30 November 2022

Target Trial Emulation With and Without Cloning

ENCePP Plenary Meeting 2022

Xabier Garcia de Albeniz, MD, ScM, PhD | xgarcia@rti.org
Director, Global Epidemiology

RTI Health Solutions, Barcelona
Disclosure & Perspectives

• Employed at RTI Health Solutions (RTI-HS), a division of RTI International, which is an independent non-for-profit research institute working for government and private and other institutions including pharma companies. As employees, work includes research, advisory roles, and regulatory deliverables, mostly funded by pharma.

• RTI-HS is a member of the SIGMA Consortium, hub for regulatory RWE studies and of Vaccine collaboration for Europe, VAC4EU

• Past employment 2012-2018 Harvard School of Public Health, Program on Causal Inference (Xabi)

Collaborator at CAUSALab, Department of Epidemiology, Harvard T.H. Chan School of Public Health (Xabi)
Questions in Drug Regulation

• **Descriptive questions**: answered by using data to provide a quantitative summary of certain features of the world
  – E.g., “What are the characteristics of patients taking drug X?”

• **Predictive questions**: answered by using data to map some features of the world to other features of the world
  – E.g., “What are the risk factors for myocarditis in individuals receiving a COVID-19 vaccine?

• **Causal inference questions**: answered by using data to predict certain features of the world, as if the world had been different
  – E.g., “What is the effect of drug X on the incidence of adverse events compared with drug Y?”

Causal Inference Tool-of-Choice: Target Trial Emulation

• You may have heard about target trial emulation if you
  – Read observational research on COVID-19 vaccines
  – Attended major pharmacoepidemiology conferences
  – Browsed funding opportunities
RWD Studies of COVID-19 Vaccines

Effectiveness in a large-scale setting

Original Article

BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting

Nea Dagan, M.D., Noam Bards, M.D., Eldad Kapten, Ph.D., Oren Miron, M.A., Shy Perchik, M.A., Mark A. Katz, M.D., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Ben Reis, Ph.D., and Ran D. Balicer, M.D.

Annals of Internal Medicine

COVID-19 Vaccination Effectiveness Against Infection or Death in a National U.S. Health Care System

A Target Trial Emulation Study

George R. Ioannidis, BMJ; Emily I. Locke, MPH; Ann M. O'Hare, MD; Amy S.B. Behnert, PhD; Edward J. Beyea, MD, MPH; Denise M. Hart, MPH, RN; and Kristin Barry, PhD

Study Design

We designed this observational study to emulate a target trial of the causal effect of the BNT162b2 vaccine on Covid-19 outcomes. Eligibility criteria

Vaccination Effectiveness: Target Trial Emulation

We designed this observational study to emulate a target trial of COVID-19 vaccination versus placebo.

Head-to-head comparisons

Original Article

Comparative Effectiveness of BNT162b2 and mRNA-1273 Vaccines in U.S. Veterans

Barbara A. Dickerman, Ph.D., Hanna Grolovin, Ph.D., Arin L. Madenci, M.D., Ph.D., Katherine E. Kurgansky, M.P.H., Brian R. Ferrolito, M.Sc., Michael J. Figueras Muhl, B.Sc., David R. Gagnon, M.D., Ph.D., M.P.H., J. Michael Guzman, M.D., M.P.H., Kelly Cho, Ph.D., Juan P. Casas, M.D., Ph.D., and Miguel A. Hernán, M.D., Dr.P.H.
RWD Studies of COVID-19 Vaccines

Safety in a large-scale setting

Effectiveness in special populations

Effectiveness of boosters in large-scale setting
International Society for Pharmacoepidemiology
Annual Conference, 2022

• Hot Topic Session: How Can We Mitigate Publication of Poorly Conducted RWE Studies?
  – Prof. Segal (Johns Hopkins University, School of Medicine), Associate Editor of Annals of Internal Medicine (IF = 51.6):
  – “If observational studies are submitted [to *Annals of Internal Medicine*], they [the reviewers] will ask you to frame these as a trial emulation, and they will send it back to you until you do so”
  – Hot Topic Session and The Final Word (vimeo.com) (57:55 minutes)
Patient-Centered Outcomes Research Institute Funding Opportunity

Antihyperglycemic Therapy and Cardiovascular Risk: Design and Emulation of a Target Trial Using Healthcare Databases

By Miguel Hernán

Miguel Hernán, MD, DrPH, is the Kolokotrones Professor of Biostatistics and Epidemiology at Harvard T.H. Chan School of Public Health.

Published May 24, 2019
What is emulating a target trial?

• Emulating a target trial is one of the main tools of *causal inference*
• Causal inference is the science that helps learn what works and what does not work by estimating the causal effect of interventions (as opposed to prediction or description)
• For each causal effect of interest, we should be able to imagine a (hypothetical) randomized experiment to quantify it, that is, the “target trial”
• Emulating a target trial using RWD comprises designing a study that is as close as possible to the trial we would have run had we had the opportunity to do so and then using specific epidemiological methods to emulate it
  – Some components that are easy to emulate include eligibility criteria, treatment strategies, outcomes, and causal contrast
  – Others may require more work, including emulation of randomization and of the proper alignment of eligibility, treatment assignment, and start of follow-up

RWD = real-world data.
## Target Trial Emulation Framework for Causal Inference

<table>
<thead>
<tr>
<th>Protocol component</th>
<th>Target trial specification</th>
<th>Target trial emulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim</td>
<td>What is the study objective?</td>
<td></td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>Who will be included in the study?</td>
<td></td>
</tr>
<tr>
<td>Treatment strategies</td>
<td>What interventions will eligible persons receive?</td>
<td></td>
</tr>
<tr>
<td>Treatment assignment</td>
<td>How will eligible persons be assigned to interventions?</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>What outcomes in eligible persons will be compared among intervention groups?</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>During which period will eligible persons be followed in the study?</td>
<td></td>
</tr>
<tr>
<td>Causal contrast (or estimand)</td>
<td>Which counterfactual contrast will be estimated using the above data?</td>
<td></td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>How will the counterfactual contrasts be estimated?</td>
<td></td>
</tr>
</tbody>
</table>

Main benefits of framing your observational study as a target trial

1. **Eases discussion**
2. **Bias mitigation**: Alignment of eligibility, time zero and start of follow-up
3. Evaluation of **clinically relevant** treatment strategies
4. Methods to study treatment strategies that are **sustained over time**
TTE eases study design discussion

• It grounds the discussion on a target trial design and **specification**
• Many agents involved in the project will be more familiar with randomized trials than with observational studies: clinicians, patients, statisticians, market access professionals, data holders, etc.
• Once the target trial is specified, epidemiologists with appropriate training can help with the target trial **emulation**
  – The most important decision points will be settled by then
Alignment of eligibility, time zero and start of follow-up

1. Avoids prevalent user bias: remember the Women Health Initiative RCT?
   - Observational studies reported a protective effect of HRT on CHD ([\textit{N Engl J Med.} 1996 Aug 15;335(7):453-61])
   - The WHI RCT reported the opposite ([\textit{N Engl J Med.} 2003 Aug 7;349(6):523-34])
   - A target trial emulation using the same observational data reconciled the estimates ([\textit{Epidemiology.} 2008 Nov;19(6):766-79])

2. Avoids immortal time bias
   - Several observational studies reported a protective effect of statins on cancer incidence (e.g., [\textit{N Engl J Med.} 2005 May 26;352(21):2184-92])
   - A meta-analysis of 20 RCT reported a HR of 1.02 ([\textit{JAMA.} 2006 Jan 4;295(1):74-80])

Alignment of eligibility, time zero and start of follow-up

Classify individuals into exposure strategies their baseline data are compatible with

<table>
<thead>
<tr>
<th>Time zero easily identifiable?</th>
<th>Intervention A vs. Intervention B</th>
<th>Intervention vs. No Intervention</th>
<th>Intervention 3y vs. Intervention 6y</th>
<th>Intervention in a grace period vs. No intervention</th>
<th>Periodic intervention vs. No intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Vaccine A</td>
<td>Statins</td>
<td>AHT initiators</td>
<td>No mammogram</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Vaccine B</td>
<td>No Statins</td>
<td>AHT initiators</td>
<td>No mammogram</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No chemo</td>
<td>No mammogram</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No chemo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No mammogram</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AHT: antihypertensive
Case Study 1: exposure defined at baseline, time zero not easily identifiable

Avoidable flaws in observational analyses: an application to statins and cancer

Barbra A. Dickerman*, Xabier Garcia-Albéniz*, Roger W. Logan#, Spiros Denaxas## and Miguel A. Hernán###

1-6 Harvard T.H. Chan School of Public Health, Boston, MA; 2 RTI-HS, Barcelona, Spain; 3-4 University College London, London, UK; 5 The Alan Turing Institute, London, UK; 7 Massachusetts Institute of Technology, Cambridge, MA

RWD = real-world data; UK = United Kingdom.
Motivation

RWD results…

<table>
<thead>
<tr>
<th>Citation</th>
<th>Exposures</th>
<th>Outcome cancer</th>
<th>Database</th>
<th>Effect, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J Clin Oncol. 2004; 22:2388-94</td>
<td>&gt; 6 m statins vs. no statins</td>
<td>Any</td>
<td>PHARMO</td>
<td>0.80 (0.66-0.96)</td>
</tr>
<tr>
<td>N Engl J Med. 2005;352:2184-92</td>
<td>&lt; 5 y vs. &gt; 5 y statins</td>
<td>Colorectal</td>
<td>Population cohort Israel</td>
<td>0.53 (0.38-0.74)</td>
</tr>
<tr>
<td>CHEST. 2007; 131:1282-88</td>
<td>&gt; 4 y vs. no statin</td>
<td>Lung</td>
<td>VHA</td>
<td>0.23 (0.20-0.26)</td>
</tr>
<tr>
<td>Am J Epidemiol. 2005;162:318-25</td>
<td>Any statin vs. no statin</td>
<td>Prostate</td>
<td>PVAFMC</td>
<td>0.38 (0.21-0.69)</td>
</tr>
</tbody>
</table>

… were followed by these RCT results.

**Cancer Incidence**

<table>
<thead>
<tr>
<th>Source</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCAI,^{27}1994</td>
<td>0.75 (0.11-4.51)</td>
</tr>
<tr>
<td>REGRESS,^{25}2004</td>
<td>0.96 (0.13-7.24)</td>
</tr>
<tr>
<td>KAPS,^{22}1995</td>
<td>0.59 (0.09-3.09)</td>
</tr>
<tr>
<td>PLAC I,^{33}1995</td>
<td>0.65 (0.13-2.78)</td>
</tr>
<tr>
<td>Belhoutzen et al.,^{34}2004</td>
<td>1.00 (0.18-5.50)</td>
</tr>
<tr>
<td>MARS,^{26}2005</td>
<td>1.23 (0.30-5.22)</td>
</tr>
<tr>
<td>LCAS,^{26}1997</td>
<td>0.74 (0.31-1.71)</td>
</tr>
<tr>
<td>PLAC II,^{34}1995</td>
<td>1.42 (0.51-4.08)</td>
</tr>
<tr>
<td>GISSI Prevenzione,^{24}2000</td>
<td>0.64 (0.32-1.24)</td>
</tr>
<tr>
<td>LIPS,^{22}2002</td>
<td>0.92 (0.60-1.43)</td>
</tr>
<tr>
<td>KLIS,^{25}2000</td>
<td>1.03 (0.72-1.50)</td>
</tr>
<tr>
<td>WOSCOPS,^{26}1995</td>
<td>1.09 (0.83-1.45)</td>
</tr>
<tr>
<td>CARE,^{26}1996</td>
<td>1.07 (0.85-1.35)</td>
</tr>
<tr>
<td>45,^{15}2004</td>
<td>0.91 (0.75-1.10)</td>
</tr>
<tr>
<td>PROSPER,^{25}2002</td>
<td>1.26 (1.03-1.54)</td>
</tr>
<tr>
<td>ALERT,^{26}2003</td>
<td>0.91 (0.75-1.11)</td>
</tr>
<tr>
<td>LIPID,^{22}2002</td>
<td>0.94 (0.82-1.07)</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS,^{22}2001</td>
<td>1.03 (0.90-1.18)</td>
</tr>
<tr>
<td>HIPS,^{26}2002</td>
<td>1.06 (0.96-1.16)</td>
</tr>
<tr>
<td>SCAT,^{26}2000</td>
<td>1.85 (0.87-4.09)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.02 (0.97-1.07)</td>
</tr>
</tbody>
</table>


CI = confidence interval; OR = odds ratio; PHARMO = PHARMO Institute for Drug Outcomes Research or PHARMO Database Network; PVAFMC = Portland Veterans Affairs Medical Center; RCT = randomized controlled trial; RWD = real-world data; VHA = Veterans Health Administration.
Why the discrepancy between RWD and RCT?

- The usual answer: “lack of randomization”
- Differences by measured confounders can be adjusted for
- Unmeasured confounding is not solvable

- Deviation from other basic principles of study design?
  - Specification of time zero
  - Specification of the treatment strategy
  - Specification of the causal contrast
  - Selection bias
  - Others

- This can be fixed using a proper design and methods: target trial emulation

**RCT** = randomized controlled trial; **RWD** = real-world data.
Case Study of a Target Trial Emulation Using EMR as RWD

Specification and emulation of a target trial of statin therapy and cancer risk using CALIBER observational data

<table>
<thead>
<tr>
<th>Protocol component</th>
<th>Target trial specification</th>
<th>Target trial emulation</th>
</tr>
</thead>
</table>
| **Eligibility criteria** | • Age ≥ 30, between 1 January 1998 and 29 February 2016  
• No history of cancer (except non-melanoma skin cancer)  
• No statin contraindication (hepatic impairment or myopathy)  
• No statin prescription within the past year  
• LDL cholesterol < 5 mmol L⁻¹  
• At least 1 y of up-to-standard data in a CPRD practice  
• At least 1 y of potential follow-up  
• Baseline is defined as the first month in which all eligibility criteria are met | • Same as for the target trial  
• We defined hepatic impairment as a code for hepatic failure or ALT ≥ 120 IU L⁻¹, and myopathy as codes for its symptoms; muscle aches, pain or weakness  
• We also required information on lab values measured during the past year and on lifestyle factors during the past 4 y |
| **Treatment strategies** | 1) **Initiation of any statin therapy at baseline and continuation over follow-up until the development of a contraindication (hepatic impairment or myopathy)**  
2) **No initiation of statin therapy over follow-up until the development of an indication (LDL cholesterol ≥ 5 mmol L⁻¹)**  
• When clinically warranted during the follow-up, patients and their physicians decide whether to start, stop or switch therapy. Participants must have a primary-care consultation at least once every 4 y to assess prognostic factors associated with adherence | • Same as for the target trial  
• We defined the date of medication initiation to be the first date of prescription. We calculated discontinuation dates using the daily dose and quantity of pills in the prescription. We considered treatment to be continuous if there was a gap of less than 30 d between successive prescriptions |
| **Treatment assignment** | • Individuals are randomly assigned to a strategy at baseline and will be aware of the strategy to which they have been assigned | • We classified individuals according to the strategy that their data were compatible with at baseline and attempted to emulate randomization by adjusting for baseline confounders |

ALT = alanine aminotransferase; CPRD = Clinical Practice Research Datalink; EMR = electronic medical record; LDL = low-density lipoprotein; RWD = real-world data.
Case Study of a Target Trial Emulation Using EMR as RWD

Specification and emulation of a target trial of statin therapy and cancer risk using CALIBER observational data

<table>
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<tr>
<th>Protocol component</th>
<th>Target trial specification</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong></td>
<td>• Total cancer and 7 site-specific cancers: female breast, colorectal, hematological, melanoma, lung, prostate, urothelial</td>
<td>• Same as for the target trial</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>• Starts at baseline and ends at the month of first cancer diagnosis, death, loss to follow-up—transfer out of the practice or incomplete follow-up (4 y after the last recorded confounder values), 10 y after baseline, or administrative end of follow-up (end of practice data collection or 29 February 2016), whichever happens first</td>
<td>• Same as for the target trial</td>
</tr>
</tbody>
</table>
| **Causal contrasts** | • Intention-to-treat effect  
• Per-protocol effect | • Observational analog of intention-to-treat and per-protocol effects |
| **Statistical analysis** | • Intention-to-treat analysis  
• Per-protocol analysis: Censor participants if and when they deviate from their assigned treatment strategy and apply inverse-probability weights to adjust for prebaseline and postbaseline prognostic factors associated with adherence  
• Subgroup analyses by baseline age, sex, and cardiovascular disease status | • Same intention-to-treat and per-protocol analyses with sequential emulation and additional adjustment for baseline covariates  
• Same subgroup analyses |

ALT = alanine transaminase; EMR = electronic medical record; RWD = real-world data.
Results

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).

CI = confidence interval; HR = hazard ratio.
Two main differences:

- Individuals were classified on the basis of their observed duration of statin use during follow-up, i.e., postbaseline info is used for treatment assignment
  - We did this in CALIBER: HR, 0.26 (95% CI, 0.23-0.30)
- Individuals that were prevalent users at baseline were included
  - We added this in CALIBER: HR, 0.27 (95% CI, 0.25-0.29)

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<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome cancer</th>
<th>Database</th>
<th>Effect, OR (95% CI)</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs study 1</td>
<td>&gt; 6 m statins vs. no statins</td>
<td>Any</td>
<td>PHARMO</td>
<td>0.80 (0.66-0.96)</td>
</tr>
<tr>
<td>Obs study 2</td>
<td>&lt; 5 y vs. &gt; 5 y statins</td>
<td>Colorectal</td>
<td>Population cohort Israel</td>
<td>0.53 (0.38-0.74)</td>
</tr>
<tr>
<td>Obs study 3</td>
<td>&gt; 4 y vs. no statin</td>
<td>Lung</td>
<td>VHA</td>
<td>0.23 (0.20-0.26)</td>
</tr>
<tr>
<td>Obs study 4</td>
<td>Any statin vs. no statin</td>
<td>Prostate</td>
<td>PVAFMC</td>
<td>0.38 (0.21-0.69)</td>
</tr>
</tbody>
</table>
Case Study 2: exposure not defined at baseline, time zero identifiable

Effect of Different Durations of Treatment With Antihypertensive Drugs With Anticholinergic Effects on the Risk of Dementia: A Target Trial Emulation Study

Jaume Aguado,1 Lia Gutierrez,1 Joan Forns,1 Kenneth J Rothman,1 Xabier García de Albéniz1,2

1 RTI Health Solutions
2 Harvard T.H. Chan School of Public Health

RWD = real-world data; UK = United Kingdom.
### Methods: Treatment Strategies

<table>
<thead>
<tr>
<th>Treatment Strategies</th>
<th>Initiation of any AC AHT at baseline and receiving it for</th>
<th>Patients can switch to another AC AHT if clinically indicated during those</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC AHT ≤ 3 y</td>
<td>≤ 3 years</td>
<td>3 years</td>
</tr>
<tr>
<td>AC AHT 3-6 y</td>
<td>3-6 years in the absence of toxicity*</td>
<td>6 years in the absence of toxicity*</td>
</tr>
<tr>
<td>AC AHT &gt; 6 y</td>
<td>&gt; 6 years in the absence of toxicity*</td>
<td>&gt; 6 years in the absence of toxicity*</td>
</tr>
</tbody>
</table>

**Endpoint:** dementia as a diagnosis, symptom, or referral, or a cognitive enhancer drug (memantine, donepezil, rivastigmine, galantamine, or tacrine)
Methods: Time Zero, Eligibility, and Treatment Strategies Assignment

Complication 1: all initiators are compliant with the 3 strategies at baseline

Solution to complication 1: cloning and artificial censoring to ensure that patients follow their assigned strategy after time zero

- AC AHT ≤ 3 y
  - Not censored if they stop AC AHT before year 3
- AC AHT 3-6 y
  - Not censored if they stop AC AHT between years 3 and 6
- AC AHT > 6 y
  - Not censored if they continue AC AHT beyond year 6

Unique subject

Cloned individuals
Methods: Statistical Methods

Complication 2: cloning eliminates immortal time bias, but artificial censoring can introduce selection bias

Solution to complication 2: g-methods

- Inverse probability weighting
  - Weights: \( W_t^A = \prod_{k=0}^{t} \frac{1}{f(A_k|A_{k-1}, \bar{T}_k, \bar{Y}_{k-1} = 0)} \)
  - Denominator estimated with pooled logistic regression

- Apply these weights to the outcome model to estimate the effect under complete adherence
  - Pooled logistic regression to obtain a HR
  - Estimate standardised survival curves and risk differences adding a product term between time and treatment to the pooled logistic regression used for the HR
  - Variance estimation: robust for the HR and bootstrap for the risk differences

HR = hazard ratio.
Results: Follow-up and Number of Events

Note: Follow-up was truncated at 10 years
Results: Fully Adjusted Parametric Risk Curves at 10 Years

Comparison at 10 y

<table>
<thead>
<tr>
<th>Risk difference (95% CI(^a))</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 6 years vs. ≤ 3 years</td>
</tr>
<tr>
<td>3-6 years vs. ≤ 3 years</td>
</tr>
</tbody>
</table>

\(^a\) 500 bootstrap samples.
Results: Adjusted Hazard Ratios at 10 Years

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR (95% CI)</th>
<th>Comparison</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 6 years vs. ≤ 3 years</td>
<td>0.80 (0.73-0.88)</td>
<td>&gt; 6 years vs. ≤ 3 years</td>
<td>0.29 (0.26-0.33)</td>
</tr>
<tr>
<td>3-6 years vs. ≤ 3 years</td>
<td>0.86 (0.79-0.94)</td>
<td>3-6 years vs. ≤ 3 years</td>
<td>0.64 (0.57-0.71)</td>
</tr>
</tbody>
</table>

IPTW = Inverse probability of treatment weighting.

a Comparison of groups based on the observed duration of treatment: no alignment, no cloning, no artificial censoring, and no weighting.

b Robust CIs.
**Intervention in a grace period vs. No intervention**

**Treatment Strategies**

- **Erlotinib**: Initiation of erlotinib within 12 weeks of gemcitabine initiation for pancreatic cancer
- **No Erlotinib**: Gemcitabine alone

<table>
<thead>
<tr>
<th>Target trial emulation result</th>
<th>Existing RCT result</th>
<th>Naïve Analysis Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>1.04 (0.86-1.42)</td>
<td>0.96 (0.74-1.24)</td>
<td>0.68 (0.54-0.87)</td>
</tr>
</tbody>
</table>
Periodic intervention vs. No intervention

Annals of Internal Medicine

Continuation of Annual Screening Mammography and Breast Cancer Mortality in Women Older Than 70 Years

Xabier García-Albéniz, MD, PhD; Miguel A. Hernán, MD, DrPH; Roger W. Logan, PhD; Mary Price, PhD; Katrina Armstrong, MD, MSCE; and John Hsu, MD, MBA, MSCE


Treatment Strategies

1. Annual mammograms for 8 years
2. No mammograms

Target trial emulation result
HR (95% CI)

0.78 (0.64-0.96)

Existing RCT result
HR (95% CI)

0.80 (0.51 to 1.28)

Naïve Analysis Result
HR (95% CI)
Conclusions

- Emulating a target trial is a fundamental approach for causal inference using observational data
- One of its key features is the alignment of the following:
  - Eligibility
  - Exposure assignment
  - Time zero (when the outcomes start to be counted)
- Target trial emulations where the exposures are well-defined at time zero do not need cloning. E.g.:
  - Initiation of Drug A vs. Drug B
  - Initiation of Drug A vs. No Treatment
- Target trial emulation where the exposures are not well-defined at time zero can use cloning. E.g.:
  - Study of different durations of treatment with a specific drug
  - Grace periods
  - Intervention happens at pre-specified intervals (e.g., vaccine boosters)
Thank You
Questions?
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Target Trial Emulation References


