TARGET GUIDELINES

Reporting comparative effectiveness studies using the Target Trial Framework

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Causal inference from observational data

- Principles of good study design and analyses have been well understood for decades

- Many observational studies do not apply them
  - As editors and reviewers, we keep making the same comments to authors over and over
  - Lots of published observational studies have provably incorrect methodology

- Methodologists aren't communicating well

Enter the Target trial framework

- **Use observational data to emulate a (hypothetical) pragmatic trial**
  - Same design/data structure as a trial
  - Same data analysis as a trial (other than baseline confounding adjustment)

- **The Target Trial framework helps investigators**
  - articulate a precise causal question
  - implement sound procedures to answer it
  - report their work in such a way that biases are more easily detected

Types of observational data

Research data

- Collected specifically for research
  - Cohort, case-control, case-crossover studies…
  - Biobanks
  - Disease registries
  - Randomized trials
  - …

Found data

- Generated for non-research purposes
  - Electronic health records
  - Insurance claims databases
  - National registers
  - …

"Real world data"

"Routinely collected data"

We analyze observational data because we don't have a randomized trial

- Observational analyses are **not** our preferred choice for causal inference

- For each observational analysis for causal inference, we can imagine a hypothetical randomized trial that we would prefer to conduct
  - If only it were possible
  - that hypothetical trial is our causal target

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 question into a target trial, then the question is not well-defined

The Target Trial 

- **Suggested more or less explicitly by many authors**
  - Dorn (1953), Wold (1954), Cochran, Rubin, Feinstein, Dawid…
  - for simple settings with a time-fixed treatment and a single eligibility point

- **Explicit generalization to time-varying treatments and multiple eligibility points**
  - Robins (1986)
  - Hernán, Robins. *Am J Epidemiol* 2016

The Target Trial concept leads to a simple algorithm for causal inference

1. **Ask the causal question** (point at the Target)
   - Specify the protocol of the Target Trial

2. **Answer the causal question** (shoot the Target)
   - Option A: Conduct the Target Trial
   - Option B : Use observational data to **explicitly** emulate Target Trial
     - Then apply appropriate causal inference analytics

Step 1
Specify Target Trial protocol

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

Step 1 Specify Target Trial protocol	Step 2 Emulate Target Trial protocol
Eligibility criteria	Data mapping for Eligibility criteria
Treatment strategies	Data mapping for each component
Assignment	Data mapping for assignment
Time zero and follow-up	Same
Outcomes	Data mapping for outcomes
Causal contrasts	Observational analogs of contrasts
Identifying assumptions	Identifying assumptions
Data analysis	Data analysis

Deviating from the Target Trial framework often leads to biased effect estimates

Two high-profile examples:

- **Postmenopausal hormone therapy and heart disease**
  - Observational studies: >30% lower risk in current vs. never users
  - Randomized trial: >20% higher risk in initiators vs. noninitiators
- **Statins and cancer**
  - Observational studies: association between statins and lower cancer risk (50-65% lower risk!)
  - Meta-analysis of randomized trials: Null effect

An observational re-analysis under the target trial framework eliminated the discrepancies

- **Postmenopausal hormone therapy and heart disease**
  - Nurses' Health Study, U.S. (Hernán et al. *Epidemiology* 2008)
- **Statins and cancer**
  - Linked CPRD primary care records accessed through the CALIBER resource, U.K (Dickerman et al. *Nature Medicine* 2019)

- **Which implies that the problem was not the observational data but how the data were used**
  - problem was **not** confounding due to lack of randomization
  - same applies to many other examples

Interesting state of affairs

- **The usual criticism of observational analyses is lack of randomization**
  - Failure to emulate randomization because of insufficient data on confounders (residual confounding)
  - Hard to fix
- **Yet mounting evidence suggests another problem**
  - Failure to design the observational analyses correctly
  - Leads to immortal time and selection biases
  - Easy to fix (this is what the target trial framework helps with)

Criticisms of target trial framework

- "You knew the right answer before emulating the target trial"
- "This target trial emulation business is just marketing"
- "Target trial emulation doesn't solve all problems of causal inference from observational data"

High-profile observational studies that were proven wrong by randomized trials

- Hormone therapy and coronary heart disease
  - *New England Journal of Medicine* 1996;335:453–461
- Statins and cancer
  - *New England Journal of Medicine* 2005; 352: 2184–2192

- Explicit target trial emulation fixed the problem
  - the problem was not the observational data but how the observational data were used
- "Yes, but you knew the right answer because these observational analyses were done after the randomized trials!"

High-profile observational studies that were proven wrong by randomized trials

- **Hormone therapy and coronary heart disease**
  - Risk was ~60% lower in postmenopausal women using therapy
    - *New England Journal of Medicine* 1996;335:453–461
- **Statins and cancer**
  - Risk of colorectal cancer was ~50% lower in people using statins
    - *New England Journal of Medicine* 2005; 352: 2184–2192
- **When to start antiretroviral therapy in persons with HIV**
  - Risk of death doubled when deferring therapy just a few months
    - *New England Journal of Medicine* 2009; 360:1815–1826

When to start antiretroviral therapy: no randomized-observational discrepancy

Annals of Internal Medicine | ORIGINAL RESEARCH

When to Initiate Combined Antiretroviral Therapy to Reduce Mortality and AIDS-Defining Illness in HIV-Infected Persons in Developed Countries

An Observational Study

Lauren Cain et al. *Annals of Internal Medicine* 2011 : 154:509-515

Comparative effectiveness of immediate antiretroviral therapy versus CD4-based initiation in HIV-positive individuals in high-income countries: observational cohort study

Sara Lodi et al. *Lancet HIV* 2015: 2:e335-343

"But you knew the right answer because these observational analyses were done after the randomized trials!"

- Nope
- The emulation of the target trial of "when to start antiretroviral therapy" was published before the randomized trial findings were known
- Let's see examples of observational emulations of target trials that were conducted BEFORE the randomized trials
  - For the treatment and preventionof COVID-19

Tocilizumab and mortality in COVID-19 patients

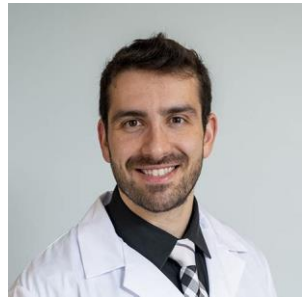
- Strong benefit. Later confirmed by a randomized trial
  - Shruti Gupta, David Leaf et al. *JAMA Internal Medicine* 2021; 181:41-51

Research

JAMA Internal Medicine | Original Investigation

Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19

Anticoagulants and mortality in COVID-19 patients



- No effect. Later confirmed by a randomized trial.
  - Hanny Al-Samkari et al. *Annals of Internal Medicine* 2021; 174:622-632

ORIGINAL RESEARCH

Annals of Internal Medicine

Thrombosis, Bleeding, and the Observational Effect of Early Therapeutic Anticoagulation on Survival in Critically Ill Patients With COVID-19

Plasma therapy and mortality in COVID-19 patients

- No effect. Later confirmed by randomized trials
  - Kelly Cho et al. *Journal of Infectious Diseases* 2021; 224: 967-975

The Journal of Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Early Convalescent Plasma Therapy and Mortality Among US Veterans Hospitalized With Nonsevere COVID-19: An Observational Analysis Emulating a Target Trial

Vaccine booster and hospitalization from SARS-CoV-2 Delta variant

- Strong benefit. Later confirmed by a randomized trial
  - Noam Barda, Noa Dagan et al. *Lancet* 2021; 398: 2093-2100
  - (the trial findings were published after Delta had disappeared)

THE LANCET

Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study

Noam Barda, Noa Dagan*, Cyrille Cohen, Miguel A Hernán, Marc Lipsitch, Isaac S Kohane, Ben Y Reis†, Ran D Balicer†*

Criticisms of target trial emulation

- ~~"You knew the right answer before emulating the target trial"~~
- "This target trial emulation business is just marketing"
- "Target trial emulation doesn't solve all problems of causal inference from observational data"

"This target trial emulation business is just marketing"

- **Define marketing**
  - "the process or technique of promoting, selling, and distributing a product or service" (Merriam-Webster dictionary)

- **Ok, then, yes, "target trial emulation" is a form of "marketing"**
  - "a technique to promote good methodology for causal inference from observational databases"

- **There are other ways to promote good methodology but they have not worked very well**
  - as so many published observational failures show

Think of "explicit target trial emulation" as a set of guidelines for improved causal research

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selection and immortal time biases that can be avoided by explicitly emulating a target trial. Alternatively, these biases can be avoided by studious application of principles of causal inference and study design, but the target-trial approach helps in implementing these principles.

Think of "explicit target trial emulation" as a checklist for safer causal research

- Airplane pilots use checklists before taking off
- Surgeons use checklists before operating

- Maybe the best pilots and surgeons don't need to use checklists

- But aren't you glad they do?
  - Surgical safety checklists greatly reduce complications and mortality
  - "marketing" checklists isn't necessarily a bad thing to do

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Criticisms of target trial emulation

- ~~"You knew the right answer before emulating the target trial"~~
- "This target trial emulation business is just marketing"
  - Yes, it is. Whatever works.
- "Target trial emulation doesn't solve all problems of causal inference from observational data"
  - Duh.

Target trial emulation eliminate design biases, not confounding due to lack of randomization

- It prevents "design" biases
  - Immortal time, selection
- It doesn't prevent "data" biases
  - Confounding, measurement error

- "Explicit emulation of a target trial using observational data helps eliminate unnecessary sources of bias so that concerns can focus on potential confounding bias due to nonrandomization."
  - Hernan. *N Engl J Med* 2021; 385:15

In summary, the target trial framework helps

- Articulate a precise causal question
- Implement methodologically sound observational analyses to answer the causal question
  - Avoid common flaws in observational analyses
  - Distinguish between question and methods used to answer it
- Report the design and analysis
  - Good reporting of design and analysis is not possible without good design and analysis
  - Reporting guidelines are effectively guidelines for good practice

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