?

Multiple Choice

3. Set the start of follow-up (time zero) as the time of treatment assignment

Component	Target trial 2 specification
Eligibility	• Diagnosis of T2DM in past 3 months • No previous use of metformin
Treatment strategies	1. Start metformin and always use 2. Never start metformin

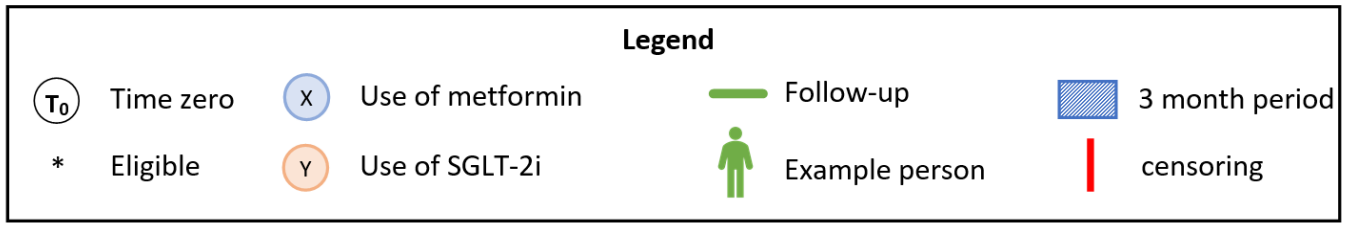


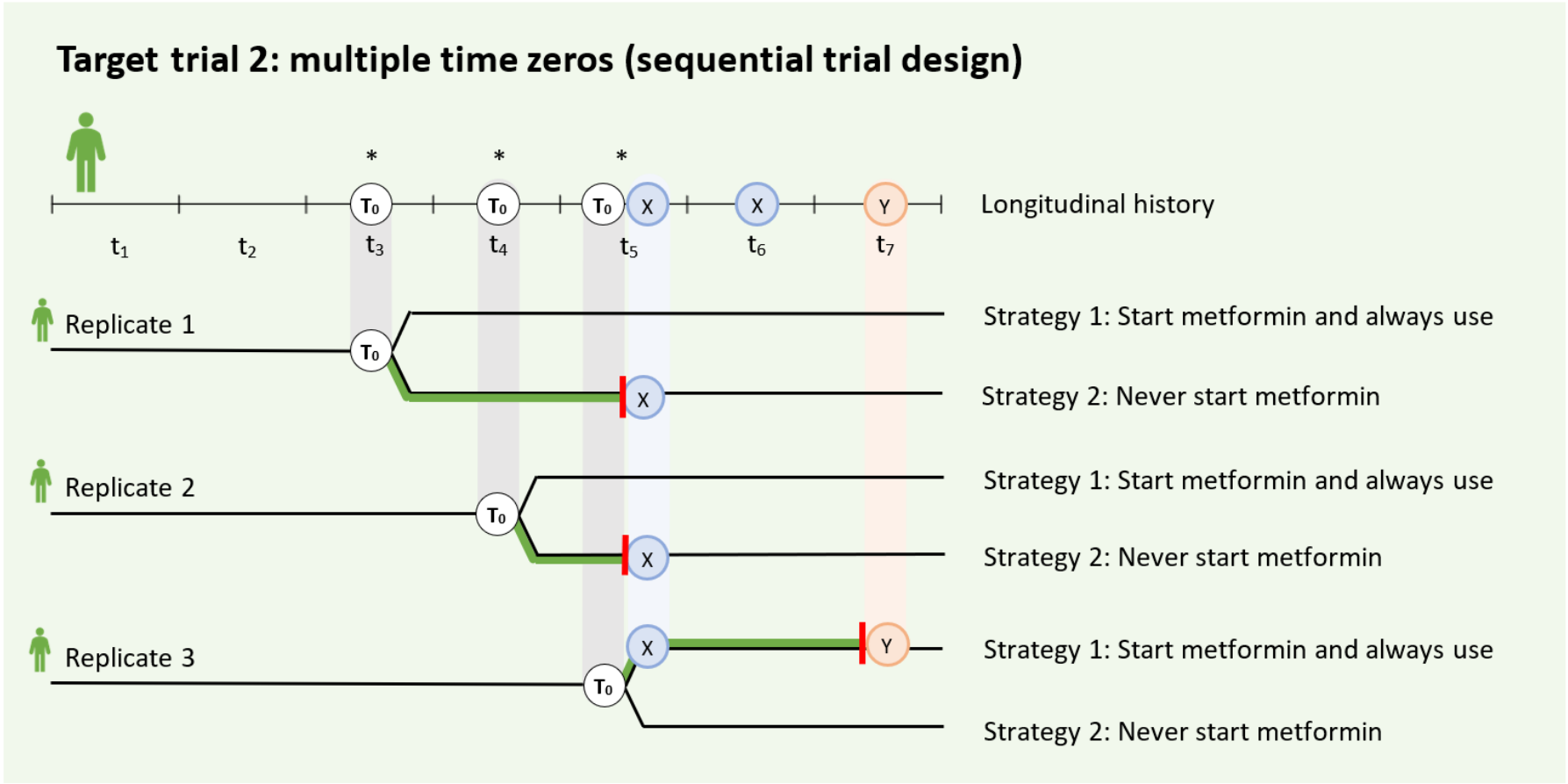
Dx T2DM diagnosis

X Filled prescription for metformin

Y Filled prescription for SGLT-2i

Replicates are assigned to both strategies

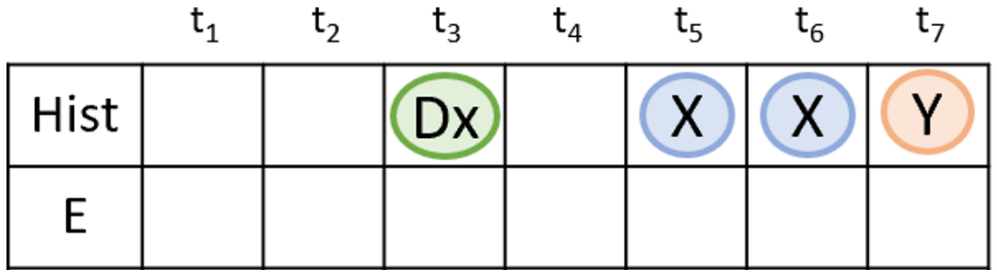


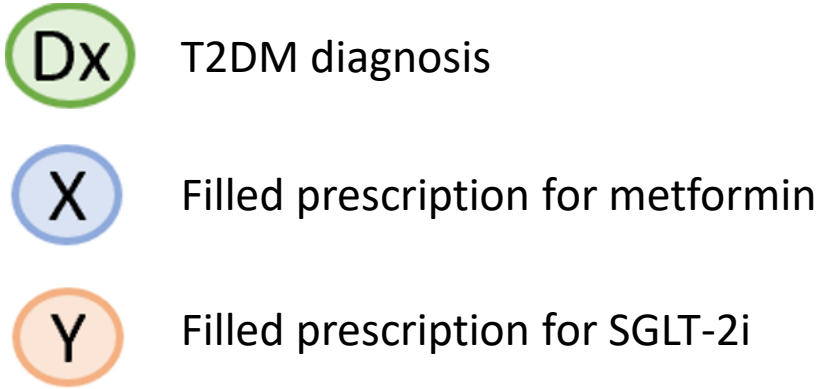


Target trial 3

1. Determine when the individual meets the eligibility criteria

Component	Target trial 3 specification
Eligibility	• Moment of type 2 diabetes diagnosis • No previous use of metformin
Treatment strategies	1. Start metformin within 3 months of diabetes diagnosis 2. Never start metformin





2. At the time of eligibility, assign the individual to the treatment strategies that are compatible with the individual's data

Component	Target trial 3 specification
Eligibility	• Moment of type 2 diabetes diagnosis • No previous use of metformin
Treatment strategies	1. Start metformin within 3 months of diabetes diagnosis 2. Never start metformin

	t_1	t_2	t_3	t_4	t_5	t_6	t_7
Hist			Dx		X	X	Y
E			✓				
TS1			**A**				
TS2			**B**				

Dx T2DM diagnosis

X Filled prescription for metformin

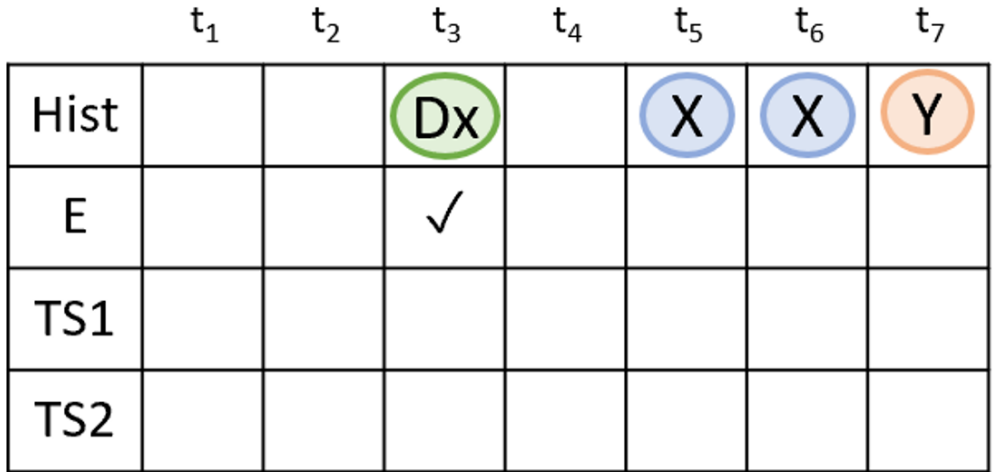
Y Filled prescription for SGLT-2i

To which strategy can the patient be assigned (choose A-B)?

Multiple Choice

2. At the time of eligibility, assign the individual to the treatment strategies that are compatible with the individual's data

Component	Target trial 3 specification
Eligibility	• Moment of type 2 diabetes diagnosis • No previous use of metformin
Treatment strategies	1. Start metformin within 3 months of diabetes diagnosis 2. Never start metformin



Dx T2DM diagnosis

X Filled prescription for metformin

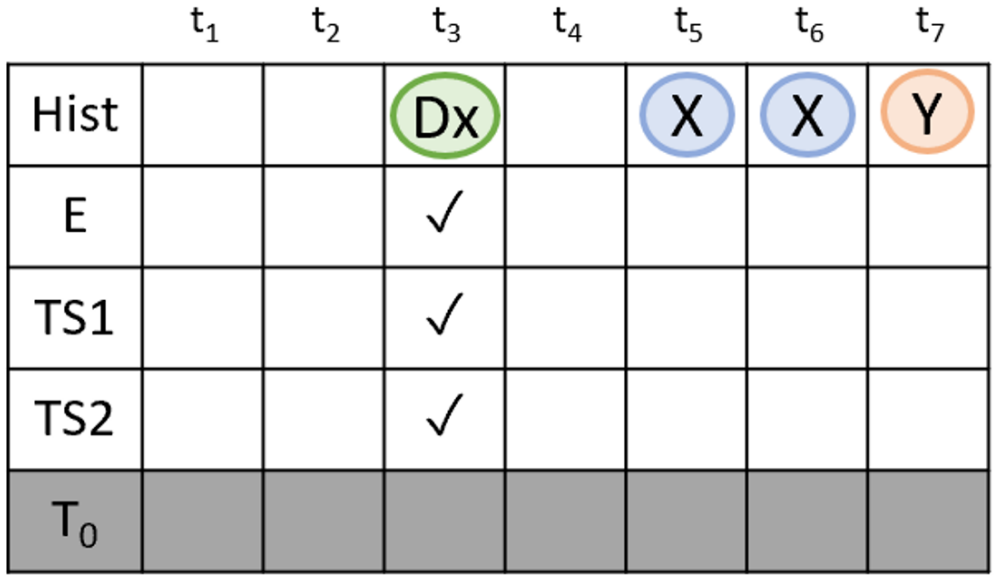
Y Filled prescription for SGLT-2i

To which strategy can the patient be assigned (choose A-B)?

Multiple Choice

3. Set the start of follow-up (time zero) as the time of treatment assignment

Component	Target trial 3 specification
Eligibility	• Moment of type 2 diabetes diagnosis • No previous use of metformin
Treatment strategies	1. Start metformin within 3 months of diabetes diagnosis 2. Never start metformin

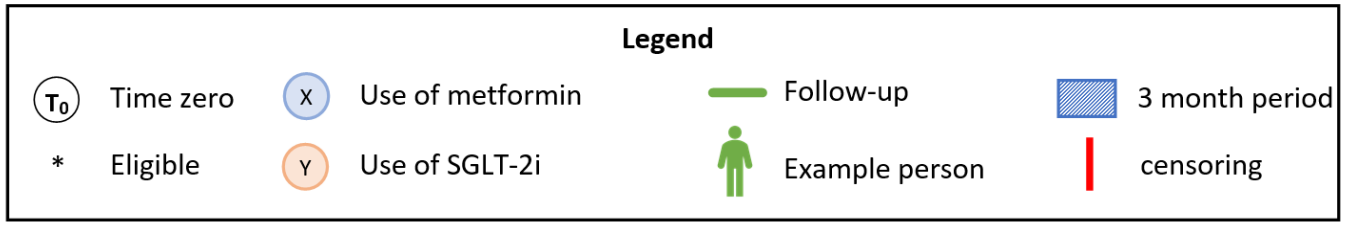


Dx T2DM diagnosis

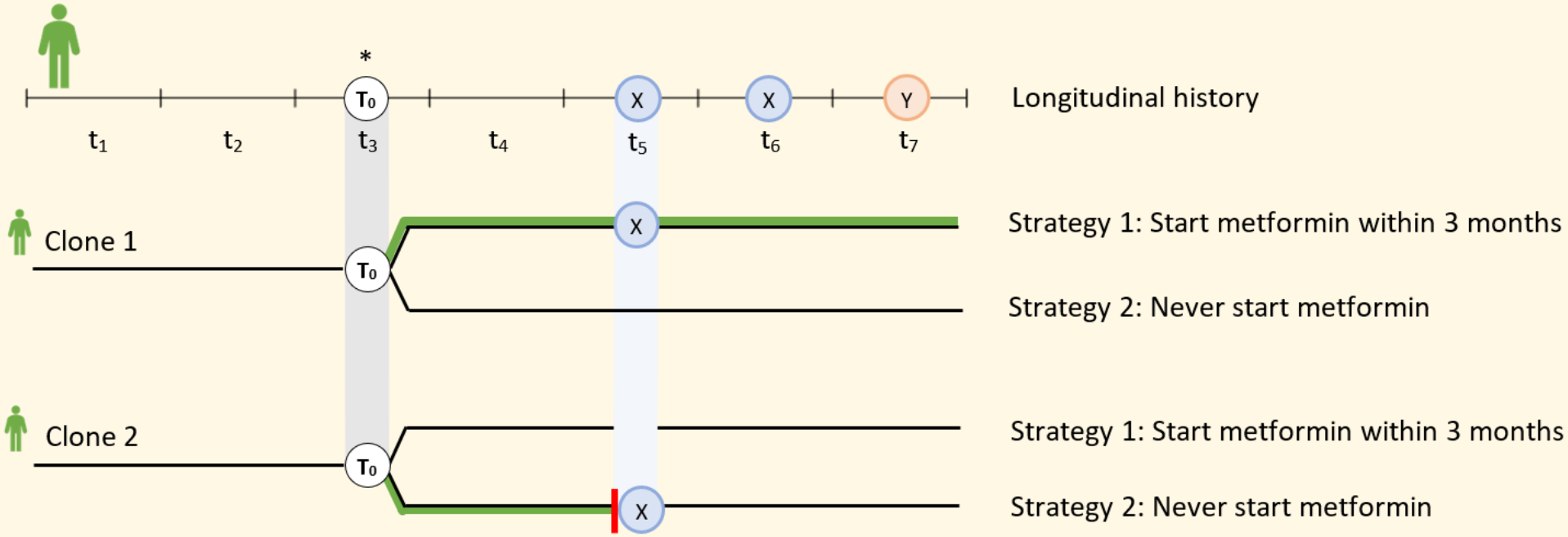
X Filled prescription for metformin

Y Filled prescription for SGLT-2i

Clones are assigned to both strategies

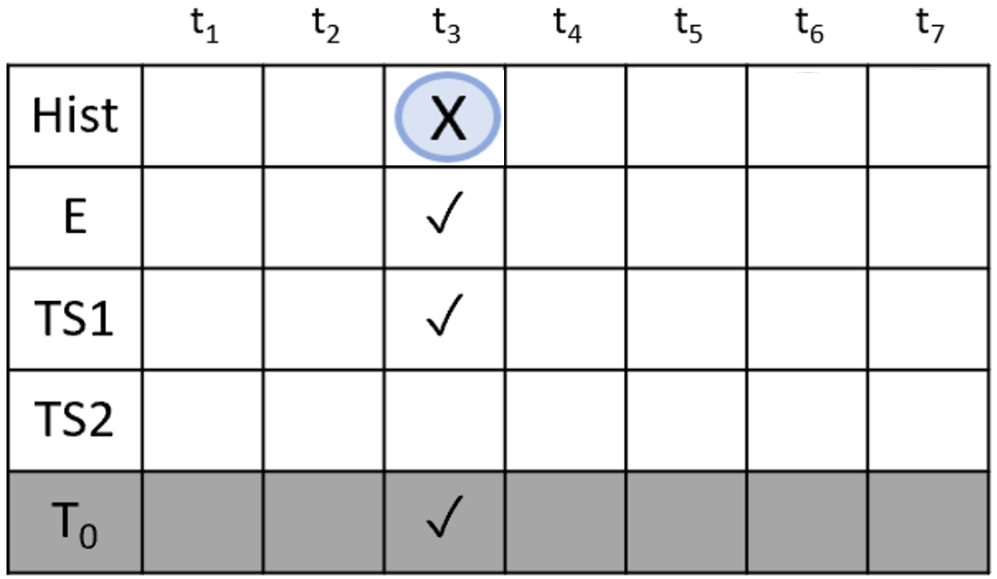


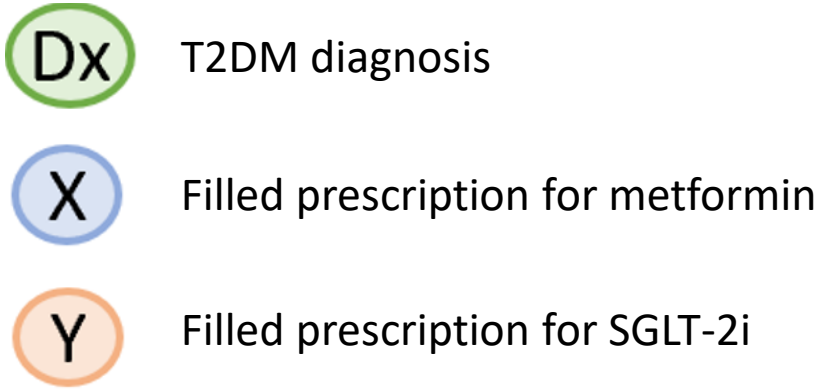
Target trial 3: Time zero with assignment to multiple strategies (clone-censor-weight design)



Not every patient is necessarily cloned

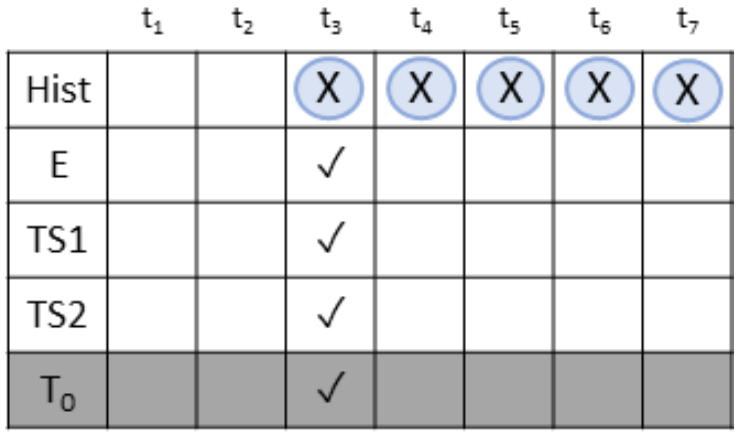
Component	Hypothetical target trial protocol specification
Eligibility	• Moment of type 2 diabetes diagnosis • No previous use of metformin
Treatment strategies	1. Start metformin within 3 months of diabetes diagnosis 2. Never start metformin





Another example of cloning: treatment duration

Component	Hypothetical target trial protocol specification
Treatment strategies	1. Start DAPT and use for 6 months 2. Start DAPT and use for 12 months

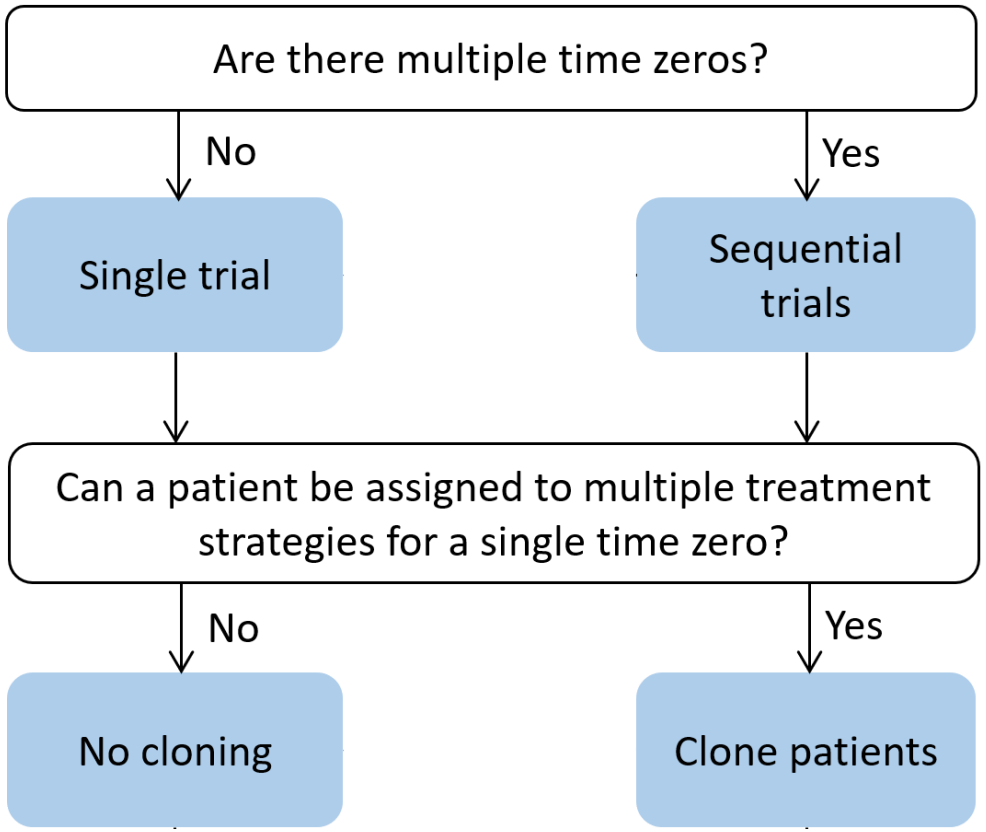


X DAPT

A summary of the steps so far

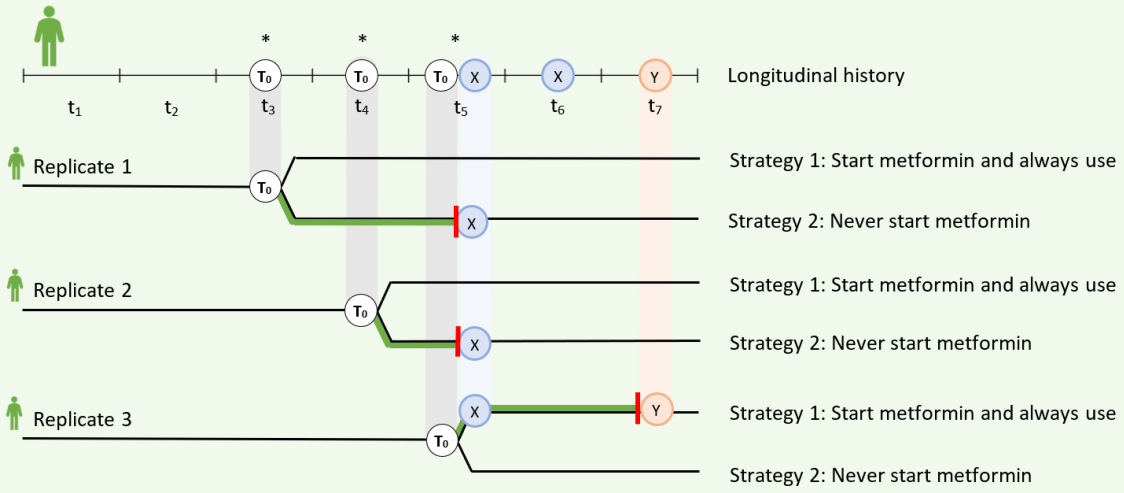
Specification of target trial 1	
Eligibility criteria	• Diagnosis of type 2 diabetes in past 3 months • No previous use of metformin or SGLT-2i
Treatment strategies	1. Start metformin immediately and continue using unless contraindications arise 2. Start SGLT-2i and continue using unless contraindications arise

	t_1	t_2	t_3	t_4	t_5	t_6	t_7
Hist			Dx		X	X	Y
E			✓	✓	✓		
TS1					✓		
TS2							
T_0					✓		

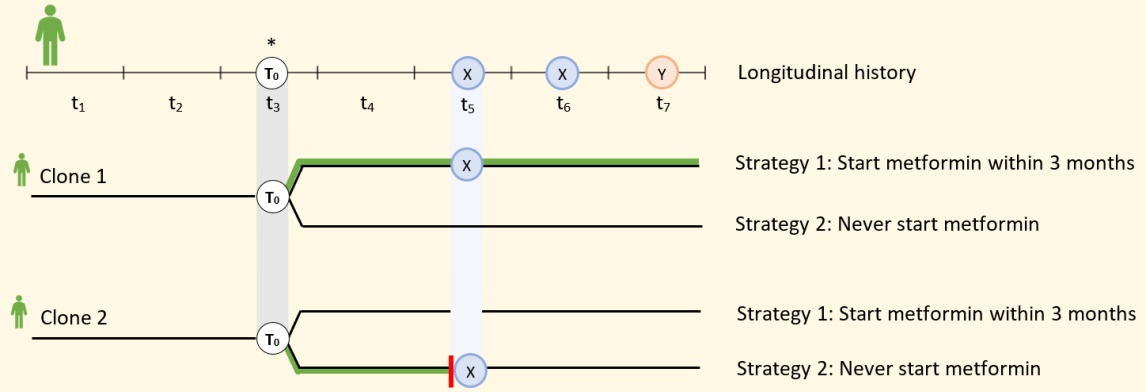


Repeated use of same individual

Target trial 2: multiple time zeros (sequential trial design)



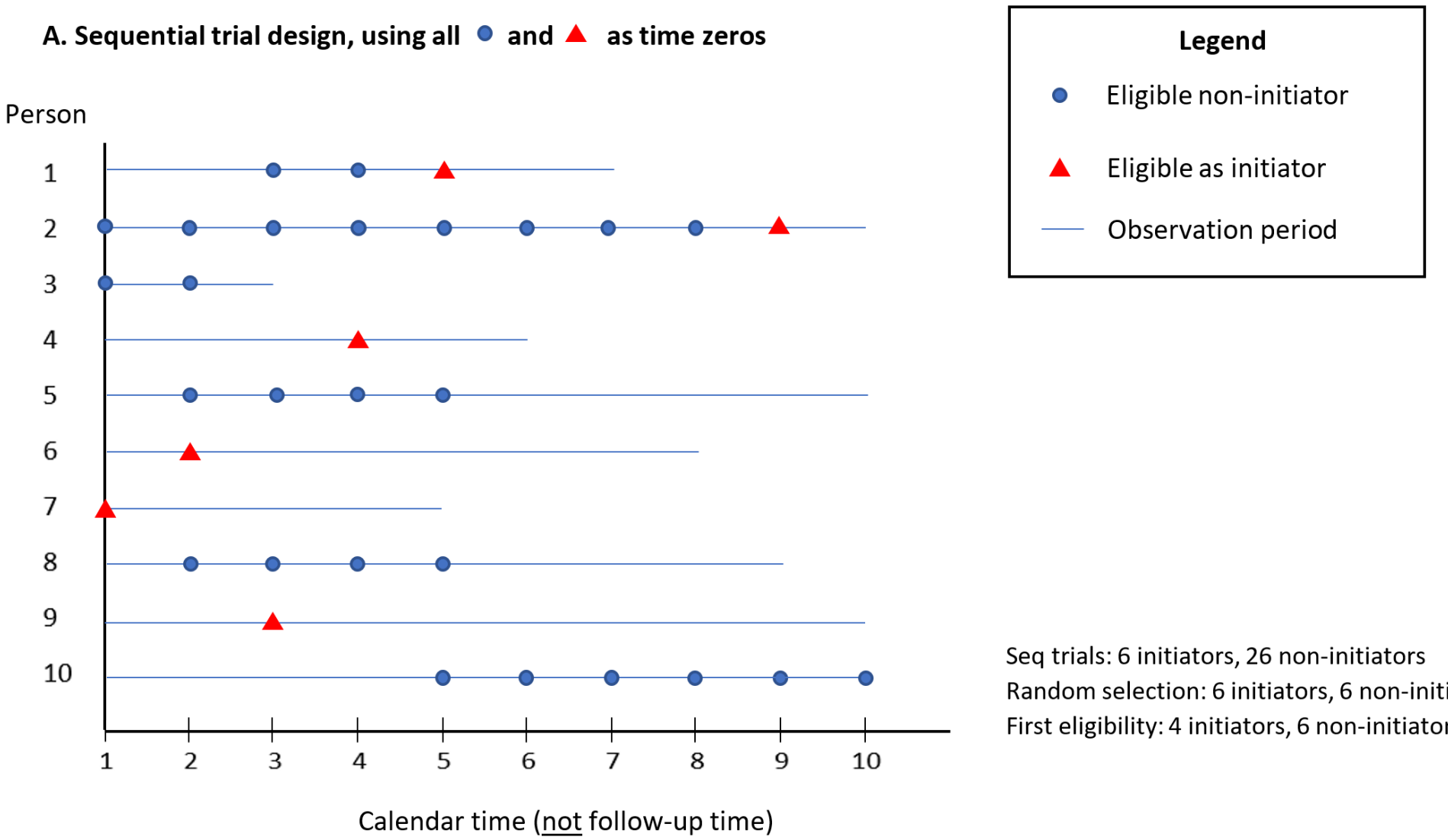
Target trial 3: Time zero with assignment to multiple strategies (clone-censor-weight design)



Legend

- T_0 Time zero
- X Use of metformin
- Follow-up
- 3 month period
- * Eligible
- Y Use of SGLT-2i
- Example person
- censoring

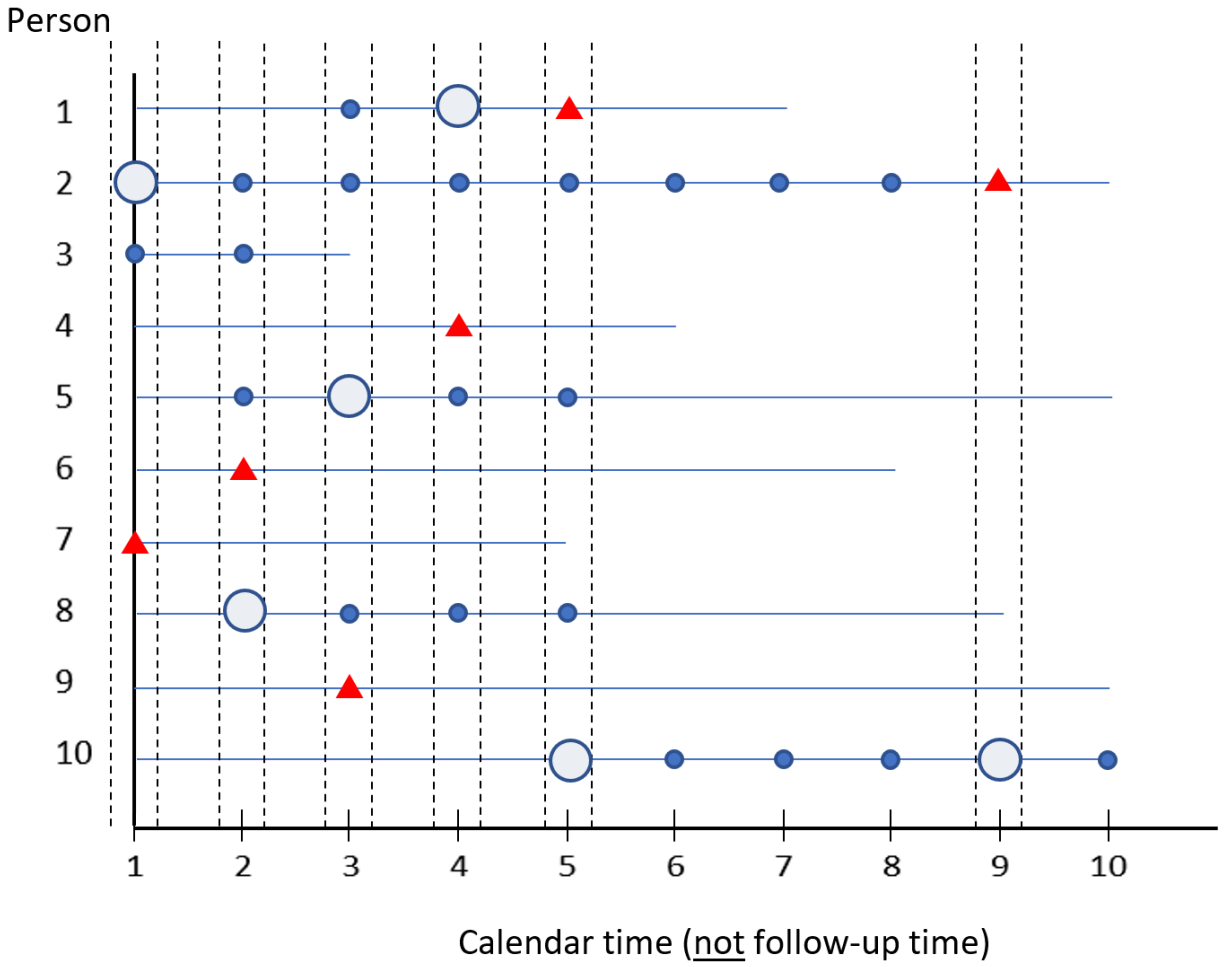
Sequential trial emulation



Seq trials: 6 initiators, 26 non-initiators
Random selection: 6 initiators, 6 non-initiators
First eligibility: 4 initiators, 6 non-initiators

Randomly selecting one non-initiator when initiator is included

B. Randomly selecting one non-initiator at same timepoint an initiator is included (e.g. in new user design, prevalent new user design)



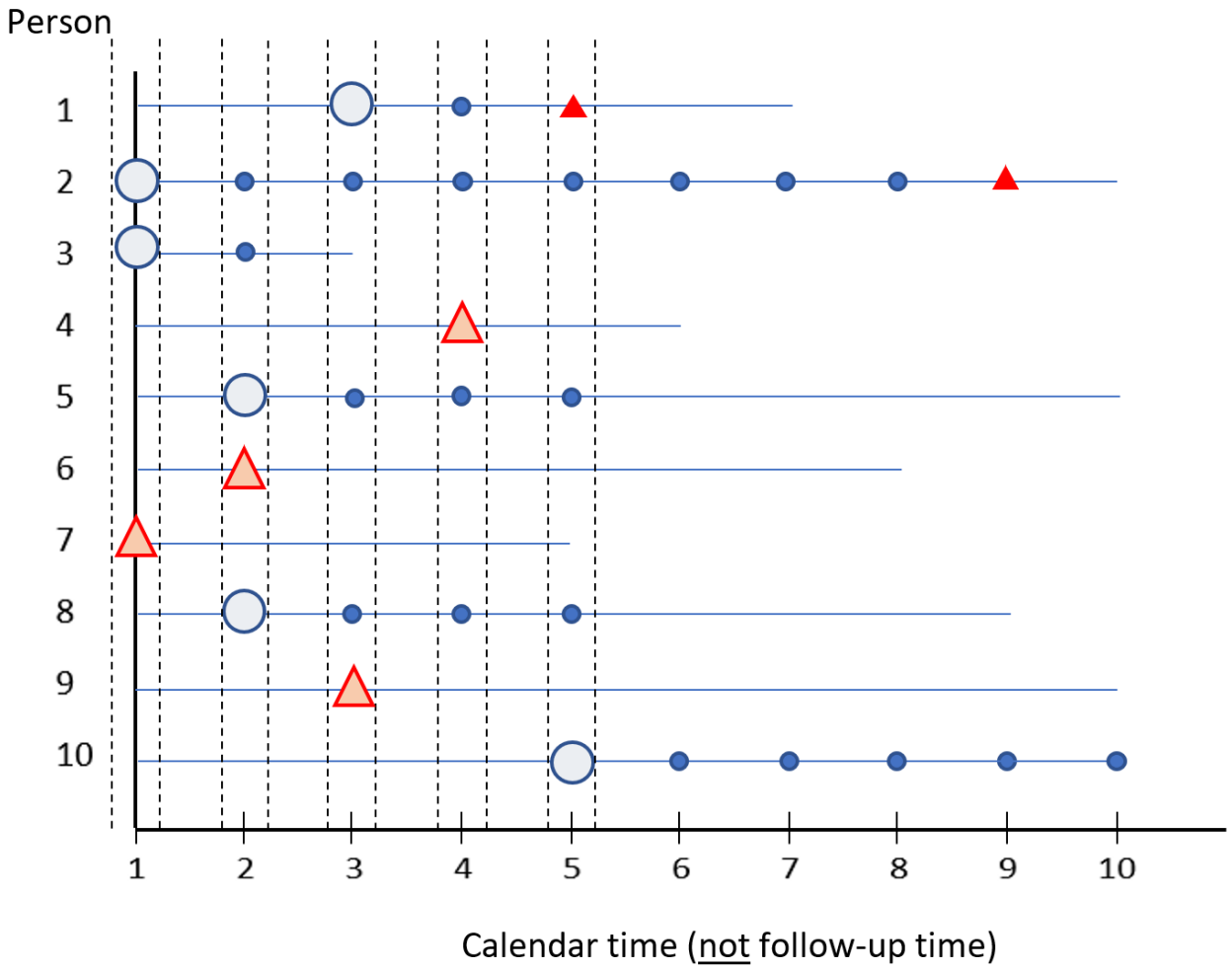
Legend

- Eligible as non-initiator
- Eligible as initiator
- Observation period
- Selected time zero as non-initiator

Seq trials: 6 initiators, 26 non-initiators
Random selection: 6 initiators, 6 non-initiators
First eligibility: 4 initiators, 6 non-initiators

Selecting individuals at first eligibility

C. Selecting individuals at first eligibility



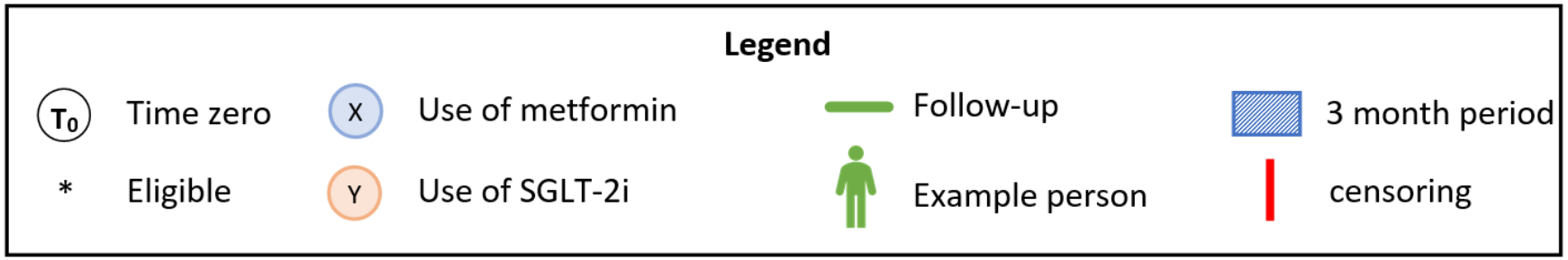
Legend

- Eligible as non-initiator
- Eligible as initiator
- Observation period
- Selected time zero as non-initiator
- Selected time zero as initiator

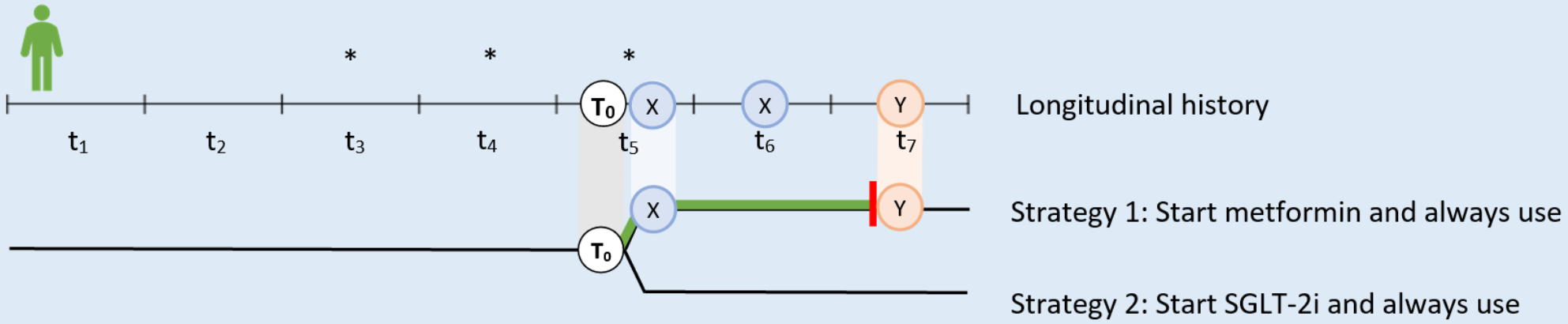
Seq trials: 6 initiators, 26 non-initiators
Random selection: 6 initiators, 6 non-initiators
First eligibility: 4 initiators, 6 non-initiators

How to ensure patients follow their assigned strategy

Example person is assigned to first strategy



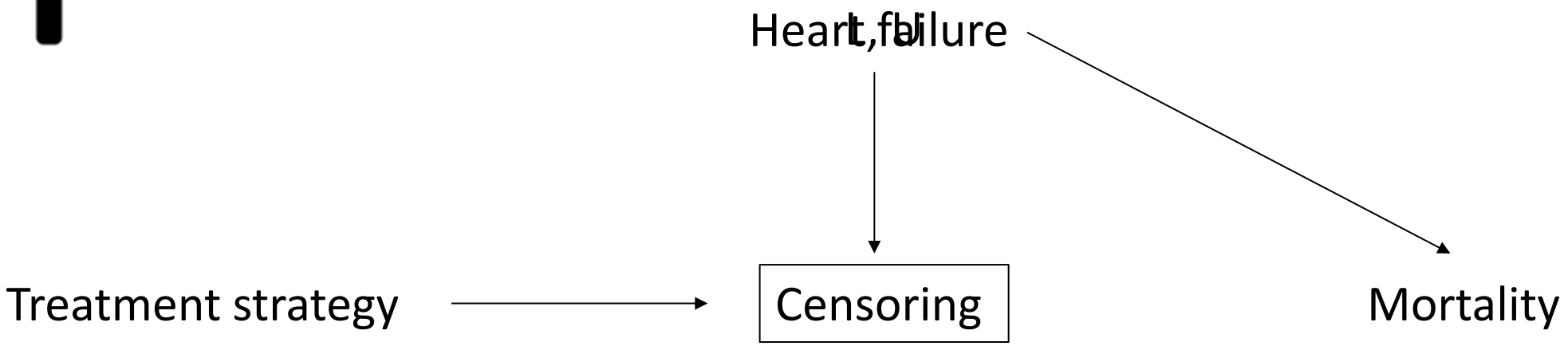
Target trial 1: single time zero, eligible multiple times



Cloning/censoring/weighting procedure

Censoring is informative. Solution?

Step 3: Weighting



Conclusions

1. Simple 3-step procedure that aligns eligibility, treatment assignment and start of follow-up
   - Prevents immortal time and selection biases

2. When multiple time zeros per patient, using all of them = sequential trial emulation

3. When patients can be assigned to multiple strategies → cloning

Useful references

- Target Trial Emulation to Improve Causal Inference from Observational Data: What, Why, and How? JASN 2023. (general paper about TTE)
- Pharmacoepidemiology for nephrologists (part 2): potential biases and how to overcome them. CKJ 2020. Fu et al. (immortal/depletion of susceptibles bias)
- Timing of dialysis initiation to reduce mortality and cardiovascular events in advanced chronic kidney disease: nationwide cohort study. BMJ 2021. Fu et al. (application of clone-censor-weight)
- Stopping Renin-Angiotensin System Inhibitors in Patients with Advanced CKD and Risk of Adverse Outcomes: A Nationwide Study. JASN 2021. Fu et al. (application of clone-censor-weight)
- Observational data for comparative effectiveness research: an emulation of randomised trials of statins and primary prevention of coronary heart disease. SMMR 2013. Danaei et al. (sequential trials)
- Causal survival analysis: A guide to estimating intention-to-treat and per-protocol effects from randomized clinical trials with non-adherence. 2021 Murray et al. (ITT and PP effects)

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Questions

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