Tuesday June 9, 2026

Target Trial Emulation*

Murray A. Mittleman, MD, DrPH
Department of Epidemiology, Harvard TH Chan School of Public Health

* Slides prepared with input from Alejandro Szmulewicz, MD, PhD

HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH

Key Concepts

- Target trial emulation
- □ Background
- Ask a causal question
- Specify the target trial

Post-menopausal Hormone Therapy and CHD

- Hormone therapy (estrogens with or without progestins) can be used to treat common menopausal symptoms (e.g., hot flashes)
- Estrogens alone can lower the risk of cardiovascular disease, but unopposed estrogen therapy may increase the risk for endometrial cancer
- Combining progestin with estrogens can reduce or eliminate the increased risk of endometrial cancer
  - But research showed that progestin increase LDL and lower HDL concentrations
  - The impact of adding progestins on cardiovascular needed to be elucidated

How do we learn if HRT increases the risk of CVD?

- The standard scientific answer:
  - Conduct a randomized experiment
- A relevant randomized trial would, in principle, answer each causal question about comparative effectiveness and safety
  - Interference/scaling up issues aside

Assuming we have the time and resources…

- We would design and conduct a randomized trial
- First step: design the protocol of the trial

Eligibility criteria
Treatment strategies
Assignment
Time zero and follow-up
Outcomes
Causal contrasts
Data analysis

Assuming we have the time and resources…

- We would design and conduct a randomized trial
- First step: design the protocol of the trial

Assuming we have the time and resources…

- We would design and conduct a randomized trial
- First step: design the protocol of the trial

Eligibility criteria

1. Postmenopausal women within 5 years of menopause between the years 2005 and 2010
2. No history of CHD and
3. No prior use of oral contraceptives in the past 2 years

Treatment strategies

Assignment

Time zero and follow-up

Outcomes

Causal contrasts

Data analysis

Assuming we have the time and resources…

- We would design and conduct a randomized trial
- First step: design the protocol of the trial

Eligibility criteria

Treatment strategies

1. Initiation of oral estrogens plus progesterone therapy
2. No initiation of oral estrogen plus progesterone therapy

Assignment

Time zero and follow-up

Outcomes

Causal contrasts

Data analysis

Assuming we have the time and resources…

- We would design and conduct a randomized trial
- First step: design the protocol of the trial

Eligibility criteria

Treatment strategies

Assignment

1. Participants will be randomly assigned to either strategy at baseline, and will be aware of the strategy they have been assigned to

Time zero and follow-up

Outcomes

Causal contrasts

Data analysis

Assuming we have the time and resources…

- We would design and conduct a randomized trial
- First step: design the protocol of the trial

Eligibility criteria

Treatment strategies

Assignment

Time zero and follow-up

1. Starts at assignment and ends at CHD diagnosis, death, loss to follow-up, or June 2000, whichever occurs earliest

Outcomes

Causal contrasts

Data analysis

Assuming we have the time and resources…

- We would design and conduct a randomized trial
- First step: design the protocol of the trial

Eligibility criteria

Treatment strategies

Assignment

Time zero and follow-up

Outcomes

1. Coronary heart disease confirmed by clinician or research staff

Causal contrasts

Data analysis

Assuming we have the time and resources…

- We would design and conduct a randomized trial
- First step: design the protocol of the trial

Eligibility criteria

Treatment strategies

Assignment

Time zero and follow-up

Outcomes

Causal contrasts

1. Intention to treat, per protocol effect

Data analysis

Assuming we have the time and resources…

- We would design and conduct a randomized trial
- First step: design the protocol of the trial

Eligibility criteria

Treatment strategies

Assignment

Time zero and follow-up

Outcomes

Causal contrasts

Data analysis

1. *Intention to treat analysis:* Compares the outcome distribution between initiators and non-initiators.
2. *Per protocol analysis:* Restricts the data to person-times before non-adherence and adjusts for baseline and post-baseline confounding due to risk factors associated with non-adherence.
3. *Subgroup analysis:* Uses stratification-based methods to explore effects in clinically relevant subgroups (e.g., Age < 50 vs. Age ≥ 50; smokers vs. non-smokers, etc.).

However, conducting a trial is not always possible

- Expensive
- Unethical
- Impractical
- Not timely

- Decisions still need to be made
  - No decision is still a decision: Keep the status quo
- What do we do?
  - We can analyze observational data
  - "The question is not whether observational data should be used, but rather how to use them most effectively." N Engl J Med 2021;385:1345-1348

The target trial

- The (hypothetical) randomized trial that we would like to conduct to answer a causal question
  - To learn what works and what harms
- A causal analysis of observational data can be viewed as an attempt to emulate some target trial
  - If we cannot translate our causal research question into a target trial, then the question is not well-defined

A simple algorithm for causal inference

- Step 1:
  - Ask the causal question
    - That is, specify the "target trial" that would, in principle, answer the research question
- Step 2:
  - Use **observational data** to explicitly emulate the target trial

Target trial protocol	
Target trial	**Target trial emulation**
Eligibility criteria	Eligibility criteria
Treatment strategies	Treatment strategies
Assignment	Assignment
Time zero and follow-up	Time zero and follow-up
Outcomes	Outcomes
Causal contrasts	Causal contrasts
Data analysis	Data analysis

Specify all Components of The Target Trial and the Emulation (Updated)

Figure. Example of specification and emulation of a target trial with the emulation based on existing data: The causal contrasts of interest are the effect of assignment and the per protocol effect.

	Specification	Emulation
Causal Estimand	Eligibility criteria	Data mapping for each criterion†
	Treatment strategies	Data mapping for each component
	Assignment (unmasked)	Data mapping for assignment‡
	Outcomes	Data mapping for each outcome
	Start/end of follow-up	Same
	Causal contrasts§	Observational analogues of causal contrasts
Identifying Assumptions*	For effect of assignment (intention-to-treat): Randomized assignment‖	Assumption of conditional exchangeability**
	If applicable, assumption of conditional exchangeability for:	List baseline confounders and describe data mapping for each one
	• Loss to follow-up (list factors)	Data mapping for each factor
	• Competing events (list factors)	Data mapping for each factor
	For per protocol effect: Assumption of conditional exchangeability (list baseline/time-varying confounders)	Data mapping for each confounder
Estimator	For each causal estimand: data analysis, including subgroup analyses, and modeling assumptions	Describe modifications required for emulation, if any,and sensitivity analyses

Hernan et al Ann Intern Med 2025

Target Trial Emulation Reporting Guidelines

Clinical Review & Education

JAMA | Special Communication

Transparent Reporting of Observational Studies Emulating a Target Trial—The TARGET Statement

Aidan G. Cashin, PhD; Harrison J. Hansford, BSc (Hons); Miguel A. Hernán, MD; Sonja A. Swanson, ScD; Hopin Lee, PhD; Matthew D. Jones, PhD; Issa J. Dahabreh, MD, ScD; Barbra A. Dickerman, PhD; Matthias Egger, MD, MSc; Xabier Garcia-Albeniz, MD, PhD; Robert M. Golub, MD; Nazrul Islam, MD, PhD; Sara Lodi, PhD; Margarita Moreno-Betancur, PhD; Sallie-Anne Pearson, PhD; Sebastian Schneeweiss, MD, ScD; Melissa K. Sharp, PhD; Jonathan A. C. Sterne, PhD; Elizabeth A. Stuart, PhD; James H. McAuley, PhD

JAMA. 2025;334(12):1084-1093. doi:10.1001/jama.2025.13350

Target Statement: Glossary of Commonly Used Terms
Causal contrast

Causal contrast	The comparison of the outcome distributions under 2 different treatment strategies. Examples of causal contrasts are being assigned to one vs another treatment strategy, irrespective of whether people actually receive the treatment assigned (the intention-to-treat effect), and the effect of fully adhering to one vs another treatment strategy as specified by the protocol (the per-protocol effect).

JAMA. 2025;334(12):1084-1093. doi:10.1001/jama.2025.13350

Target Statement: Glossary of Commonly Used Terms
Causal estimand

Causal estimand	The causal quantity (typically, an effect) that would be estimated to answer a causal question of interest. Key components of the causal estimand are the target population (eligibility criteria), the treatment strategies, the outcome, the timing of follow-up, and the causal contrast (see above).

JAMA. 2025;334(12):1084-1093. doi:10.1001/jama.2025.13350

Target Statement: Glossary of Commonly Used Terms Confounding

Confounding	Confounding occurs when groups receiving different treatment strategies differ in their distribution of prognostic factors at time zero.[17] When there is confounding, differences in the outcome distribution between treatment groups may be explained by differences in prognostic factors rather than differences in treatment. A key concern for target trial emulation is whether some confounding bias remains after adjustment for measured confounders.

JAMA. 2025;334(12):1084-1093. doi:10.1001/jama.2025.13350

Target Statement: Glossary of Commonly Used Terms Design-related biases

Design-related biases	Design-related biases refer to those that arise from decisions made by investigators when designing their analyses of observational data,[1,5] rather than biases associated with the observational study design (eg, confounding, measurement error). Common design-related biases include selection and misclassification, which may produce periods of time in the analysis when an individual cannot develop an outcome of interest (immortal time). These biases are due to misalignment of the start of follow-up (time zero) with the time an individual becomes eligible and is classified into a treatment strategy; selection bias may arise when eligibility occurs after assignment to a treatment strategy (selection depends on the outcome), and misclassification bias may arise when assignment occurs after eligibility (classification depends on the outcome).[6,18]

JAMA. 2025;334(12):1084-1093. doi:10.1001/jama.2025.13350

Target Statement: Glossary of Commonly Used Terms
Identifying assumptions

Identifying assumptions	Informally, assumptions that link the causal estimand to the observed data. Some examples of identifying assumptions for the per-protocol effect are[19] (1) Within levels of the adjustment variables, groups receiving each treatment strategy at each time have the same counterfactual risk of the outcome (conditional exchangeability). (2) For every combination of the adjustment variables, there is a nonzero (ie, positive) probability of receiving each treatment strategy at each time. (3) The treatment strategies are sufficiently well-defined.

JAMA. 2025;334(12):1084-1093. doi:10.1001/jama.2025.13350

Target Statement: Glossary of Commonly Used Terms
Target trial framework

Target trial framework	A methodological framework for causal inference from observational data, which applies the design principles of randomized trials. This involves designing observational analyses to explicitly emulate a hypothetical pragmatic randomized trial that would answer the question at hand: the target trial. The framework has 2 components: specification of the target trial and mapping that target trial to the data (emulation).

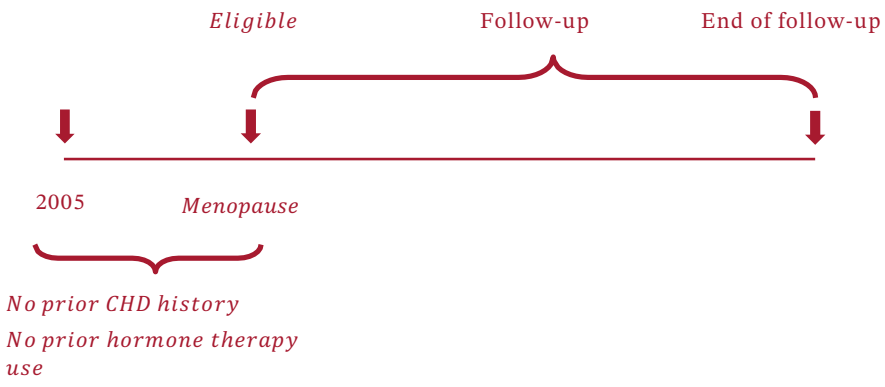
JAMA. 2025;334(12):1084-1093. doi:10.1001/jama.2025.13350

Observational data for emulation: The Nurses Health Study

- Follow-up (cohort) study
- ~80,000 women with complete data in 1980
- Information updated by questionnaire every two years
  - Use of hormone therapy
  - Diagnosis of CHD (confirmed by physician review)
  - Other medical diagnoses
  - Lifestyle data: diet, exercise, smoking…
  - Other risk factors for CHD

Target trial emulation using observational data Eligibility criteria

- Follow-up (cohort) study
- Post-menopausal women within 5 years of menopause
- No history of CHD and
- No use of hormone therapy in the past 2 years



Target trial emulation using observational data
Eligibility criteria

- We can think of the inclusion/exclusion criteria as the membership-defining event for entry into the closed cohort
  - E.g., the first time an individual meets all eligibility criteria
- We can only emulate a target trial with eligibility criteria for which we have sufficient data to emulate
- We should not define eligibility criteria based on post-baseline information
  - E.g., not exclude those that do not interact with research staff during follow-up

Target trial emulation using observational data
Treatment strategies

- We use data on the treatment of individuals at the time they meet eligibility criteria
  - If they initiate HRT, we label them as *initiators*
  - Otherwise, as *non-initiators*
- One consideration is that very few participants happen to initiate HRT the first time they meet eligibility criteria
  - Although it is very tempting to look at future information, it can lead to bias
    - *Hernán MA, et al, Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol. 2016*
  - Emulating more than one trial may be necessary (see EPI207 for details)

Target trial emulation using observational data
Treatment strategies

- Defining treatment strategies in observational research in an identical way as we would in a randomized trial ensures that we are comparing **well-defined interventions** e.g., think about an observational study that compares BMI above vs. below 25 kg/m^2
- Ensures that the consistency assumption is met
  - Provided there are individuals in the data following the strategies
- We cannot compare strategies that include
  - Placebo
  - Decisions that do not exist in clinical practice

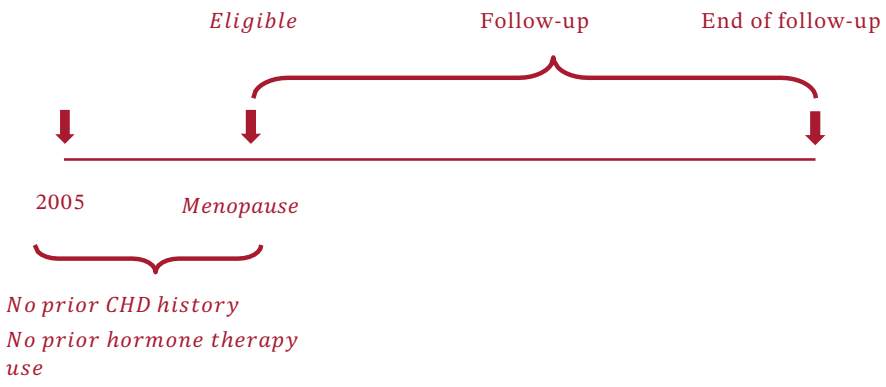
Target trial emulation using observational data
Treatment assignment

- To emulate the random assignment, we need to adjust for baseline confounding
  - i.e., we will assume randomization conditional on the following variables: age, race, sex, physical activity, cholesterol levels, statin use, …
  - Essentially, we "pretend" the data comes from a conditionally randomized experiment
- If the observational database does not contain sufficient information on confounders or if we fail to identify them, successful emulation of the target trial's random assignment is not possible.

Target trial emulation using observational data
Treatment assignment

- Unmeasured or residual confounding works against the successful emulation of the treatment assignment component of the target trial
  - i.e., conditional exchangeability assumption is not met
  - our effect estimates may not correspond to those from a trial
- Stated differently, the reason we adjust for confounding is to emulate a target trial
  - If the conditional exchangeability assumption is met, causal interpretation is possible (assuming no other sources of bias).
  - Since this assumption is not verifiable, most medical journals reject the use of causal language in observational analyses even after adjustment for the measured confounders

Target trial emulation using observational data
Time zero and follow-up



- Misalignment of eligibility, treatment ascertainment, and time zero is another frequent source of bias in observational analysis
  - See slides on immortal person-time bias

Target trial emulation using observational data
Outcomes

- Using observational data, we may need to be more concerned about outcome misclassification
- If we are using electronic health records data, we will probably have to rely on diagnoses/procedural codes (e.g., ICD)
  - e.g., dementia using ICD codes?
  - e.g., all-cause mortality using the national death index?
- Treatment status may influence a doctor's decision to look for the outcome
  - Such differential ascertainment may result in an increased incidence of CHD diagnosis among hormone users even in the absence of a biological effect.
  - i.e., **differential** misclassification of the outcome

Target trial emulation using observational data
Intention to treat analysis

- **In the target trial**
  - Compares the outcome distribution between the two groups assigned at baseline
  - If, by chance, there are imbalances between groups at baseline, we would adjust for those
- **In the target trial emulation**
  - Just as in the target trial, in the presence of imbalances between groups, we must adjust
  - We may prefer methods such as IPW or standardization to the marginal population that do not make assumptions about effect modification by participant characteristics that are adjusted for

Target trial emulation using observational data
Per protocol and subgroup analyses

- The per-protocol analysis is identical in the target trial and in the target trial emulation
  - See EPI 207 for details
- The subgroup analysis is identical in the target trial and in the target trial emulation
  - Stratification-based methods to look at stratum-specific estimates in clinically relevant subgroups

Postmenopausal HRT and risk of CHD
Full specification of the protocol

	Target trial	Target trial emulation
Eligibility criteria	Postmenopausal women with no history of coronary heart disease and other diseases, and no use of hormone therapy in the last 2 years	Same as the target trial
Treatment strategies	1. **Initiate** estrogen plus progestin hormone therapy 2. Do not **initiate** hormone therapy during follow-up	Same as the target trial
Assignment	Participants will be randomly assigned to either strategy at baseline, and will be aware of the strategy they have been assigned to	Treatment assignment was assumed at random, conditional on: age, education, ethnicity, age at menopause, cholesterol, blood pressure, BMI, smoking, physical activity, …
Time zero and follow-up	Starts at assignment and ends at coronary heart disease diagnosis, death, loss to follow-up, or June 2000, whichever occurs earlier	Same as the target trial
Outcomes	Coronary heart disease diagnosed by a cardiologist	Same as the target trial, but using information from the electronic health record
Causal contrasts	Intention-to-treat, per-protocol effect	Same as the target trial
Data analysis	Intention-to-treat, non-naïve per-protocol analysis	Same as the target trial, but we adjust for confounding in the ITT

Summary: A unified approach

- Design and analysis of randomized trials is very similar to the design and analysis of observational studies:
  - inclusion/exclusion criteria
  - longitudinal follow-up of included patients
  - statistical planning (e.g., sample size calculation)
  - validated definition of outcome
  - losses-to-follow-up and lack of adherence
- In fact, we can think of observational studies as randomized trials without baseline randomization
  - this is exactly why we adjust for confounding!
  - other than that, why would data analysis of both be different?

When is this approach most useful

- When the target trial is urgent and we cannot wait for a randomized trial to be funded, conducted, and reported:
  - e.g., vaccine boosters
- When the target trial is unlikely to be funded:
  - e.g., head-to-head comparison of vaccines
- When the target trial is unethical
  - e.g., exposures during pregnancy
- When we need to extend results from an existing randomized trial
  - e.g., subgroup analyses

Why is this approach helpful?

- In 2006, an observational study found a 30% **lower risk** of heart disease comparing current and never users of hormone replacement therapy.
  - HR: 0.68 (Grodstein et al. 2006, JWomen's Health)
- In 2003, a randomized controlled trial conducted in postmenopausal women found a nearly 20% **higher risk** of heart disease comparing initiators and non-initiators of hormone replacement therapy.
  - HR: 1.24 (Manson et al. 2003, New England Journal of Medicine)

Confounding is unlikely to be the cause of the discrepancy The models adjusted for:

- Age, past hormone use, parental history of myocardial infarction before age 60, education, husband's education, ethnicity, age at menopause, calendar time, high cholesterol, high blood pressure, diabetes, angina, stroke, coronary revascularization, osteoporosis, body mass index, smoking, aspirin use, alcohol intake, physical activity, diet score, multivitamin use, fruit/vegetable intake, …
  - Unlikely that they are missing such an important confounder that would explain the discrepancy
- In 2008, an observational study using the target trial emulation approach based on the same underlying data as the 2006 Grodstein paper and adjusting for the same confounders found a 42% higher risk of heart disease comparing initiators and non-initiators of hormone replacement therapy.
  - HR: 1.42 (Hernán et al. 2008, Epidemiology)

What was the problem with the original observational study?

Target Trial Emulation

- Treatment strategies in the observational study with target trial emulation
  1. Initiation of HRT therapy **at baseline**
  2. No HRT initiation **at baseline**
- Implemented using a 2-year washout period (using prior questionnaire)

No Target Trial Emulation

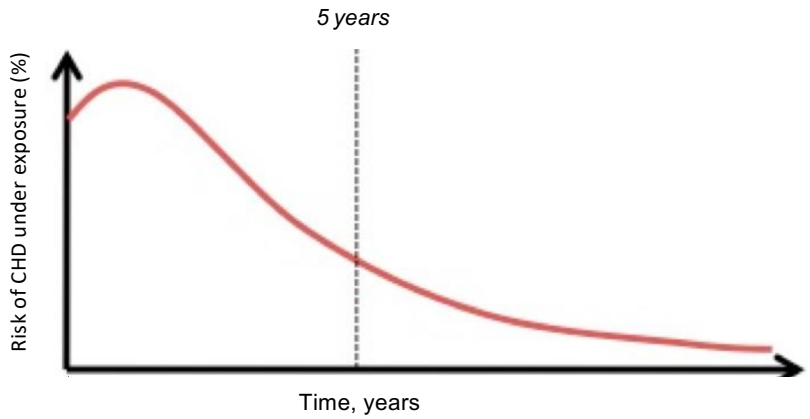
- Treatment strategies in the observational study without target trial emulation
  1. Current use of HRT at baseline: **current users**
  2. Never use of HRT during follow-up: **never users**
- Implemented using current questionnaire (exposed) and all future questionnaires (unexposed)

What was the problem with the original observational study?

- The comparison of current vs. never users not only would rarely take place in a randomized trial:
  - a randomized trial would assign people to initiate or not the treatment strategies of interest (i.e., **incident-users**)
  - The problem with the "**never users**" is that you use future information to define the treatment strategy at baseline
  - The problem with the "**current users**" is that we do not know exactly when they initiated HRT.

What was the problem with the original observational study?

- Prevalent-user bias (aka depletion of susceptible population)



Summary: A look forward

- If you are designing an observational study:
  - Think about the target trial that would answer the same research question
  - Carefully design your observational study following the key aspects of the target trial

- If you are reading an observational study:
  - Think about the target trial that would answer the same research question
  - Carefully assess the study to detect deviations from the target trial

Key Concepts

- Target trial emulation
- □ Background
- Ask a causal question
- Specify the target trial