

Chapter 22: Target Trial Emulation

Contents

1	22.1 Intention-to-Treat Effect and Per-Protocol Effect (p. 305)	1
1.1	Differences Between ITT and PP	2
1.2	Per-Protocol Analysis in Observational Data	2
2	22.2 A Target Trial with Sustained Treatment Strategies (p. 309)	2
2.1	Why Sustained Strategies Are Important	3
3	22.3 Emulating a Target Trial with Sustained Strategies (p. 313)	3
3.1	Emulating Each Component	3
3.2	The Per-Protocol Estimand in the Emulation	4
4	22.4 Time Zero (p. 315)	4
4.1	Immortal Time Bias	5
4.2	Sequential Trials	5
5	22.5 A Unified Approach to Answering What If Questions with Data (p. 317)	5
5.1	Benefits of the Target Trial Approach	6
6	Summary	6
7	References	7

Randomized clinical trials are the gold standard for causal inference, but they are often infeasible, unethical, too slow, or too narrow in scope to answer the questions most relevant to clinical and policy decision-making. Observational databases — electronic health records, insurance claims, disease registries — contain rich longitudinal data on millions of patients and offer an opportunity to answer causal questions at scale. But the translation from “data we have” to “causal question we want to answer” is fraught with opportunities for bias.

The **target trial emulation** framework provides a principled solution: explicitly specify the randomized trial you *would* have conducted if resources and ethics permitted (the **target trial**), then use observational data to emulate it as faithfully as possible.

This chapter is based on Hernán and Robins (2020, chap. 22, pp. 305–320).

Central message: Many biases in observational pharmacoepidemiology studies arise from implicit design choices that would not occur in a well-designed trial. By making the target trial explicit — including its eligibility criteria, treatment strategies, outcome, follow-up, and analysis plan — analysts are forced to confront these choices and mitigate the resulting biases.

1 22.1 Intention-to-Treat Effect and Per-Protocol Effect (p. 305)

In a randomized trial, two causal estimands are commonly of interest:

Definition 1.1 (Intention-to-Treat (ITT) Effect). The **intention-to-treat effect** is the causal effect of the *assigned* treatment strategy, regardless of whether participants actually adhered to their assigned strategy.

$$\text{ITT effect} = E[Y^{a_{\text{assigned}}=1}] - E[Y^{a_{\text{assigned}}=0}].$$

Definition 1.2 (Per-Protocol (PP) Effect). The **per-protocol effect** is the causal effect of *adhering* to the assigned treatment strategy throughout follow-up.

$$\text{PP effect} = E[Y^{\bar{a}=\text{adhere to arm 1}}] - E[Y^{\bar{a}=\text{adhere to arm 0}}].$$

1.1 Differences Between ITT and PP

The ITT analysis is straightforward in a randomized trial: randomization ensures that assigned treatment is independent of all baseline characteristics, so a simple comparison of outcomes by assigned group is valid. The ITT effect is often conservative (toward the null) when adherence is incomplete, because some participants in the active arm will not take the treatment.

The PP analysis is harder because **non-adherence is not random**: participants who discontinue treatment differ from those who continue in ways that are prognostically important. In a trial, PP analysis requires adjustment for post-randomization confounders (covariates that predict both adherence and the outcome), using precisely the methods from Chapters 19–21.

Why PP effects matter:

Policy questions are often best answered by the PP effect. For example, the question “do statins reduce cardiovascular events?” is really asking about the effect of *taking* statins, not merely being assigned to the statin group. If adherence is poor, the ITT estimate will underestimate the biological efficacy of the drug.

In observational data, there is no randomization, so the concept of “assigned treatment” must be replaced by “treatment initiated.”

Definition 1.3 (As-Initiated Analysis). The closest analogue to the ITT effect in observational data is the **as-initiated analysis** (also called “intent-to-treat” by analogy), which compares outcomes between individuals who initiated treatment versus those who did not, regardless of subsequent adherence.

1.2 Per-Protocol Analysis in Observational Data

In observational data, a per-protocol analysis compares individuals who adhered to a specific treatment strategy throughout follow-up. This is a problem of time-varying treatment: treatment initiation, continuation, and discontinuation all occur over time, and all may be confounded by time-varying covariates. The g-methods of Chapter 21 — particularly IP weighting with censoring weights — are the appropriate tools.

2 22.2 A Target Trial with Sustained Treatment Strategies (p. 309)

To make the target trial concept concrete, consider a clinical question: “What is the effect of starting and maintaining antiretroviral therapy immediately versus deferring therapy until CD4 count falls below 350 cells/mm³ on the five-year risk of AIDS or death in HIV-positive individuals?”

The **target trial** for this question would specify:

Example 2.1 (Target Trial for ART Timing).

Component	Specification
Eligibility criteria	HIV-positive adults with $CD4 > 350$, no prior ART
Treatment strategies	(1) Initiate ART immediately; (2) Defer until $CD4 < 350$
Assignment	Random at time zero
Follow-up	From randomization until AIDS, death, or 5 years
Outcome	Composite: AIDS diagnosis or death within 5 years
Causal contrasts	Risk difference, risk ratio, hazard ratio between strategies
Analysis plan	ITT and PP (adjusted for non-adherence via IP weighting)

Definition 2.1 (Sustained Treatment Strategies). A **sustained strategy** specifies a sequence of treatment decisions over the entire follow-up period, not just a single decision at baseline.

The treatment strategies in the target trial above are sustained strategies. Strategy 1 is “always treat” ($\bar{a} = \bar{1}$); strategy 2 is the dynamic strategy “do not treat until $CD4 < 350$, then treat.”

2.1 Why Sustained Strategies Are Important

Many real-world clinical interventions involve decisions made repeatedly over time. The causal effect of sustained “always treat” versus sustained “never treat” is often different — sometimes radically so — from the effect of a single treatment initiation at baseline. The target trial framework makes this explicit by requiring the analyst to specify what the treatment strategy *is* over the entire follow-up, not just at the moment of treatment initiation.

Definition 2.2 (Active Comparator Design). A well-designed target trial uses **active comparators** rather than comparing treated to completely untreated individuals. The “new user, active comparator” design, in which both strategies begin treatment (just of different types or at different thresholds), tends to produce better-calibrated observational estimates because it more closely mirrors the actual clinical decision.

Comparing new users of drug A to non-users of any drug conflates the effect of drug A with the effect of the clinical decision to initiate any treatment.

Intention-to-treat in the target trial: The target trial ITT effect compares individuals by their *assigned* strategy at time zero, regardless of subsequent deviations. In the emulation with observational data, this translates to comparing individuals by their *actual* treatment initiation at time zero, ignoring later changes in treatment. This is easier to implement but often not the most clinically relevant estimand.

3 22.3 Emulating a Target Trial with Sustained Strategies (p. 313)

Emulating the target trial means reproducing each component of the trial specification using observational data.

3.1 Emulating Each Component

Eligibility criteria: Apply the same eligibility criteria to the observational cohort as would have been used in the trial (e.g., HIV-positive, $CD4 > 350$, no prior ART). Any individual who meets the

criteria at some calendar time can serve as a “trial participant” at that time, creating **sequential trials** (discussed in Section 22.4).

Treatment strategies: Observe which individuals followed the target strategies (initiated immediately or waited until $CD4 < 350$). For the per-protocol analysis, censor individuals when they deviate from the strategy.

Assignment mechanism: In the trial, assignment is random. In the emulation, treatment initiation is not random — it depends on measured and unmeasured clinical characteristics. Sequential exchangeability (conditional on measured covariates) is the identifying assumption.

Follow-up and outcome: Use the same outcome definition and follow-up rules as specified in the target trial. Informative censoring (due to loss to follow-up or deviating from protocol) is handled via censoring IP weights.

Analysis: Apply the g-methods of Chapter 21. For the ITT analysis, compare the two initiation groups without adjustment for post-baseline treatment. For the PP analysis, use IP weighting to adjust for time-varying confounders of adherence.

Why emulation is not trivial:

Each component of the target trial introduces potential sources of bias when emulated with observational data:

- **Eligibility criteria:** Selecting a “baseline” requires defining a point in time that matches the trial’s entry criterion. In longitudinal databases this may be complex (see time zero, Section 22.4).
- **Treatment strategies:** Real-world treatment patterns may not map cleanly onto trial strategies; grace periods and adherence windows are needed.
- **Confounding:** The absence of randomization requires adjustment for baseline and time-varying confounders, introducing the challenges of Chapters 19–21.
- **Outcome ascertainment:** Administrative data may under-code events, requiring validation studies.

3.2 The Per-Protocol Estimand in the Emulation

In the emulation, the PP analysis requires censoring participants when they deviate from their “assigned” strategy (the strategy they were on at time zero). For example, under strategy 2 (“defer ART until $CD4 < 350$ ”), a participant is censored if they initiate ART before their $CD4$ reaches 350. This censoring is informative — sicker patients are more likely to start ART early — so censoring IP weights are needed.

The per-protocol analysis thus requires:

- Unstabilized or stabilized treatment IP weights (SW^A), to adjust for confounding of treatment decisions.
- Censoring IP weights (SW^C), to adjust for selection bias from protocol deviations.
- A MSM or g-formula to estimate the counterfactual mean outcome.

4 22.4 Time Zero (p. 315)

Time zero — the moment at which follow-up begins for each individual — is one of the most consequential choices in any observational study. Errors in defining time zero are responsible for a large class of systematic biases in the observational literature.

Definition 4.1 (Time Zero). Time zero for an individual is the point in calendar time at which:

1. The individual meets the eligibility criteria of the target trial.
2. The individual’s treatment strategy is assigned (or, in the emulation, observed).

3. Follow-up for outcomes begins.
All three conditions must be satisfied simultaneously at time zero.

4.1 Immortal Time Bias

Definition 4.2 (Immortal Time Bias). Immortal time bias arises when there is a period of follow-up before time zero during which individuals cannot experience the outcome by design (because they must survive to meet the eligibility criterion or to be “assigned”).

If this immortal time is misclassified — for example, attributed to the treated group when it actually preceded treatment initiation — the treated group appears to have better outcomes simply because they could not have died during the immortal period.

Example 4.1 (Immortal Time Bias: Statin and Mortality). Suppose we study whether statin use reduces mortality using an insurance claims database. We define “statin users” as individuals who filled a statin prescription at any point during a one-year observation window, and we compare their mortality during that year to “non-users.” Individuals who died in the first week cannot fill a prescription, so they are automatically in the non-user group. Statin users, by definition, survived long enough to fill a prescription. This immortal time — the gap between study entry and first prescription — is misattributed to the treated group, inducing a spurious survival advantage.

4.2 Sequential Trials

One practical approach to correct time zero assignment in observational databases is the sequential trials design.

Definition 4.3 (Sequential Trials Design). For each calendar time t at which individuals satisfy the eligibility criteria, create a separate “trial” with time zero at t . Individuals can appear in multiple such trials (each with a different time zero), and their data are then pooled across all trials with appropriate adjustment for the time-varying covariates at each trial’s time zero.

This design ensures that each participant’s follow-up genuinely begins at the moment of eligibility and strategy assignment, eliminating immortal time bias by construction.

Definition 4.4 (Prevalent User Bias and the New User Design). **Prevalent user bias** arises when a study includes individuals who are already on treatment at the start of the observation window, rather than restricting to **new users**: prevalent users have survived on treatment long enough to be observed, so they are a selected, healthier subset of all who ever initiated treatment, and comparing prevalent users to never-users confounds the treatment effect with the selective survival required to be a prevalent user. The **new user design** (also called the active comparator, new user design) restricts to individuals who recently initiated treatment, eliminating prevalent user bias and aligning the observational study more closely with a randomized trial.

5 22.5 A Unified Approach to Answering What If Questions with Data (p. 317)

The target trial emulation framework provides a unifying conceptual scaffolding for all observational causal inference:

Algorithm 5.1 (Steps in Target Trial Emulation).

1. **Specify** the target trial — the idealized randomized experiment that would answer the causal question.
2. **Identify** the components of the target trial that can be emulated with the available observational data, and those that cannot.
3. **Apply** the appropriate *g*-method to estimate the trial’s estimand from the observational data under the required identifying assumptions.
4. **Conduct** sensitivity analyses to assess the robustness of conclusions to violations of the identifying assumptions.

Theorem 5.1 (The Target Trial as a Unifying Framework). *Any causal question about a medical or social intervention can be expressed as a target trial with:*

- Eligibility criteria defining the target population.
- Treatment strategies defining the interventions to compare.
- A time zero aligning eligibility, assignment, and follow-up.
- An outcome and follow-up period.
- An analysis plan (ITT, PP, or both).

*The choice of *g*-method (*g*-formula, IP weighting, *g*-estimation) is secondary — what matters is first getting the trial specification right.*

5.1 Benefits of the Target Trial Approach

The target trial framework:

- **Makes implicit choices explicit:** Eligibility, time zero, and strategies that are often decided ad hoc in practice must be pre-specified.
- **Connects to a clearly defined estimand:** The causal question is framed as a comparison between specific strategies in a specific population, leaving no ambiguity about what is being estimated.
- **Organizes the analytic steps:** Once the trial is specified, it is clear what confounders must be measured, what models must be fit, and what biases must be mitigated.
- **Facilitates replication and critique:** Other researchers can evaluate whether the emulation is faithful to the target trial and whether the assumptions are plausible.

When observational emulation is insufficient:

Not every causal question can be answered by emulating a target trial with available observational data. The emulation may fail if:

- Key eligibility criteria require data not available in the database.
- The treatment strategies of interest were never observed (positivity violations).
- Unmeasured confounders are strong enough that sequential exchangeability is implausible.
- The outcome is too rare or too poorly measured in the database.

In these cases, the target trial framework helps clarify *why* the emulation is limited and what additional data or study design changes would be needed. This is itself valuable — it prevents researchers from publishing biased estimates while presenting them as valid.

Further reading: The target trial emulation framework was developed by Hernán and Robins. Key papers include Hernán & Robins (2016), “Using Big Data to Emulate a Target Trial” in the *American Journal of Epidemiology*, and the series of application papers in pharmacoepidemiology that followed.

6 Summary

-
- The **intention-to-treat (ITT) effect** compares outcomes by assigned strategy; the **per-protocol (PP) effect** compares outcomes by strategy actually adhered to.
 - In observational data, the PP analysis requires time-varying IP weighting to handle confounding of adherence decisions.

- The **target trial** is the explicit specification of the randomized experiment that the observational analysis attempts to emulate. It includes eligibility criteria, treatment strategies, time zero, outcomes, and analysis plan.
- **Time zero** must simultaneously mark eligibility, strategy assignment, and follow-up start. Misalignment of these leads to **immortal time bias**, **prevalent user bias**, and other systematic errors.
- The **sequential trials** design eliminates immortal time bias by defining a new “trial” at each calendar time an individual becomes eligible.
- The **new user design** eliminates prevalent user bias by restricting to individuals who recently initiated treatment.
- The target trial framework **unifies** observational causal inference: specify the trial first, then choose the g-method for estimation.

7 References

Hernán, Miguel A, and James M Robins. 2020. *Causal Inference: What If*. Chapman & Hall/CRC. <https://miguelhernan.org/whatifbook>.