Target trial emulation:
Because not all causal questions can be answered by randomized trials

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Why causal inference?
Because decisions must be made

- Regulatory decisions
  - Approve or reject a new drug?
  - Add stronger warnings to a drug label?
  - Recall an already approved drug?
- HTA decisions
  - Recommend against reimbursement of a new drug?
  - Recommend a drug for high-risk patients only?
  - Remove a listed drug from reimbursement?

Causal inference is about learning what works to help people (including regulators and HTA agencies) make better decisions

Decision making needs to be guided by causal evidence obtained from data

- How do we generate data to guide decision making?
  - How do we make causal inferences?
  - How do we learn what works?

- 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

But randomized trials can't possibly answer all questions

expensive unethical impractical untimely




- or too many populations of interest, or too many outcomes
- or simply nobody is willing to fund it (head-to-head trials?)

Decisions still need to be made. What do we do?

- We generate or repurpose observational data
- or else we wouldn't have any human data to support decisions

A boring debate

- "I believe all regulatory and HTA decisions should be based on randomized trials"
- "But that's impossible."
- "I still believe all regulatory and HTA decisions should be based on randomized trials"
- "But…"

The question isn't WHETHER to use observational data, but HOW to use observational data in the best possible way

Types of observational data

Research data

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

Found data

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

"Real world data"

"Routinely collected data"

We have LOTS of observational data

- In the 1970s epidemiologists started to work with healthcare databases
- Data quantity and quality keep increasing
  - Millions of individuals followed for many years
  - Detailed information on their therapies, clinical and sociodemographic factors, health outcomes…
- This is so promising, and yet…

The medical literature is full of spectacular failures of causal inference from observational data

- Let's see 2 examples
  - 1 with research data
  - 1 with found data

Claim: Hormone therapy prevents coronary heart disease in postmenopausal women

- Observational study

The New England
Journal of Medicine

VOLUME 335 AUGUST 15, 1996 NUMBER 7

POSTMENOPAUSAL ESTROGEN AND PROGESTIN USE AND THE RISK OF CARDIOVASCULAR DISEASE

Results We observed a marked decrease in the risk of major coronary heart disease among women who took estrogen with progestin, as compared with the risk among women who did not use hormones

Hormone therapy DOES NOT prevent coronary heart disease in postmenopausal women

- Randomized trial (7 years later)

Estrogen plus Progestin and the Risk of Coronary Heart Disease

CONCLUSIONS

Estrogen plus progestin does not confer cardiac protection and may increase the risk of CHD among generally healthy postmenopausal women, especially during the first year after the initiation of hormone use. This treatment should not be prescribed for the prevention of cardiovascular disease.

Claim:
Statin therapy prevents cancer

Observational study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Statins and the Risk of Colorectal Cancer

N Engl J Med 2005;352:2184-92.

CONCLUSIONS

The use of statins was associated with a 47 percent relative reduction in the risk of colorectal cancer after adjustment for other known risk factors. Because the absolute risk reduction is likely low, further investigation of the overall benefits of statins in preventing colorectal cancer is warranted.

Statin therapy DOES NOT prevent cancer

- Meta-analysis of randomized trials (months later)

Statins and Cancer Risk

JAMA, January 4, 2006—Vol 295, No. 1

A Meta-analysis

Krista M. Dale, PharmD
Craig I. Coleman, PharmD
Nickole N. Henyan, PharmD
Jeffrey Kluger, MD
C. Michael White, PharmD

Context Statins are cholesterol-lowering drugs that have been proven in randomized controlled trials to prevent cardiac events. Recent retrospective analyses have suggested that statins also prevent cancer.

Objectives To investigate the effect of statin therapy on cancer incidence and cancer death and to analyze the effect of statins on specific cancers and the effect of statin lipophilicity or derivation.

Conclusions Statins have a neutral effect on cancer and cancer death risk in randomized controlled trials. We found that no type of cancer was affected by statin use and no subtype of statin affected the risk of cancer.

Just two examples from a very long list

- The selected examples have serious design flaws
  - though, interestingly, neither were retracted
    - NOTE: Publication of observational results may interfere with the design and recruitment of future trials
      - not only observational estimates are wrong, but they prevent us from getting the correct ones

- Why so many observational analyses have biased effect estimates?

Two possible explanations for the failures of causal inference from observational data

- **Observational datasets are bad**
  - Too much confounding and measurement error
    - "Because treatments are not randomly assigned, outcome differences between treatment groups are due to differences in the characteristics of treated and untreated individuals rather than to treatment"
  - Data biases

- **Observational datasets are used badly**
  - Data analysis doesn't respect basic principles of study design
  - Design biases

Design biases: How do we ensure that the design of observational analyses is sound?

- Easy

- We have well established principles to analyze data from randomized trials
  - for example: start the follow-up at the time that eligible individuals are assigned to a treatment strategy

- Let's apply the same principles to the observational data
  - structure the observational dataset and analyze it as you'd do for a randomized trial

Reminder: 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
- Start/end of 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
Outcomes	Data mapping for outcomes
Start/end of follow-up	Same
Causal contrasts	Observational analogs of contrasts
Identifying assumptions	Identifying assumptions
Data analysis	Data analysis

Explicitly emulating a target trial eliminates most design biases

- But not data biases like confounding
  - because of lack of randomization
- How important is it to eliminate design biases?
  - due to deviations from the emulation of the target trial
- What happens if we adopt the target trial framework to the 2 previous examples of observational failures?

Hormone therapy and coronary heart disease: No randomized-observational discrepancy

Observational Studies Analyzed Like Randomized Experiments

An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease

Miguel A. Hernán,[a,b] *Alvaro Alonso,*[c] *Roger Logan,*[a] *Francine Grodstein,*[a,d] *Karin B. Michels,*[a,d,e] *Walter C. Willett,*[a,d,f] *JoAnn E. Manson,*[a,d,g] *and James M. Robins*[a,h]

Epidemiology 2008; 19: 766-779

Authors' Response, Part I: Observational Studies Analyzed Like Randomized Experiments

Best of Both Worlds

Miguel A. Hernán[a] *and James M. Robins*[b]

Epidemiology 2008; 19: 789-792

Statins and cancer: No randomized-observational discrepancy

Barbra Dickerman et al. *Nature Medicine* 2019; 25: 1601-1606

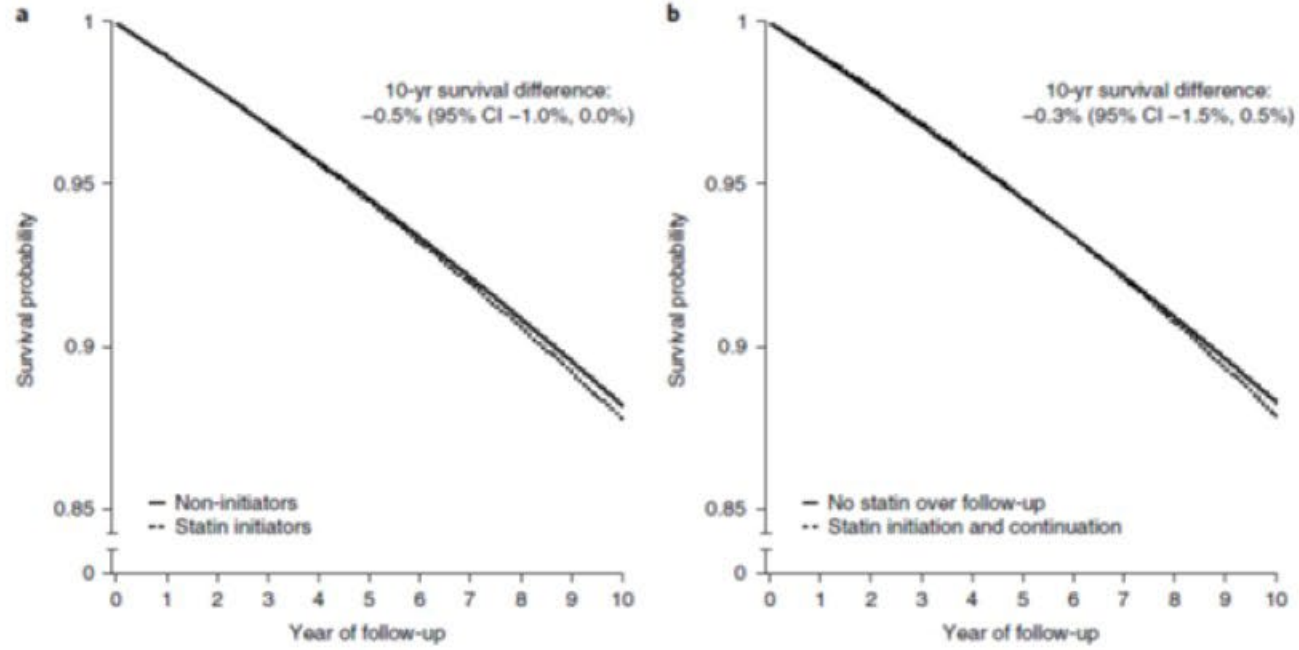


Fig. 2 | Standardized cancer-free survival curves comparing statin therapy with no statin therapy, CALIBER, 1999–2016. Observational analog to an intention-to-treat analysis (**a**) and per-protocol analysis (**b**).

Contrary to popular belief, the problem wasn't the lack of randomization

- But the incorrect design of the observational analyses
  - Determination of eligibility and treatment assignment were not synchronized at the start of follow-up (time zero)
  - Immortal time and selection bias
    - Hernán et al. *J Clin Epidemiol* 2016; *Epidemiology* 2025

- Nothing wrong with the observational data but with HOW the data were used

~~Two~~ A possible explanation~~s~~ for the failure of causal inference from observational data

- Observational datasets are bad
  - Too much confounding?
  - Data biases

- ~~Observational datasets are not used well~~
  - ~~Data analysis doesn't respect basic principles of study design~~
  - ~~Design biases~~

All of this begs the question: How bad is the lack of randomization by itself?

- To answer this question, we first need to ensure that that the observational analyses are well designed

- That is,
  - First, we explicitly emulate a target trial
  - Second, we worry about confounding

- We can't even try to adjust for confounding when there is immortal time and selection bias

A possible criticism of the previous two examples

- "You knew the right answer because these observational analyses were done after the randomized trials!"
- Let's review other observational emulations of target trials that were conducted BEFORE the randomized trials

Early antiretroviral therapy for persons with HIV: Benefit, later confirmed by randomized trial

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

Tocilizumab and mortality in critically ill 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 critically ill 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†*

But randomized trials and observational emulations are not in competition

- Randomized trials and observational emulations are complementary approaches

- Trials can answer some questions but not all questions
  - Even for a particular treatment, multiple questions arise about subgroups of patients, duration of follow-up, outcomes…
- Observational emulations can be used to extend the inferences from a trial to other causal questions
  - But only after having replicated the same answers as the trial

Benchmarking

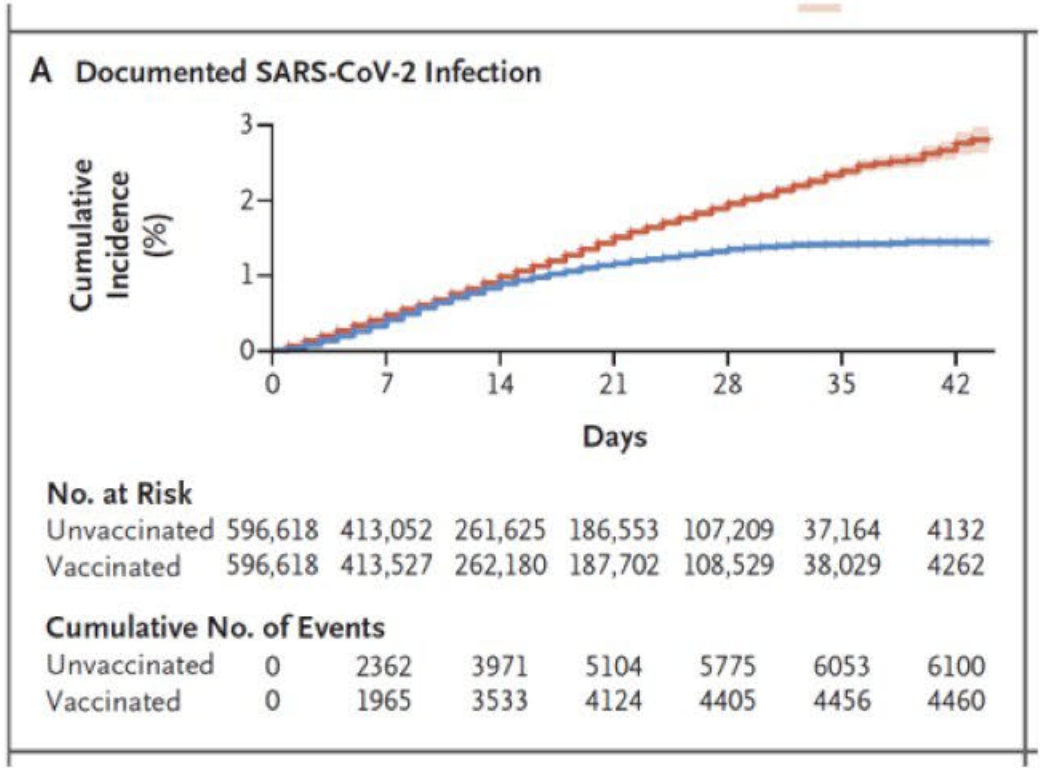
- Use effect estimates from randomized trials to benchmark effect estimated from observational emulations

- If benchmarking is successful, extend the inferences from the trials using the observational data
  - Dahabreh et al. *Epidemiology* 2020

mRNA vaccine effectiveness for serious outcomes after benchmarking for less severe ones (infection)

Observational emulation

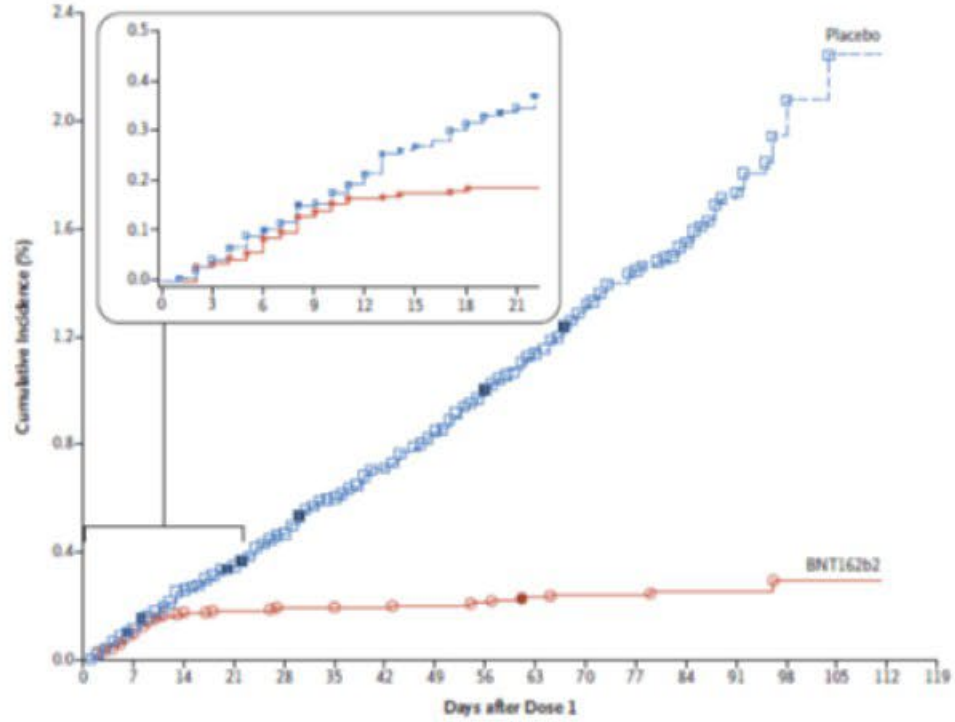
Dagan et al. *N Engl J Med* 2021; 384;1412-23



No. at Risk							
Unvaccinated	596,618	413,052	261,625	186,553	107,209	37,164	4132
Vaccinated	596,618	413,527	262,180	187,702	108,529	38,029	4262

Cumulative No. of Events							
Unvaccinated	0	2362	3971	5104	5775	6053	6100
Vaccinated	0	1965	3533	4124	4405	4456	4460

Phase 3 randomized trial



Cancer treatment and overall survival

- Estimates in underrepresented populations after benchmarking to other populations
  - Lucia Petito, Xabier García-Albéniz et al. *JAMA Network Open* 2020; 3

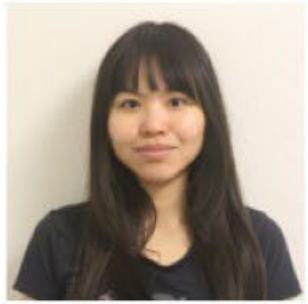
JAMA Network | Open

Original Investigation | Oncology

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

Effectiveness and safety of infertility treatments



- Estimate effects on rare outcomes (maternal and neonatal complications) after benchmarking to common ones
  - Yu-Han Chiu et al. *Fertility and Sterility* 2022; 117: 981-991

Effectiveness and safety of infertility treatments

- Estimate effects on rare outcomes (teratogenic effects) after benchmarking to common ones
  - Jennifer Yland et al. *Human Reproduction* 2022; 37: 793-805

human reproduction

ORIGINAL ARTICLE **Reproductive endocrinology**

Emulating a target trial of the comparative effectiveness of clomiphene citrate and letrozole for ovulation induction

Is the Target Trial Framework necessary?

- Don't we already have other frameworks to articulate causal questions?

- PICO
  - This is a simplified version of the target trial framework
- **Estimand framework (ICH E9 Addendum)**
  - This is an element (or two, it's confusing) of the target trial framework

PICO is an incomplete version of the target trial framework

Target trial protocol
Eligibility criteria
Treatment strategies
Assignment
Outcomes
Start/end of follow-up
Causal contrasts
Identifying assumptions
Data analysis

- P for Eligibility criteria
- IC for Treatment strategies
  - but typically oversimplified
    - Intervention: Treatment
    - Control: No treatment
- O for Outcome

- Other elements of the protocol are not explicitly defined by PICO

The ICH E9 Estimand framework is about one element of the target trial framework

Target trial protocol

- Eligibility criteria
- Treatment strategies
- Assignment
- Outcomes
- Start/end of follow-up
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Causal estimand

- An estimand is just something we want to estimate
  - A causal estimand is defined by the elements of the target trial protocol

The ICH E9 Estimand framework is about one element of the target trial framework

Target trial protocol

- Eligibility criteria
- Treatment strategies
- Assignment
- Outcomes
- Start/end of follow-up
- Causal contrasts
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- The "estimand framework" focuses on the causal contrast only
  - Intention-to-treat effect (treatment policy effect??)
  - Per-protocol effect (again, under other names)
- and conflates it with other elements of the estimand
  - "intercurrent events" combine definitions of deviations from protocol (treatment strategies) with competing events (causal contrast)

Evidence-based decision making requires evidence

- Other things being equal, reasonable people will always prefer their evidence from randomized trials
- But we can't expect to have evidence from randomized trials to support all decisions at all times
- When we don't have the target trial of interest, we try to emulate it using observational data

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