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Target trials: Emulating trials from observational data

CTU lecture

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Learning objectives

After this CTU lecture you understand

- **Why** a target trial emulation might be helpful/necessary
- The **core elements** and **steps** of a target trial emulation
- **Selection bias** and **immortal time bias** as important bias examples when analyzing observational data

Lecture overview

- **Why emulation?**
- **Principles of causal inference from observational studies**
- **Key elements of a target trial emulation**

Why emulation?

- Randomized controlled trials (RCTs) **gold standard** for assessing effectiveness of health care interventions

- RCTs **might not be performed** (ethically, resources) or not **timely** (we still wait on their results)

- RCTs might be restricted to a ”narrow” study population, for example, when excluding older patients

Example: Colorectal cancer (CRC) screening

- CRC is one of the most common cancer types

- Colonoscopy or fecal occult blood testing (FOB) widely used screening tools

- Results from RCT on FOB exist, but **no results** (yet) from RCTs on colonoscopy

Example: Colonoscopy RCTs

Endoscopy 2012; 44(07): 695-702
DOI: 10.1055/s-0032-1306895

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Special report

The NordICC Study: Rationale and design of a randomized trial on colonoscopy screening for colorectal cancer

M. F. Kaminski , M. Bretthauer , A. G. Zauber , E. J. Kuipers , H.-O. Adami , M. van Ballegooijen , J. Regula , M. van Leerdam , T. Stefansson , L. Påhlman , E. Dekker , M. A. Hernán , K. Garborg , G. Hoff , for the NordICC Study Group

Actual Enrollment :	95000 participants
Study Start Date :	May 2009
Estimated Primary Completion Date :	June 2026
Estimated Study Completion Date :	July 2036

https://clinicaltrials.gov/ct2/show/NCT00883792

ORIGINAL CONTRIBUTIONS: SMALL BOWEL

Colonoscopy vs. Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer (CONFIRM): Rationale for Study Design

Dominitz, Jason A MD, MHS[1,17]; Robertson, Douglas J MD, MPH[2,17]; Ahnen, Dennis J MD[3]; Allison, James E MD[4]; Antonelli, Margaret AS[5]; Boardman, Kathy D RPh, MS[6]; Ciarleglio, Maria PhD[7]; Del Curto, Barbara J BS[6]; Huang, Grant D MPH, PhD[8]; Imperiale, Thomas F MD[9]; Larson, Meaghan F MPH[10]; Lieberman, David MD[11]; O'Connor, Theresa MPH, PhD[5]; O'Leary, Timothy J MD, PhD[12]; Peduzzi, Peter PhD[7]; Provenzale, Dawn MD, MS[13]; Shaukat, Aasma MD, MPH[14]; Sultan, Shahnaz MD, MHSc[14]; Voorhees, Amy MPA, MPH[15]; Wallace, Robert ScD[5]; Guarino, Peter D MPH, PhD[16] for the CONFIRM Study Group

Author Information

American Journal of Gastroenterology: November 2017 - Volume 112 - Issue 11 - p 1736-1746
doi: 10.1038/ajg.2017.286

Actual Enrollment :	50126 participants
Actual Study Start Date :	April 30, 2012
Estimated Primary Completion Date :	September 29, 2028
Estimated Study Completion Date :	September 29, 2028

https://clinicaltrials.gov/ct2/show/NCT01239082

Observational studies

- **Lower costs** than RCTs
- **Often broader range** of information, variables and patients
- More «**real-world evidence**»
- For **research** purposes or **non-research** purposes
- Routinely collected (insurance claims data, eMedical records, registry data)

! **BUT**: Biases affect treatment comparisons (among others, confounding, see ROBINS-I doi: 10.1136/bmj.i4919)

Which questions are causal?
Do you need a RCT to answer it?

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Does colonoscopy screening reduce 8-year mortality of colorectal cancer?

How many colonoscopies were performed over the last 8 years?

What is the probability of death (due to colorectal cancer) comparing patients who received colonoscopy screening vs no screening?

Counterfactual outcomes

Patient A received no screening:
Death within 8 years

★ **Actually never observed**

Patient A, if she **would have** received screening: Alive

Population causal effects

Knowledge of individual counterfactuals would allow to estimate population causal effects!

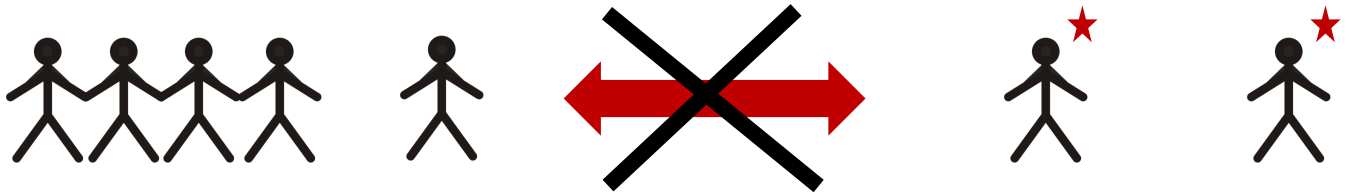
Randomized controlled trials

Counterfactual outcomes are exchangeable
Estimation of causal estimand possible

Screening **No screening**

Randomize

Observational studies



Counterfactual outcomes are in general NOT exchangeable

Screening **No screening**

Confounders

“Tools” from causal inference

Counterfactual outcomes are conditional exchangeable under certain (strong) assumptions* (no free lunch) and analysis techniques*

! We **can** answer causal questions using observational data **too**.

* Not discussed in this lecture.

Which questions are causal?

Does screening colonoscopy reduce 8-year colorectal cancer mortality? **Causal – What if…**

How many colonoscopies were performed over the last 8 years? **Description**

What is the chance of death (due to colorectal cancer) comparing patients who received colonoscopy screening vs no screening? **Prediction/Modelling**

How can we answer our causal question? Target trial!

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Does screening colonoscopy reduce the 8-year risk of CRC mortality?

Target trial

- A **target trial** defines the core elements of a **planned** randomized experiment to answer our **causal question**

- Study aim, eligibility criteria, treatment strategies, treatment assignment, causal contrasts (please compare with CONSORT checklist)

- Does screening colonoscopy reduce the 8-year risk of CRC mortality?

Target trial: How can we answer our causal question?

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Component	Target trial
Aim	To estimate the effect of screening colonoscopy on the 8-year risk of CRC in U.S. individuals aged 70–74 years
Eligibility	Persons without gastrointestinal symptoms aged 70–74 years with no history of CRC, and continuously enrolled in Medicare for 5 years with no adenoma, inflammatory bowel disease, colectomy, or CRC screening in that period, and who were regular users of preventive services (at least 2 of the following: influenza vaccine, preventive visit, breast or prostate screening, in the 2 years before enrollment)
Treatment strategies	1. Screening colonoscopy at baseline 2. No screening for CRC at baseline Patients receive usual care after the intervention
Treatment assignment	Patients ar randomly assigned to either strategy
Follow-up	Follow-up starts at treatment assignment and ends at CR diagnosis, at death, at loss to follow-up, 8 years after baseline, or on 31 December 2012, whichever occurs
Outcome	CRC diagnosis within 8 years of baseline
Causal contrast	Intention-to-treat effect, i.e., effect of being assigned to screening colonoscopy versus no screening at baseline protocol effect, i.e., effect of receiving screening colono versus no screening at baseline
Statistical analysis	Intention-to-treat analysis. Per-protocol analysis: compar of 8-year CRC risk between groups receiving each trea strategy with adjustment for baseline covariates (and p baseline covariates when adjusting for loss to follow-u

García-Albéniz, Hsu, Hernán: **The value of explicitly emulating a target trial when using real world evidence: an application to colorectal cancer screening**. Eur J Epidemiol. 2017 Jun;32(6):495-500. doi: 10.1007/s10654-017-0287-2

Target trial emulation: If RCT is not possible

A **target trial** from **observational data** emulates a (pragmatic) RCT in a structured way:

➡️ Similar **principles** as in RCTs (eligibility criteria, treatment strategies, causal contrasts, …)

➡️ **Minimizes** certain biases (selection bias, immortal time bias, …)

❗ **Does NOT** convert an observational study into a RCT: Limitations of observational data (for example, confounding) remain.

Target trial: How can we answer our causal question?

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Table 1 Specification and emulation of a target trial of screening colonoscopy using real world data from U.S. Medicare 1999–2012

Component	Target trial	Emulated trial using real world data
Aim	To estimate the effect of screening colonoscopy on the 8-year risk of CRC in U.S. individuals aged 70–74 years	Same
Eligibility	Persons without gastrointestinal symptoms aged 70–74 years with no history of CRC, and continuously enrolled in Medicare for 5 years with no adenoma, inflammatory bowel disease, colectomy, or CRC screening in that period, and who were regular users of preventive services (at least 2 of the following: influenza vaccine, preventive visit, breast or prostate screening, in the 2 years before enrollment)	Same, except CRC history is evaluated in the 5 years before enrollment
Treatment strategies	1. Screening colonoscopy at baseline 2. No screening for CRC at baseline Patients receive usual care after the intervention	Same
Treatment assignment	Patients are randomly assigned to either strategy	Patients are assigned to screening colonoscopy if they receive a screening colonoscopy in the 7 days following eligibility and to no screening otherwise. Randomization is emulated via adjustment for baseline

doi: 10.1007/s10654-017-0287-2

Colonoscopy observational data

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- Insurance claims data or regulatory data often collects relevant information about treatment procedures

- In Switzerland: Inpatient and outpatient hospital data, health insurance data (Helsana, …), …

- In US: Medicare (health insurance program for persons older 65 years or disabled persons), …

Colonoscopy observational data

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ID	AGE	OTHER PATIENT CHAR.	TREAT_DATE	TREATMENT
1	68		09.04.2018	39.0015 (TARMED: Grundkonsultation Radiologie)
1	68		…	
1	70		01.02.2020	00.0060 (TARMED: Besuch, erste 5 Min.)
1	70		10.02.2020	00.0060 (TARMED: Besuch, erste 5 Min.)
1	70		10.02.2020	19.1010 (TARMED: Koloskopie, vollständig)
1	70		17.02.2020	Krebsdiagnose
1	70		15.03.2020	45.74 (CHOP: Resektion des Colon)
1	70		10.04.2020	39.6280 (TARMED: Grundelement Chemotherapie)
1	70		…	…

Fictive data

Treatment

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ID	AGE	OTHER PATIENT CHAR.	TREAT_DATE	TREATMENT
1	68		09.04.2018	39.0015 (TARMED: Grundkonsultation Radiologie)
1	68		…	
1	70		01.02.2020	00.0060 (TARMED: Besuch, erste 5 Min.)
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1	70		10.02.2020	**19.1010 (TARMED: Koloskopie, vollständig)**
1	70		17.02.2020	Krebsdiagnose
1	70		15.03.2020	45.74 (CHOP: Resektion des Colon)
1	70		10.04.2020	39.6280 (TARMED: Grundelement Chemotherapie)
1	70		…	…

Fictive data

Eligibility

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Age<70 years

No previous CRC

No previous diagnostic or surveillance colonscopy in the past 5 years

ID	AGE	OTHER PATIENT CHAR.	TREAT_DATE	TREATMENT
1	68		09.04.2018	39.0015 (TARMED: Grundkonsultation Radiologie)
1	68		…	
1	70		01.02.2020	00.0060 (TARMED: Besuch, erste 5 Min.)
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1	70		…	…

Fictive data

Steps for a target trial emulation

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1) Define (causal) research question: “What is the target trial?” ✅
2) Define target trial with protocol ✅
3) Check data validity/quality/availability ➡ SOON
4) Define time zero ➡ SOON
5) Define analysis strategies 🕒
6) Benchmark, if possible 🕒

Hernán, Robins: **Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available**. Am J Epidemiol, 2016 Apr 15;183(8):758-64. doi: 10.1093/aje/kwv254

Data availability/validity/quality of observational studies

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- Important information might be **missing** (for example, diagnosis information) or requires **linkage** of data (for example, mortality): Check carefully what you need and **if it's available**!

- **Quality** of exposure and outcomes in observational data (especially non-research) likely less good as in RCTs and requires in-depth validation

- "**Just because an analysis can be done does not mean it should be done**", Weiss NS doi: 10.1097/EDE.0b013e318210aca5

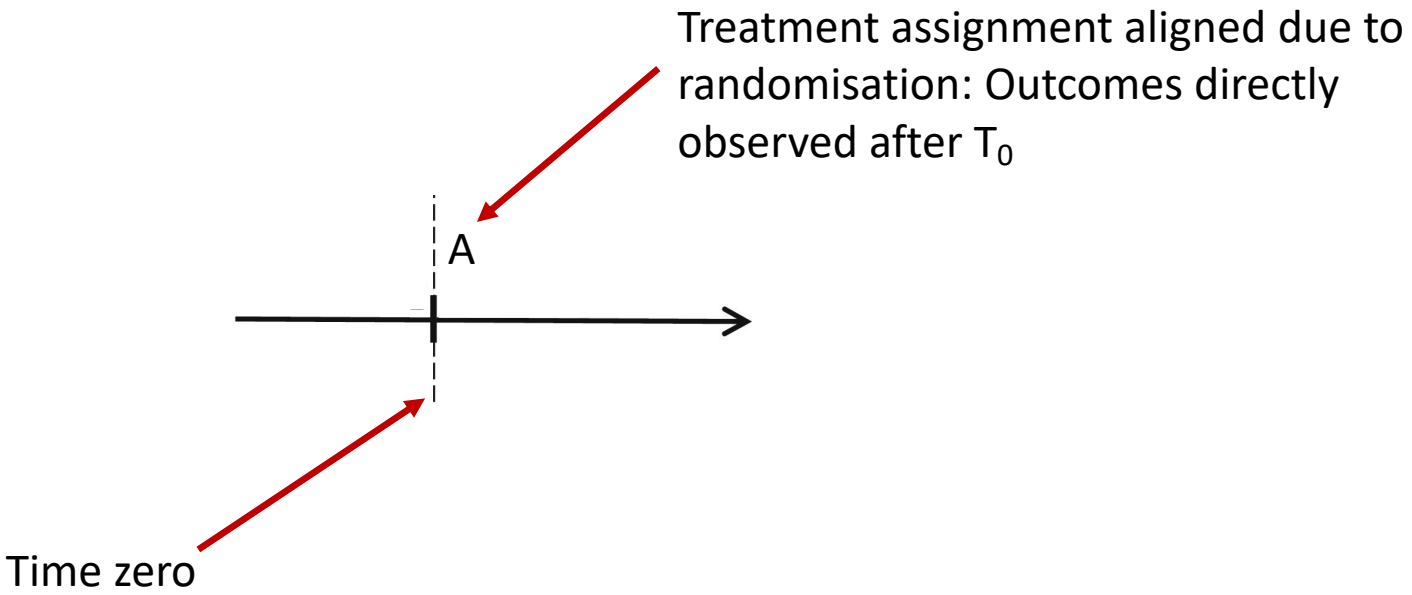
Time zero

- Definition of time zero (baseline) in observational data is **non-trivial**, compared to RCTs

- If treatment assignment is not aligned with time zero and eligibility **biases might arise** (for example, selection bias and immortal time bias)

Time zero: Simple RCT

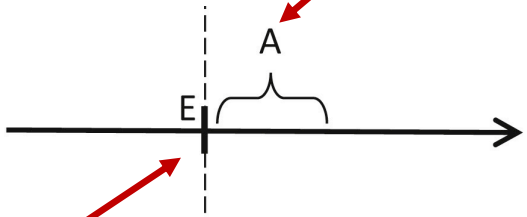
- Treatment regime: Randomize “at least 3 aspirin” vs no aspirin



Time zero: Immortal time bias

- Treatment regime: “At least 3 aspirins” vs no aspirin

A: Time period until “3 aspirins” is reached
Treatment assignment happens after T_0!
Individuals are immortal

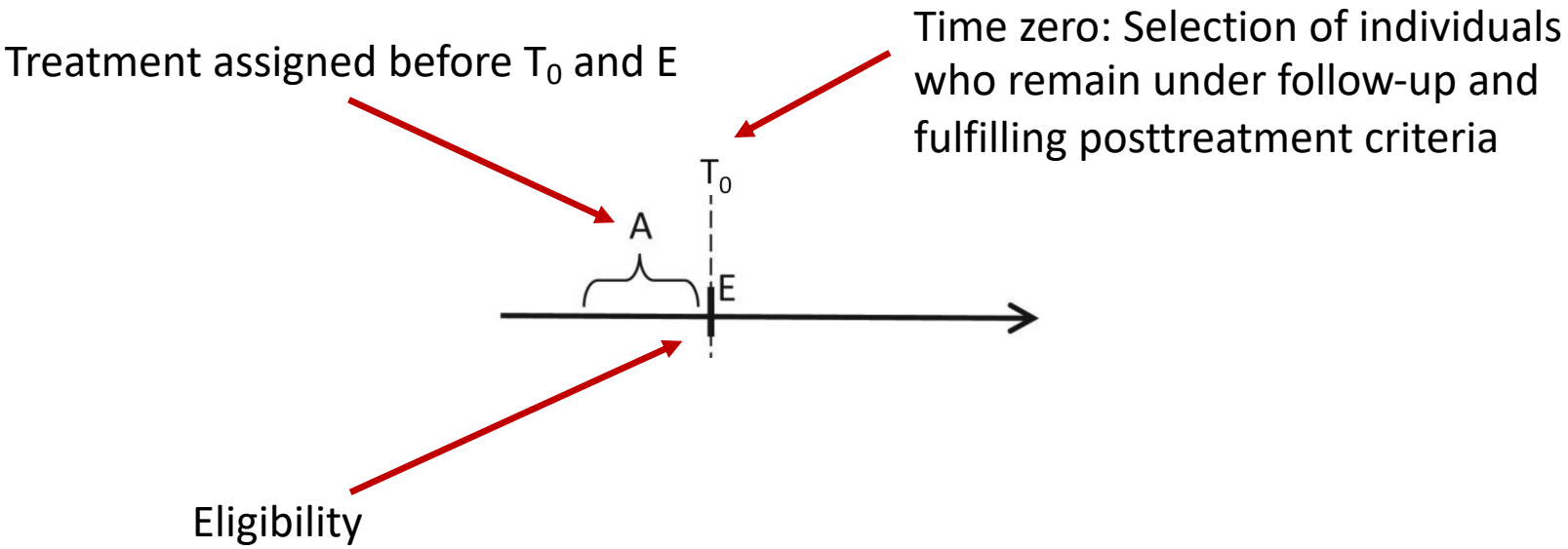


Eligibility and T_0

10.1016/j.jclinepi.2016.04.014

Time zero: Selection bias

- Treatment regime: “At least 3 aspirins” vs no aspirin



10.1016/j.jclinepi.2016.04.014

ORIGINAL RESEARCH

Annals of Internal Medicine

Effectiveness of Screening Colonoscopy to Prevent Colorectal Cancer Among Medicare Beneficiaries Aged 70 to 79 Years

A Prospective Observational Study

Xabier García-Albéniz, MD, PhD; John Hsu, MD, MBA, MSCE; Michael Bretthauer, MD, PhD; and Miguel A. Hernán, MD, DrPH

Background: No randomized, controlled trials of screening colonoscopy have been completed, and ongoing trials exclude persons aged 75 years or older. The Medicare program, however, reimburses screening colonoscopy without an upper age limit.

Objective: To evaluate the effectiveness and safety of screening colonoscopy to prevent colorectal cancer (CRC) in persons aged 70 to 74 and those aged 75 to 79 years.

Design: Large-scale, population-based, prospective study. The observational data were used to emulate a target trial with 2 groups: colonoscopy screening and no screening.

Setting: United States.

Participants: 1 355 692 Medicare beneficiaries (2004 to 2012) aged 70 to 79 years at average risk for CRC who used Medicare preventive services and had no previous diagnostic or surveillance colonoscopies in the past 5 years.

Measurements: 8-year risk for CRC and 30-day risk for adverse events.

Results: In beneficiaries aged 70 to 74 years, the 8-year risk for CRC was 2.19% (95% CI, 2.00% to 2.37%) in the screening colonoscopy group and 2.62% (CI, 2.56% to 2.67%) in the no-screening group (absolute risk difference, −0.42% [CI, −0.24% to −0.63%]). Among those aged 75 to 79 years, the 8-year risk for CRC was 2.84% (CI, 2.54% to 3.13%) in the screening colonoscopy group and 2.97% (CI, 2.92% to 3.03%) in the no-screening group (risk difference, −0.14% [CI, −0.41 to 0.16]). The excess 30-day risk for any adverse event in the colonoscopy group was 5.6 events per 1000 individuals (CI, 4.4 to 6.8) in the 70- to 74-year age group and 10.3 per 1000 (CI, 8.6 to 11.1) in the 75- to 79-year age group.

Limitation: CRC-specific mortality was not available, but CRC incidence and stage were studied at diagnosis.

Conclusion: Screening colonoscopy may have had a modest benefit in preventing CRC in beneficiaries aged 70 to 74 years and a smaller benefit in older beneficiaries. The risk for adverse events was low but greater among older persons.

Primary Funding Source: National Institutes of Health.

Ann Intern Med. 2017;166:18-26. doi:10.7326/M16-0758 **www.annals.org**

For author affiliations, see end of text.

This article was published at www.annals.org on 27 September 2016.

More examples

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> Circulation. 2021 Mar 9;143(10):1002-1013. doi: 10.1161/CIRCULATIONAHA.120.051718. Epub 2020 Dec 17.

Cardiology

Emulating Randomized Clinical Trials With Nonrandomized Real-World Evidence Studies: First Results From the RCT DUPLICATE Initiative

Jessica M Franklin [1], Elisabetta Patorno [1], Rishi J Desai [1], Robert J Glynn [1], David Martin [2], Kenneth Quinto [2], Ajinkya Pawar [1], Lily G Bessette [1], Hemin Lee [1], Elizabeth M Garry [3], Nileesa Gautam [1], Sebastian Schneeweiss [1]

Affiliations + expand

PMID: 33327727 PMCID: PMC7940583 DOI: 10.1161/CIRCULATIONAHA.120.051718

Free PMC article

> Ann Intern Med. 2022 Mar;175(3):352-361. doi: 10.7326/M21-3256. Epub 2021 Dec 21.

COVID-19 Vaccination Effectiveness Against Infection or Death in a National U.S. Health Care System : A Target Trial Emulation Study

George N Ioannou [1], Emily R Locke [2], Ann M O'Hare [3], Amy S B Bohnert [4], Edward J Boyko [5], Denise M Hynes [6], Kristin Berry [2]

Affiliations + expand

PMID: 34928700 PMCID: PMC8697485 DOI: 10.7326/M21-3256

Free PMC article

COVID-19 Vaccination

> Am J Epidemiol. 2021 Nov 2;190(11):2395-2404. doi: 10.1093/aje/kwab158.

Effect of Delays in Concordant Antibiotic Treatment on Mortality in Patients With Hospital-Acquired Acinetobacter Species Bacteremia: Emulating a Target Randomized Trial With a 13-Year Retrospective Cohort

Cherry Lim, Yin Mo, Prapit Teparrukkul, Maliwan Hongsuwan, Nicholas P J Day, Direk Limmathurotsakul, Ben S Cooper

PMID: 34048554 PMCID: PMC8561124 DOI: 10.1093/aje/kwab158

Free PMC article

Antibiotics

Which questions are causal? Do you need a RCT to answer it?

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Does screening colonoscopy reduce 8-year colorectal cancer mortality? **Causal -> RCT/Observational data**

How many colonoscopies were performed over the last 8 years? **Description -> Observational data**

What is the chance of death (due to colorectal cancer) comparing patients who received colonoscopy screening vs no screening?

Prediction/Modelling -> Observational data

Take home messages

- Observational data can be used to emulate a target trial and to answer causal questions

- A target trial emulation uses similar principles as RCTs, but requires a careful accounting of biases

- A target trial emulation does not convert an observational study into a RCT

Thank you for your attention!

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Causal effects are not binary signals that are either detected or undetected;

causal effects are numerical quantities that need to be estimated.

Hernán MA, doi: 10.1016/j.clinepi.2021.08.028

Some references

Hernán, Robins: **Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available**. Am J Epidemiol, 2016 Apr 15;183(8):758-64. doi: 10.1093/aje/kwv254

García-Albéniz, Hsu, Bretthauer, Hernán: **Effectiveness of Screening Colonoscopy to Prevent Colorectal Cancer Among Medicare Beneficiaries Aged 70 to 79 Years: A Prospective Observational Study**. Ann Intern Med. 2017 Jan 3;166(1):18-26. doi: 10.7326/M16-0758

García-Albéniz, Hsu, Hernán: **The value of explicitly emulating a target trial when using real world evidence: an application to colorectal cancer screening**. Eur J Epidemiol. 2017 Jun;32(6):495-500. doi: 10.1007/s10654-017-0287-2

Labrecque, Swanson: **Target trial emulation: teaching epidemiology and beyond**. Eur J Epidemiol. 2017 Jun;32(6):473-475. doi: 10.1007/s10654-017-0293-4

Sterne JAC et al.: **ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions**. BMJ. 2016; 355: i4919. doi: 10.1136/bmj.i4919