30 November 2022

Target Trial Emulation With and Without Cloning

ENCePP Plenary Meeting 2022

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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?”

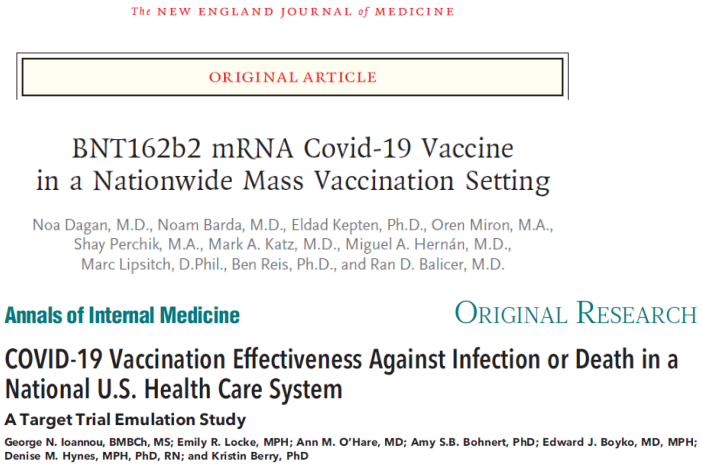
Hernán MA, Hsu J, Healy B. A second chance to get causal inference right: a classification of data science tasks. Chance. 2019;32:1,42-9.

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



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Noa Dagan, M.D., Noam Barda, M.D., Eldad Kepten, Ph.D., Oren Miron, M.A., Shay 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 ORIGINAL RESEARCH

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

A Target Trial Emulation Study

George N. Ioannou, BMBCh, MS; Emily R. Locke, MPH; Ann M. O'Hare, MD; Amy S.B. Bohnert, PhD; Edward J. Boyko, MD, MPH; Denise M. Hynes, MPH, PhD, RN; and Kristin Berry, PhD

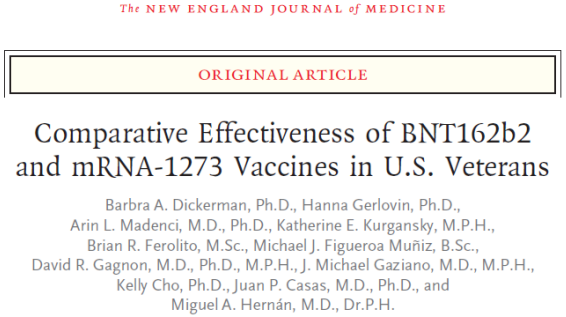
STUDY DESIGN

We designed this observational study to emulate a target trial of the causal effect of the BNT162b2 vaccine on Covid-19 outcomes.[4] Eligibility criteria

Vaccination Effectiveness: Target Trial Emulation

We designed this observational study to emulate a target trial of COVID-19 vaccination versus placebo (10).

Head-to-head comparisons



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Barbra A. Dickerman, Ph.D., Hanna Gerlovin, Ph.D., Arin L. Madenci, M.D., Ph.D., Katherine E. Kurgansky, M.P.H., Brian R. Ferolito, M.Sc., Michael J. Figueroa Muñiz, B.Sc., David R. Gagnon, M.D., Ph.D., M.P.H., J. Michael Gaziano, 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.

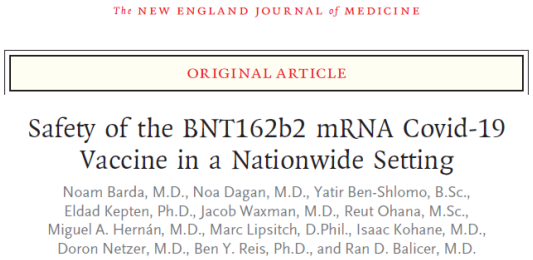
SPECIFICATION OF THE TARGET TRIALS

We designed this observational analysis to emulate a target trial (i.e., a hypothetical pragmatic trial that would have answered the causal question of interest) of BNT162b2 as compared with mRNA-1273 for the prevention of Covid-19 outcomes in the VA health care system. The key com-

RWD Studies of COVID-19 Vaccines

RTI (h)(s) Health Solutions

Safety in a large-scale setting



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting

Noam Barda, M.D., Noa Dagan, M.D., Yatir Ben-Shlomo, B.Sc., Eldad Kepten, Ph.D., Jacob Waxman, M.D., Reut Ohana, M.Sc., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Isaac Kohane, M.D., Doron Netzer, M.D., Ben Y. Reis, Ph.D., and Ran D. Balicer, M.D.

STUDY SETTING

We analyzed observational data from Clalit Health Services (CHS) in order to emulate a target trial of the effects of the BNT162b2 vaccine on a broad range of potential adverse events in a population without SARS-CoV-2 infection. CHS is the larg-

Effectiveness in special populations

nature medicine

BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-021-01490-8

Check for updates

Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy

Noa Dagan[1,2,3,4,14], Noam Barda[1,2,3,4,14], Tal Biron-Shental[5,6], Maya Makov-Assif[1], Calanit Key[7], Isaac S. Kohane[3,4], Miguel A. Hernán[8,9], Marc Lipsitch[10], Sonia Hernandez-Diaz[8], Ben Y. Reis[4,11,12] and Ran D. Balicer[1,4,13]

Study design and study population. We conducted an observational cohort study that emulates a target trial to estimate the effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnant women. We used a similar methodology

Effectiveness of boosters in large-scale setting

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†

Study design and participants

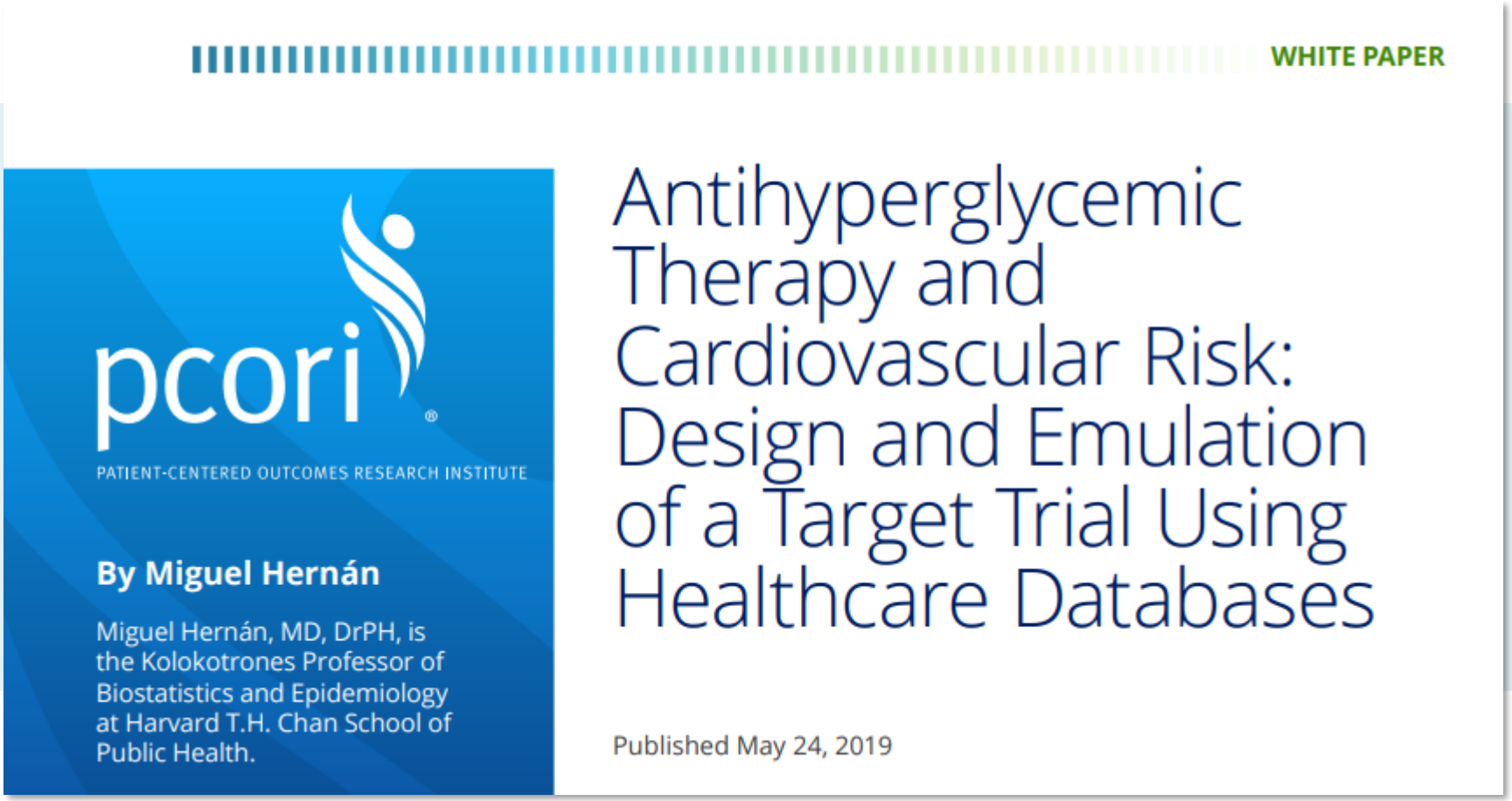
This study was designed to emulate a target trial[14] of the effects of a third dose of the BNT162b2 vaccine in a population of individuals who had already received two doses of the vaccine at least 5 months before recruitment. The study design is similar to our previous

The power of knowledge. The value of understanding.

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



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

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

Sources: Hernan MA. New Engl J Med. 2021;385:1345-8; Garcia-Albeniz X, et al. Eur J Epidemiol. 2017 Jun;32(6):495-500.

Main benefits of framing your observational study as a target trial

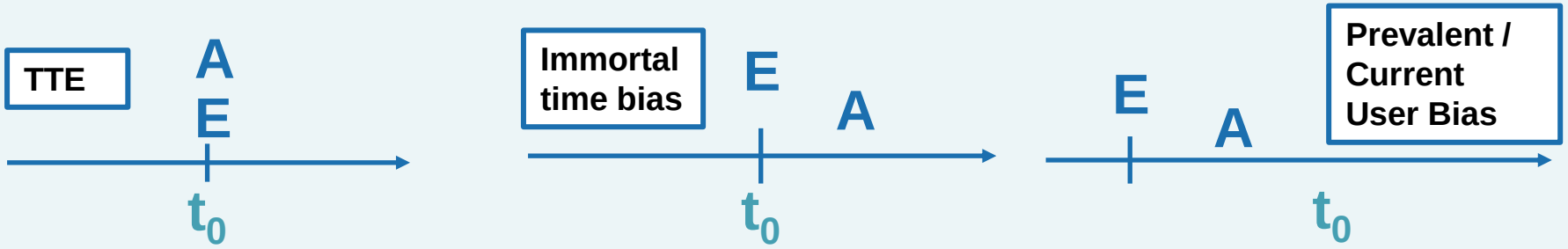
1. **Eases discussion**
2. **Bias mitigation:** Alignment of eligibility, time zero and start of follow-up
3. Evaluation of **clinically relevant** treatment strategies
4. Methods to study treatment strategies that are **sustained over time**

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 (N Engl J Med. 1996 Aug 15;335(7):453-61)
    - The WHI RCT reported the opposite (N Engl J Med. 2003 Aug 7;349(6):523-34)
    - A target trial emulation using the same observational data reconciled the estimates (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., N Engl J Med. 2005 May 26;352(21):2184-92)
    - A meta-analysis of 20 RCT reported a HR of 1.02 (JAMA. 2006 Jan 4;295(1):74-80)
    - A target trial emulation reconciled the estimates (Nat Med. 2019 Oct;25(10):1601-1606)

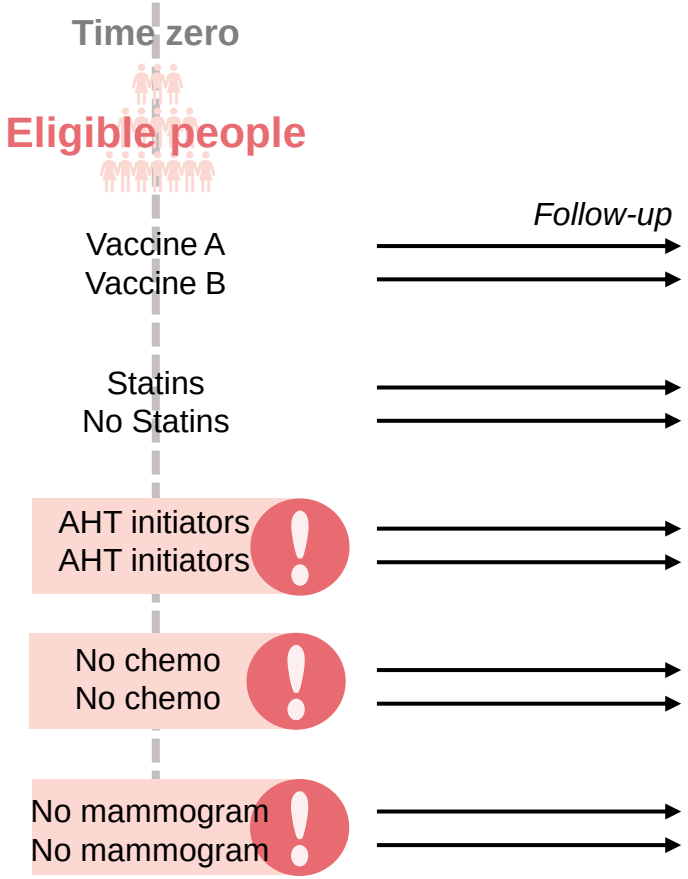


Garcia de Albeniz X Beyond Controlling for Confounding: Design Strategies to Avoid Selection Bias and Improve Efficiency in Observational Studies. https://www.rtihs.org/sites/default/files/Webinar_Beyond_Controlling_for_Confounding.pdf

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

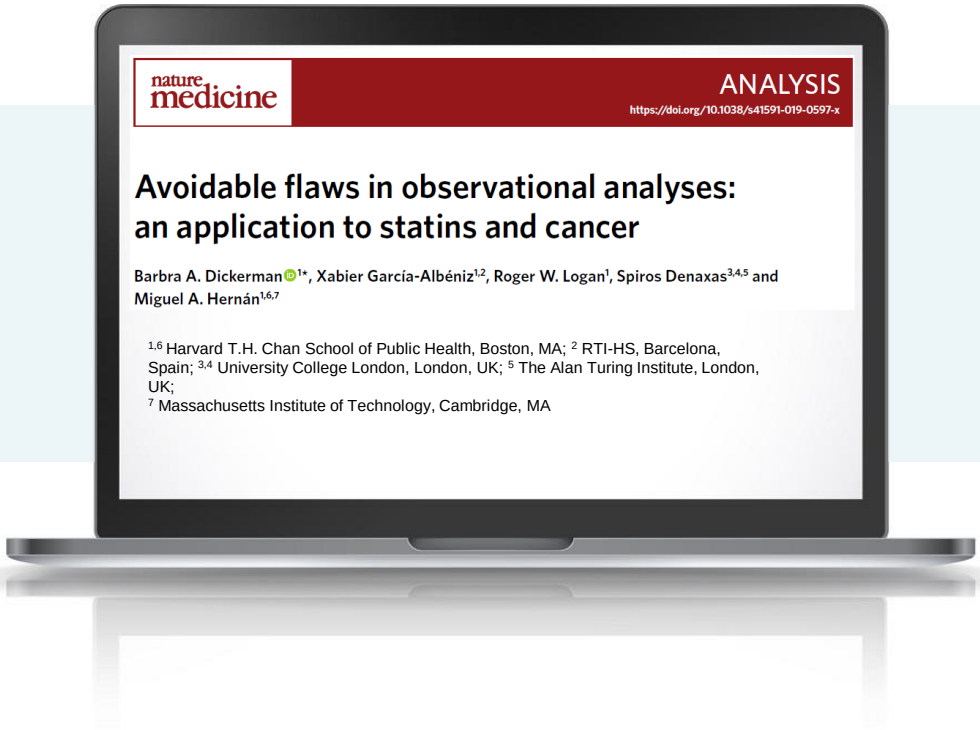
Classify individuals into exposure strategies their baseline data are compatible with

Time zero easily identifiable?	
Yes	**Intervention A vs. Intervention B**
No	**Intervention vs. No Intervention**
Yes	**Intervention 3y vs. Intervention 6y**
No	**Intervention in a grace period vs. No intervention**
Yes	**Periodic intervention vs. No intervention**



AHT: antihypertensive

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



RWD = real-wold data; UK = United Kingdom.

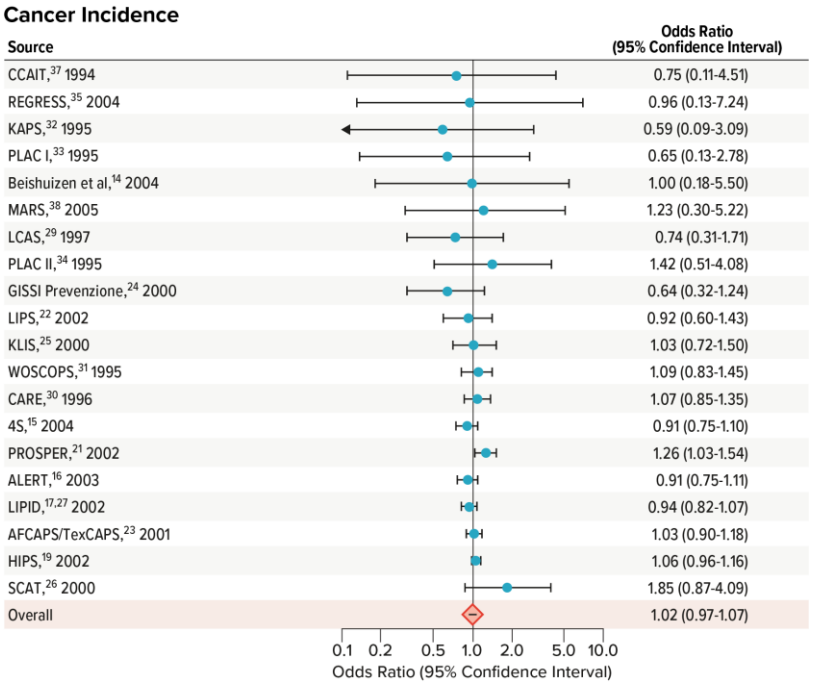
Motivation

RTI (h)(s) Health Solutions

RWD results…

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

… were followed by these **RCT** results.



Source: Dale KM et al. JAMA. 2006 Jan 4;295(1):74-80.

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

Protocol component	Target trial specification	Target trial emulation
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

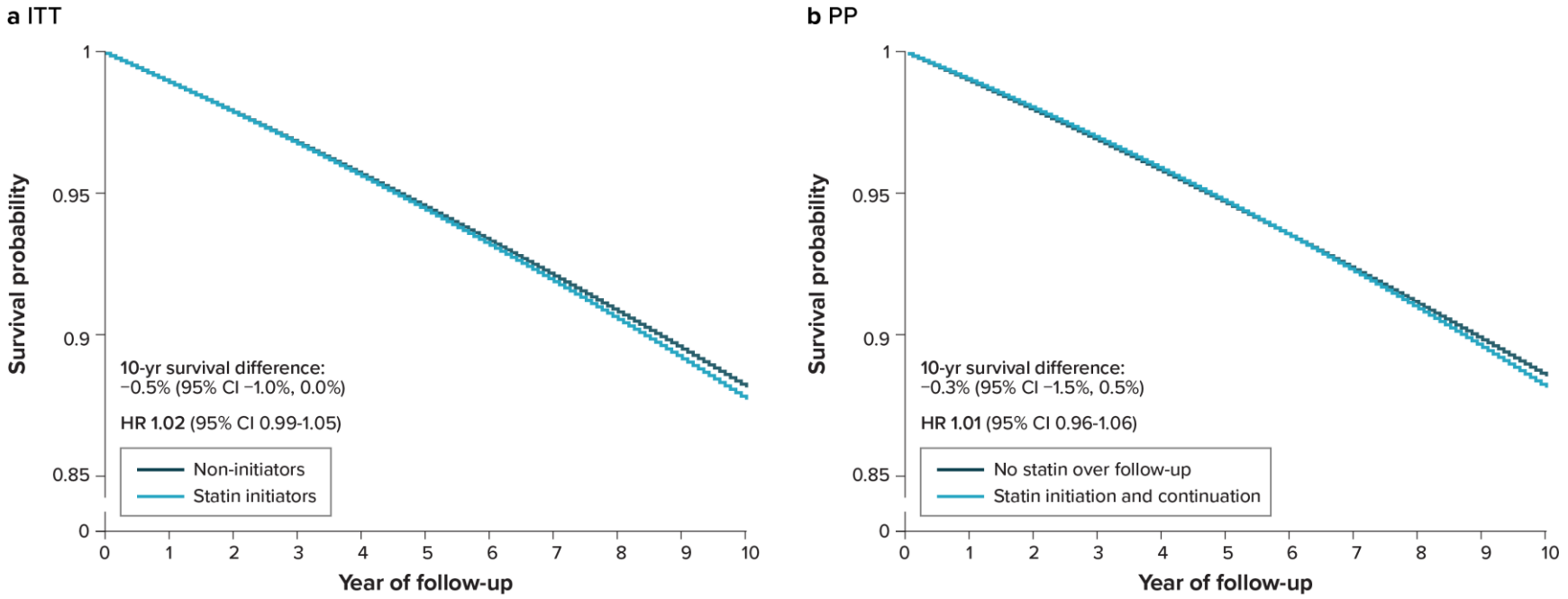
Specification and emulation of a target trial of statin therapy and cancer risk using CALIBER observational data

Protocol component	Target trial specification	Target trial emulation
Outcomes	• Total cancer and 7 site-specific cancers: female breast, colorectal, hematological, melanoma, lung, prostate, urothelial	• Same as for the target trial
Follow-up	• 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	• Same as for the target trial
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 medial 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.

What if we reproduce the methods of previous studies?

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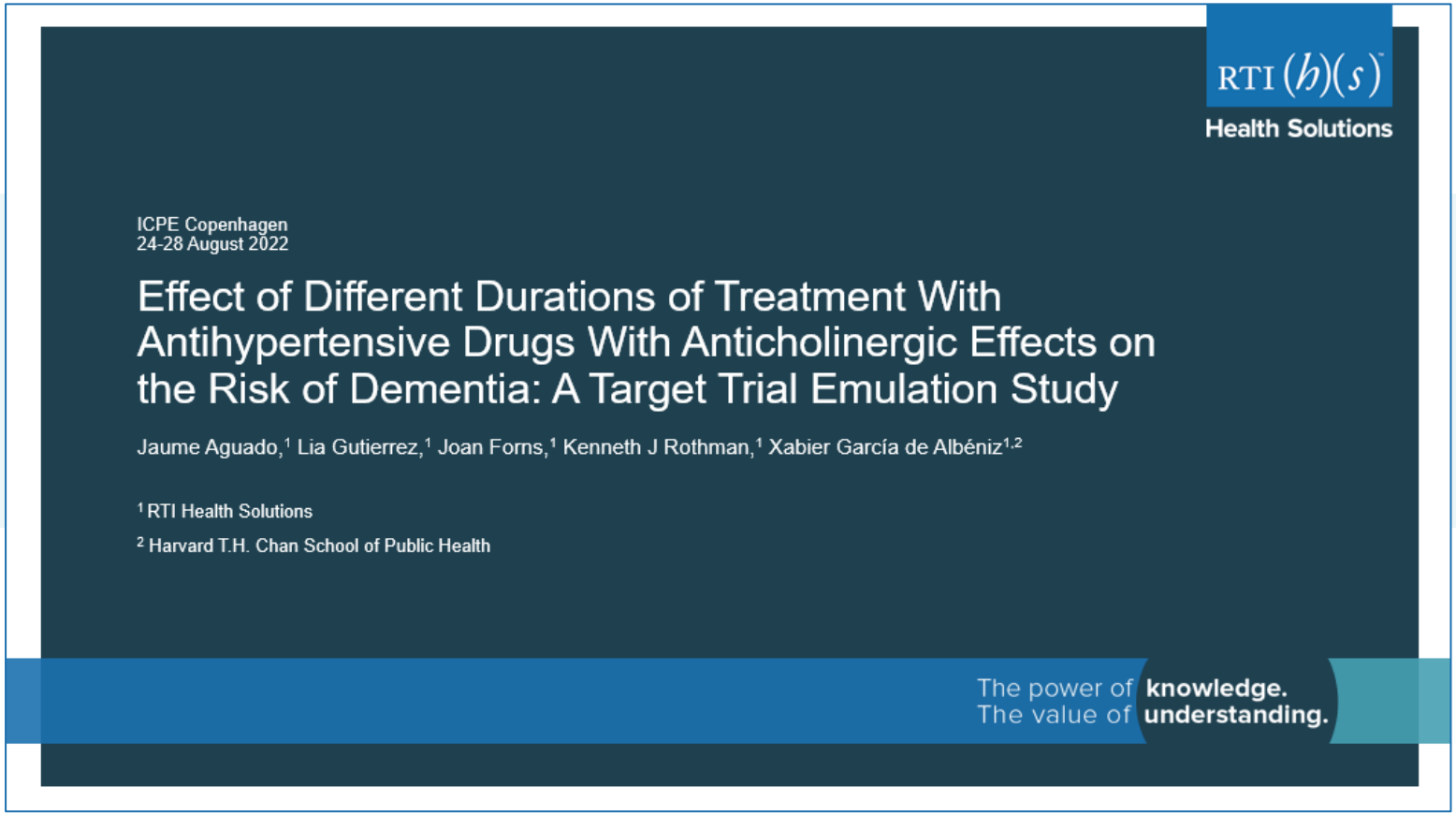
…maybe the database is the reason for different results?

	Exposure	Outcome cancer	Database	Effect, OR (95% CI)	Citation
Obs study 1	> 6 m statins vs. no statins	Any	PHARMO	0.80 (0.66-0.96)	J Clin Oncol 2004; 22:2388-94
Obs study 2	< 5 y vs. > 5 y statins	Colorectal	Population cohort Israel	0.53 (0.38-0.74)	N Engl J Med 2005; 352: 2184-92
Obs study 3	**> 4 y vs. no statin**	**Lung**	**VHA**	**0.23 (0.20-0.26)**	**CHEST 2007; 131:1282-8**
Obs study 4	Any statin vs. no statin	Prostate	PVAFMC	0.38 (0.21-0.69)	Am J Epidemiol 2005; 162:318-25

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)**

Case Study 2: exposure not defined at baseline, time zero identifiable



RWD = real-wold data; UK = United Kingdom.

Methods: Treatment Strategies

Treatment Strategies

AC AHT ≤ 3 y	Initiation of any AC AHT at baseline and receiving it for **≤ 3 years**	Patients can switch to another AC AHT if clinically indicated during those 3 years
AC AHT 3-6 y	Initiation of any AC AHT at baseline and receiving it for **3-6 years** in the absence of toxicity*	Patients can switch to another AC AHT if clinically indicated during those 6 years
AC AHT > 6 y	Initiation of any AC AHT at baseline and receiving it for **> 6 years** in the absence of toxicity*	Patients can switch to another AC AHT if clinically indicated at any time

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

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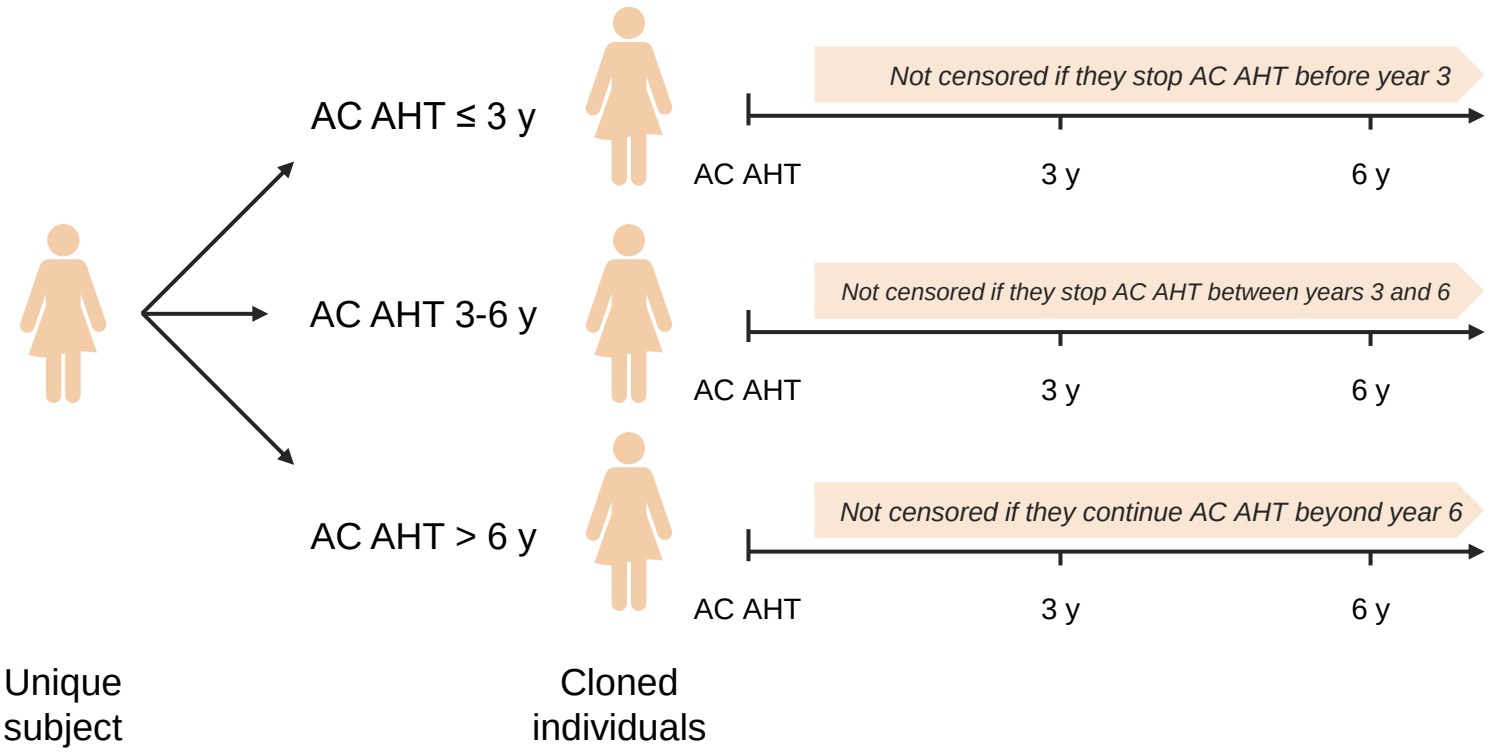
Complication 1: all initiators are compliant with the 3 strategies at baseline

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



Methods: Statistical Methods

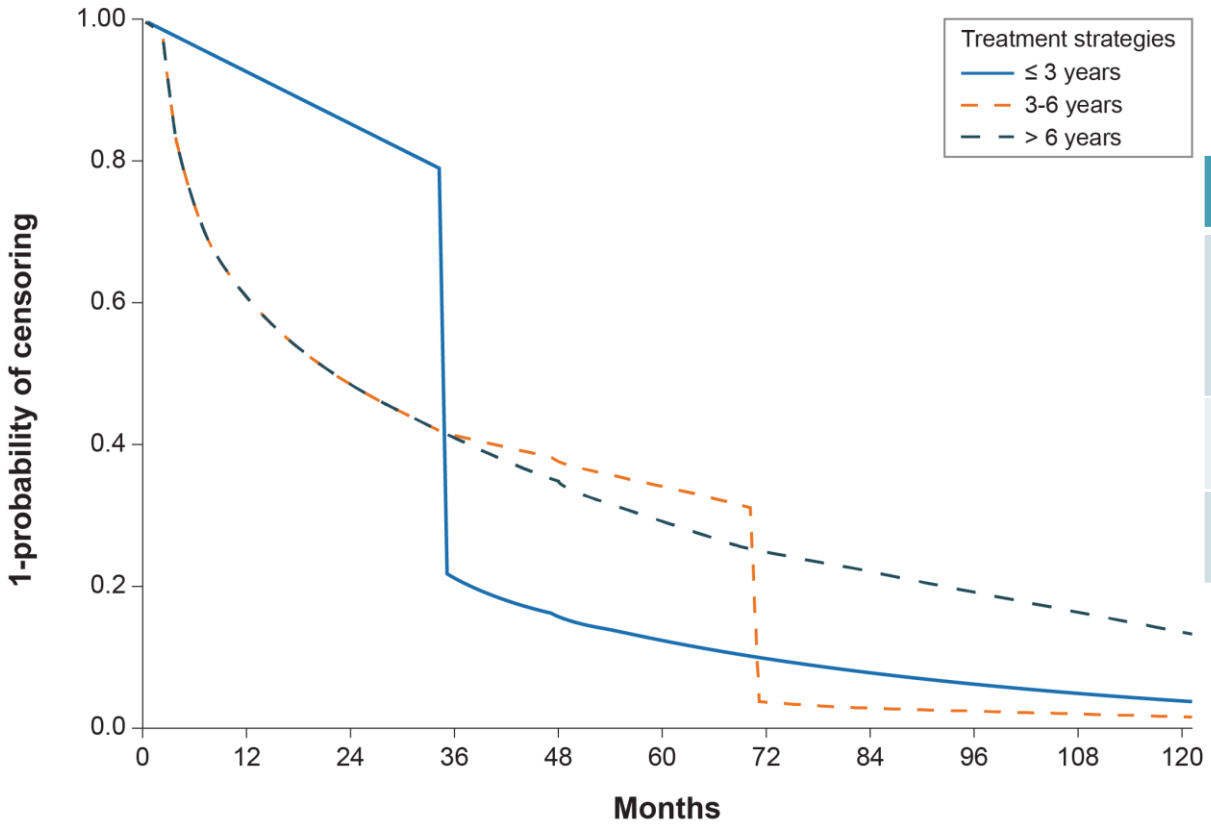
Complication 2: cloning eliminates immortal time bias, but artificial censoring can introduce selection bias

Solution to complication 2: g-methods

- Inverse probability weighting
  - Weights: $W_t^A = \prod_{k=0}^{t} \frac{1}{f(A_k|\overline{A}_{k-1},\overline{L}_k,\overline{Y}_{k-1}=0)}$
  - 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.

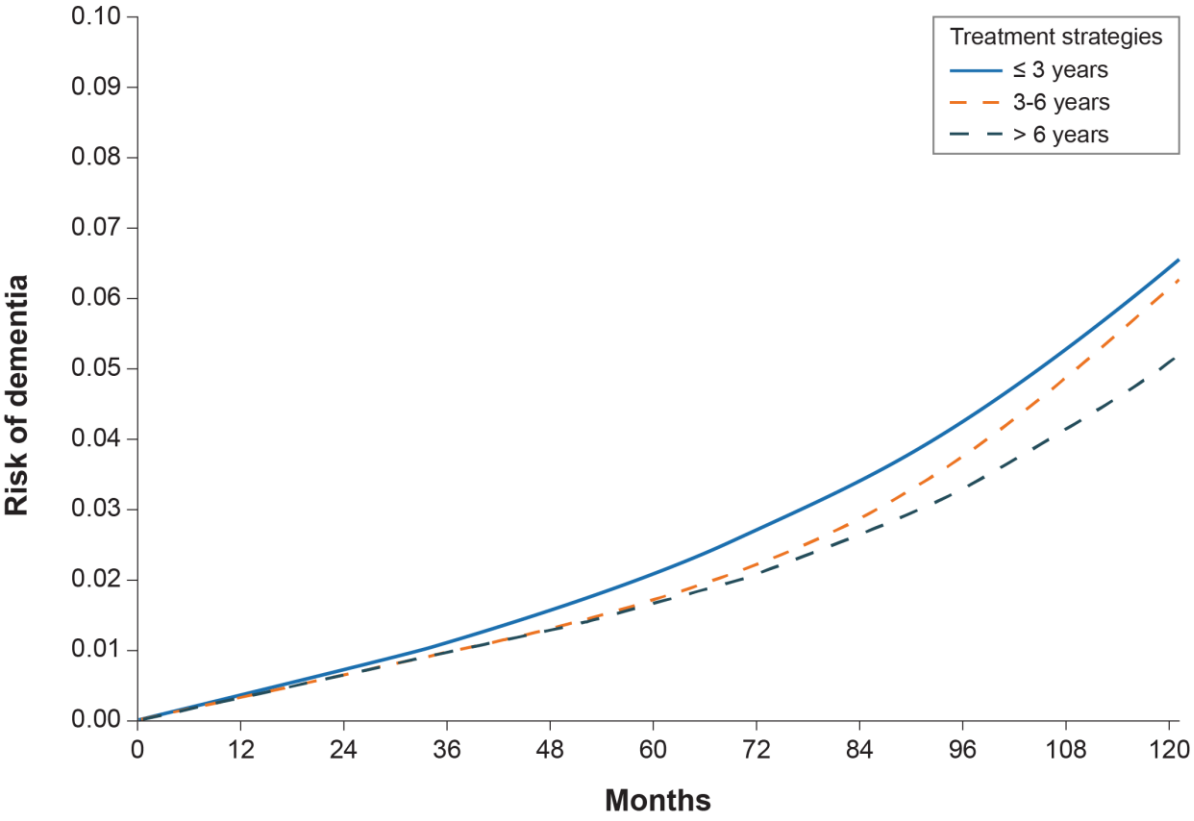
Results: Follow-up and Number of Events



	Treatment strategies		
	≤ 3 years (N = 77,365)	**3-6 years (N = 77,365)**	**> 6 years (N = 77,365)**
Follow-up (years)	234,133	221,680	171,421
Dementia, n (%)	597 (0.8)	443 (0.6)	443 (0.6)

Note: Follow-up was truncated at 10 years

Results: Fully Adjusted Parametric Risk Curves at 10 Years



Comparison at 10 y	Risk difference (95% CI[a])
> 6 years **vs.** ≤ 3 years	–1.3% (–2.0 to –0.6)
3-6 years **vs.** ≤ 3 years	–0.3% (–1.3 to 1.0)

[a] 500 bootstrap samples.

Results: Adjusted Hazard Ratios at 10 Years

HR adjusted by baseline covariates and using IPTW

Comparison of groups based on the observed duration of treatment[a]

Comparison	HR (95% CI[b])	Comparison	HR (95% CI[b])
> 6 years **vs.** ≤ 3 years	0.80 (0.73-0.88)	> 6 years **vs.** ≤ 3 years	0.29 (0.26-0.33)
3-6 years **vs.** ≤ 3 years	0.86 (0.79-0.94)	3-6 years **vs.** ≤ 3 years	0.64 (0.57-0.71)

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

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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

Lucia C. Petito, PhD; Xabier García-Albéniz, MD, PhD; Roger W. Logan, PhD; Nadia Howlader, PhD; Angela B. Mariotto, PhD; Issa J. Dahabreh, MD, ScD; Miguel A. Hernán, MD, DrPH

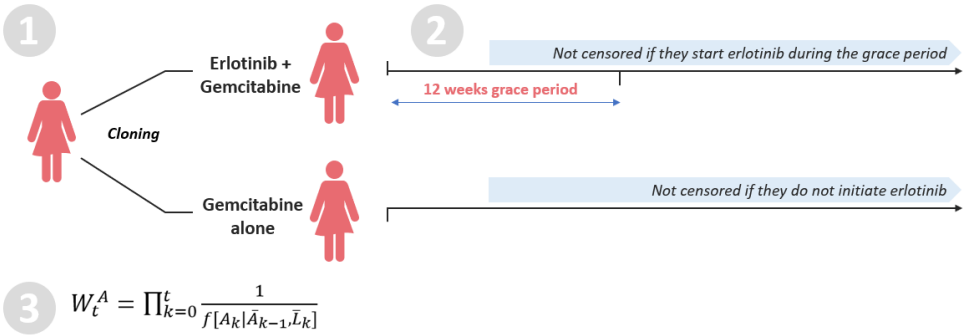
Treatment Strategies

Erlotinib

Initiation of erlotinib within 12 weeks of gemcitabine initiation for pancreatic cancer

No Erlotinib

Gemcitabine alone



Target trial emulation result HR (95% CI)	Existing RCT result HR (95% CI)	Naïve Analysis Result HR (95% CI)
1.04 (0.86-1.42)	0.96 (0.74-1.24)	0.68 (0.54-0.87).

Periodic intervention vs. No intervention

Annals of Internal Medicine ORIGINAL RESEARCH

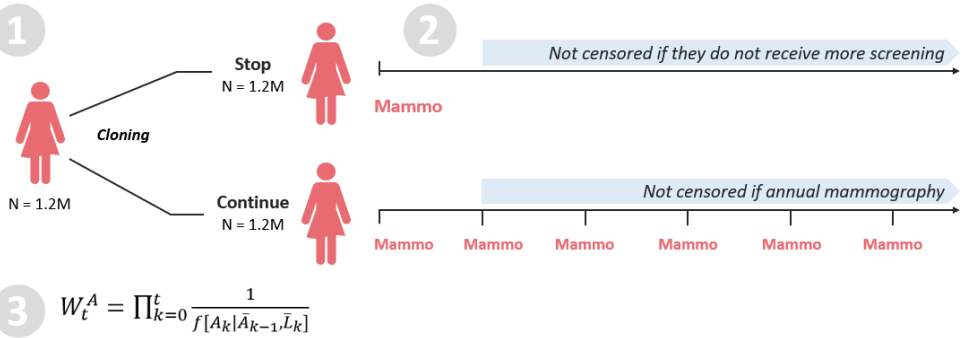
Continuation of Annual Screening Mammography and Breast Cancer Mortality in Women Older Than 70 Years

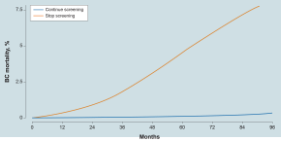
Xabier García-Albéniz, MD, PhD; Miguel A. Hernán, MD, DrPH; Roger W. Logan, PhD; Mary Price, PhD; Katrina Armstrong, MD, MSCE; and John Hsu, MD, MBA, MSCE

Ann Intern Med. 2020;172:381-389. doi:10.7326/M18-1199

Treatment Strategies

- **Continue screening**: Annual mammograms for 8 years
- **Stop screening**: No mammograms



Target trial emulation result HR (95% CI)	Existing RCT result HR (95% CI)	Naïve Analysis Result HR (95% CI)
0.78 (0.64-0.96)	0.80 (0.51 to 1.28)	

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)

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Health Solutions

Thank You

Questions?

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