UNIVERSITÄT BERN

Preventing immortal time and other biases in observational studies via the target trial methodology

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On today's program – clearly with "causal"/ "what if we do this or that" questions

- Does Informed Consent Prevent School-Based Caries Prevention Programs from Successfully Targeting High Risk Populations? A Longitudinal Study of Medicaid Claims Data with Clinical Oral Health

- Estimating the causal effect of number of teeth on critical outcomes of COVID-19: Based on three different propensity score methods

- Regular dental attendance in children has long term benefit in adulthood: Evidence from the 1970 British Cohort Study

Today also descriptive and other topics

- Higher prevalence of tooth loss in people with abdominal obesity: findings from the US and Scottish non-obese population

- Inequality of children's oral health in the UK can be mediated by lifestyle behaviours

Three common types of questions/topics in health research

- Description
  - What are the observed rates of dental implant interventions in different regions (per person, per region or country)?
- Clinical prediction
  - What is the observed 1-year revision rate after a dental implant in different dental clinics?
- Evaluation of hypothetical clinical or policy interventions
  - Does the introduction of required minimal annual number of dental implant interventions per dentist reduce the 1-year revision rate?

  → «What if» questions

Hernán MA et al: A Second Chance to Get Causal Inference Right: A Classification of Data Science Tasks. CHANCE 2019, 32:42-9

	Data Science Task		
	Description	**Prediction**	**Causal inference**
Example of scientific question	How can women aged 60–80 years with stroke history be partitioned in classes defined by their characteristics?	What is the probability of having a stroke next year for women with certain characteristics?	Will starting a statin reduce, on average, the risk of stroke in women with certain characteristics?
Data	• Eligibility criteria • Features (symptoms, clinical parameters …)	• Eligibility criteria • Output (diagnosis of stroke over the next year) • Inputs (age, blood pressure, history of stroke, diabetes at baseline)	• Eligibility criteria • Outcome (diagnosis of stroke over the next year) • Treatment (initiation of statins at baseline) • Confounders • Effect modifiers (optional)
Examples of analytics	Cluster analysis …	Regression Decision trees Random forests Support vector machines Neural networks …	Regression Matching Inverse probability weighting G-formula G-estimation Instrumental variable estimation …

Hernán MA et al: CHANCE 2019, 32:42-9

Description can be important

Trends, regional variation, and clinical characteristics of COVID-19 vaccine recipients: a retrospective cohort study in 23.4 million patients using OpenSAFELY.

The OpenSAFELY Collaborative: Brian MacKenna[1*] Helen J Curtis[1*], Caroline E Morton[1], Peter Inglesby[1], Alex J Walker[1], Jessica Morley[1], Amir Mehrkar[1], Seb Bacon[1], George Hickman[1], Chris Bates[3], Richard Croker[1], David Evans[1], Tom Ward[1], Jonathan Cockburn[3], Simon Davy[1], Krishnan Bhaskaran[2], Anna Schultze[2], Christopher T Rentsch[2], Elizabeth Williamson[2], William Hulme[1], Helen I McDonald[2], Laurie Tomlinson[2], Rohini Mathur[2], Henry Drysdale[1], Rosalind M Eggo[2], Kevin Wing[2], Angel YS Wong[2], Harriet Forbes[2], John Parry[3], Frank Hester[3], Sam Harper[3], Ian J Douglas[2], Stephen JW Evans[2] Liam Smeeth[2], Ben Goldacre[1]

medRxiv preprint doi: https://doi.org/10.1101/2021.01.25.21250356

Methods

Study design

We conducted a retrospective cohort study using general practice primary care electronic health record data from NHS England. The cohort study began on 7th December 2020, chosen as the day before the start of the national vaccination campaign and ended on January 13th to produce this analysis. We will update this analysis regularly with extended follow-up time using our near real time data as the vaccination campaign progresses.

Data Source

Primary care records managed by the GP software provider TPP were accessed through OpenSAFELY-TPP, an open source data analytics platform created by our team on behalf of NHS England to address urgent COVID-19 research questions (https://opensafely.org). OpenSAFELY-TPP provides a secure software interface allowing the analysis of pseudonymized primary care patient records from England in near real-time within the EHR vendor's highly secure data centre, avoiding the need for large volumes of potentially disclosive pseudonymised patient data to be transferred off-site. This, in addition to other technical and organisational controls, minimizes any risk of re-identification. Similarly pseudonymized datasets from other data providers are securely provided to the EHR vendor and linked to the primary care data, such as Office of National Statistics (ONS) death data. The dataset analysed within OpenSAFELY-TPP is based on 23.4 million people currently registered with GP surgeries using TPP SystmOne software to record and retrieve patient information. It includes pseudonymised data such as coded diagnoses, medications and physiological parameters. No free text data are included. Further details on our information governance can be found under information governance and ethics.

Table 1. *COVID vaccinations among 80+ population not resident in care homes as at 13th Jan 2021. Values <7 suppressed. Patient counts are rounded to the nearest 7. "coverage over last 7d" is the absolute percentage increase in coverage since the previous week.*

		Vaccinated at 13th Jan (n)	Vaccinated at 13th Jan (%)	Total	Vaccinated at 6th Jan 2021 (%)	coverage over last 7d (%)
Category	**Group**					
Overall	**Overall**	476,376	41.1	1,160,062	24.5	16.6
Sex	**F**	265,076	39.6	669,278	23.2	16.4
	M	211,295	43.1	490,774	26.3	16.8
Ethnicity broad categories	**Black**	2,121	20.5	10,329	11.6	8.9
	Mixed	756	27.0	2,805	16.2	10.8
	Other	1,498	27.0	5,539	15.8	11.2
	South Asian	7,945	29.5	26,936	17.7	11.8
	Unknown	129,199	39.7	325,637	23.3	16.4
	White	334,852	42.5	788,806	25.5	17.0
	African	329	15.9	2,072	9.5	6.4

Often we want to know how to decide NOW

- Treat with A or with B?
- Treat now or later?
- When to switch to C?

→A randomized trial would answer each of these questions

If RCTs are not available – can real «world data» help?

Yes

→ Avoid naive and flawed methods to obtain effect estimates !

30-day mortality comparing two different treatment approaches

What can you/we conclude from this data?

	Treatment A			Treatment B		
	Number of patients	Deaths	Proportion dead (percent)	Number of patients	Deaths	Proportion dead (percent)
Total	800	40	5.0	800	81	10.1

Stratified by sex

	Treatment A			Treatment B		
	Number of patients	Deaths	Proportion dead (percent)	Number of patients	Deaths	Proportion dead (percent)
Total	800	40	5.0	800	81	10.1
Men	400	25	6.3	510	61	12.0
Women	400	15	3.8	290	20	6.9

Sex, Age and Severity

			Hospital A			Hospital B		
			Number of patients	Deaths	Proportion dead (percent)	Number of patients	Deaths	Proportion dead (percent)
Total	Age	Seve-rity	800	40	5.0	800	81	10.1
Men	<60	Low	200	4	2.0	50	1	2.0
	<60	High	60	6	10.0	100	10	10.0
	60+	Low	100	5	5.0	200	10	5.0
	60+	High	40	10	25.0	160	40	25.0
Women	<60	Low	200	2	1.0	100	1	1.0
	<60	High	60	3	5.0	40	2	5.0
	60+	Low	100	4	4.0	50	2	4.0
	60+	High	40	6	15.0	100	15	15.0

For “point” interventions and baseline confounding many methods help to get “causal effect” estimate

Analytical approach	Odds Ratio (B versus A) and 95% CI
Logistic regression including only hospital (**no adjustment**)	2.14 (1.45- 3.17)
Logistic regression including sex, age and severity independently	0.98 (0.64 – 1.52)
Logistic regression including sex, age, severity with all 2-way interactions between sex, age and severity	1.0 (0.65 – 1.55)
IPTW weighted analysis with weights constructed with sex, age and severity independently in the model for the defining the weights	0.99 (0.65 – 1.51)
IPTW weighted analysis with weights constructed with all 2-way interactions between sex, age and severity in the model for the defining the weights	1.0 (0.65 – 1.53)

Zwahlen M, Salanti G: Causal inference from experiment and observation. Evidence Based Mental Health 2018, 21:34-8.

Causes and potential outcomes

Individual level

- Person A was treated with TrA and died

- What would have happened if person A had not been treated with TrA but with TrB?

  the “potential” outcome

Death in first week after heart transplant for Greek Gods

ID	Received no heart transplant $Y_{a=0}$	Received heart transplant $Y_{a=1}$	
Rheia	0	1	
Kronos	1	0	Tr made difference
Demeter	0	0	
Hades	0	0	
Hestia	0	0	Tr made no difference
Poseidon	1	0	
Hera	0	0	
Zeus	0	1	
Artemis	1	1	Tr made no difference
Apollo	1	0	
Circe	0	1	
Ares	1	1	
Athene	1	1	
Eros	0	1	
Aphrodite	0	1	
Prometheus	0	1	
Selene	1	1	
Hermes	1	0	
Eos	1	0	
Helios	1	0	

Hernan MA. A definition of causal effect for epidemiological research. J Epidemiol Community Health 2004;58:265–271

	Received (y/n) heart transplant	Died (y/n)	Potential outcomes no transplant	Potential outcomes with transplant
ID	A	Y	$Y_{a=0}$	$Y_{a=1}$
Rheia	0	0	0	?
Kronos	0	1	1	?
Demeter	0	0	0	?
Hades	0	0	0	?
Hestia	1	0	?	0
Poseidon	1	0	?	0
Hera	1	0	?	0
Zeus	1	1	?	1
Artemis	0	1	1	?
Apollo	0	1	1	?
Circe	0	0	0	?
Ares	1	1	?	1
Athene	1	1	?	1
Eros	1	1	?	1
Aphrodite	1	1	?	1
Prometheus	1	1	?	1
Selene	1	1	?	1
Hermes	1	0	?	0
Eos	1	0	?	0
Helios	1	0	?	0

We (almost) never observe the individual Trx effects – but perhaps we can estimate the average Tr effect on the whole group

-> we need to fill in the "?" so that the average on the whole group with or without Trx is right

Randomized controlled trials allow you to "see" the average potential outcomes under each treatment

	Treatment A			Treatment B		
	Number of patients	Deaths	Proportion dead (percent)	Number of patients	Deaths	Proportion dead (percent)
Total	800	40	5.0	800	81	10.1

If all 1600 would have received A

If all 1600 would have received B

Point versus sustained interventions

A big difference !

Covid-vaccination for pregnant women?

An example of a point intervention – but no RCT exists

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] ✉

Published online 7 September 2021

«Real World Data» well used

CHS is an integrated healthcare payer-provider organization that serves 52% of the Israeli population.

Medical insurance in Israel is mandatory for all residents, and covers a wide range of services, including prenatal care.

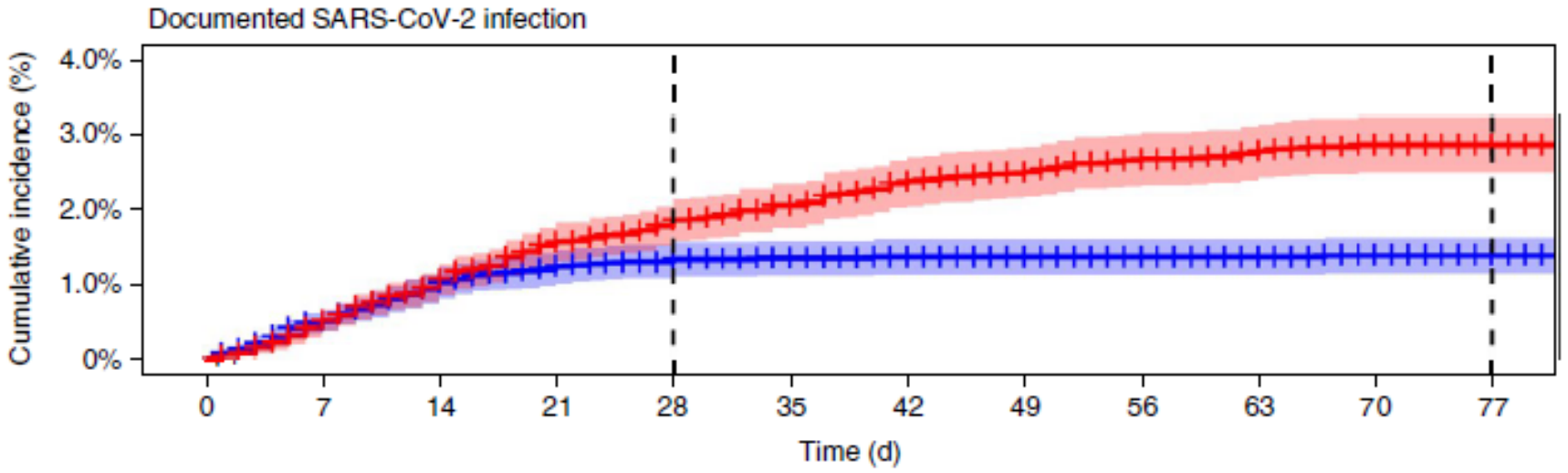
The present study was based on CHS data covering patients vaccinated from the start of the vaccination campaign in Israel on 20 December 2020 through to 3 June 2021.

CHS data systems contain medical and claims data covering all facets of patient care, including primary care, specialist care, imaging, laboratory diagnostics and hospitalizations, with over 20 years of historical depth for most individuals. CHS community care includes dedicated systems for prenatal care, with specific data fields for ‘date of last menstrual period’ and ‘projected birth date’. Pregnancies are recorded in these dedicated systems from the moment a woman begins prenatal care, which is freely and universally available in Israel.

These data are integrated daily with data collected centrally by the Israeli Ministry of Health regarding COVID-19 vaccines, SARS-CoV-2 tests and COVID-19-related hospitalizations, disease severity and death.

Matching approach for every calendar day

"Each day during the study period, eligible women vaccinated on that day were individually matched to eligible women who had not yet been vaccinated and who were not previously matched as controls. Matching factors included age (in 3-year bins), trimester of pregnancy, geostatistical living area (corresponding to a small town or a single neighborhood within a large city or city/town of residence when the smaller geostatistical living area was not available), population sector (General Jewish, Arab or Ultraorthodox Jewish), count of influenza vaccinations in the last 5 years (in 2 bins) and existence of at least 1 Centers for Disease Control and Prevention risk factor for severe COVID-19."



Estimated vaccine effectiveness from 7 through to 56 d after the second dose was 96% (95% confidence interval 89–100%) for any documented infection,
97% (91–100%) for infections with documented symptoms and
89% (43–100%) for COVID-19-related hospitalization.

The situation of a sustained intervention

Next slides “taken” from teachings of Miguel Hernán in the Wengen Epi Winterschool over the last 5 years

https://www.epi-winterschool.org/

Also explained in

Hernán M: How to estimate the effect of treatment duration on survival outcomes using observational data. BMJ 2018, 360:k182

Researchers are often interested in the effect of treatment duration on survival

- How to quantify this effect when using observational data?

- By definition, individuals with longer treatment duration have survived longer
  - a naïve survival comparison between individuals with longer and shorter treatment duration will be generally biased

Example: A randomized trial to estimate the effect of aspirin duration on survival

- Three groups
  - no aspirin (durA=0)
  - one year of aspirin (durA=1)
  - two years of aspirin (durA=2)
- Perfect adherence
- No losses to follow-up
- No random variability
  - View each subject as representing a million subjects with the same data

Data from a randomized trial

Individual	durA	A_0	D_1	A_1	D_2
1	0	0	0	0	0
2	0	0	0	0	1
3	0	0	1		1
4	0	0	1		1
5	1	1	0	0	0
6	1	1	0	0	1
7	1	1	1		1
8	1	1	1		1
9	2	1	0	1	0
10	2	1	0	1	1
11	2	1	1		1
12	2	1	1		1

- D_1 and D_2 are death status (1: dead, 0: alive) at the end of the 1st and 2nd years
- A_0 and A_1 are aspirin use (1: yes, 0: no) at the start of the 1st and 2nd years

Data from a randomized trial

Individual	durA	A_0	D_1	A_1	D_2
1	0	0	0	0	0
2	0	0	0	0	1
3	0	0	1		1
4	0	0	1		1
5	1	1	0	0	0
6	1	1	0	0	1
7	1	1	1		1
8	1	1	1		1
9	2	1	0	1	0
10	2	1	0	1	1
11	2	1	1		1
12	2	1	1		1

- Causal risk ratio at year 2 for "2 years of aspirin" vs. "no aspirin"?
  - $\frac{\Pr[D_2=1|durA=2)}{\Pr[D_2=1|durA=0)}$
- Correct analysis

  (3/4) / (3/4) =1

Data from a randomized trial
Causal risk ratio: Naïve analysis

Individual	durA	A_0	D_1	A_1	D_2
1	0	0	0	0	0
2	0	0	0	0	1
3	0	0	1		1
4	0	0	1		1
5	1	1	0	0	0
6	1	1	0	0	1
7	1	1	1		1
8	1	1	1		1
9	2	1	0	1	0
10	2	1	0	1	1
11	2	1	1		1
12	2	1	1		1

- risk in those who received 2 years of treatment
  - 1 death in (#9, #10)
- divided by risk in those who received 0 years of treatment
  - 3 deaths in (#1, #2, #3, #4)

(½)/(3/4)=2/3

The naïve analysis introduces immortal time bias

- Those who received 2 years of treatment have lived into starting year 2 on treatment
  - They were by definition “immortal” during that time
  - Longer treatment looks incorrectly beneficial

Data from an observational study without confounding

Individual	~~durA~~	A_0	D_1	A_1	D_2
1	~~0~~	0	0	0	0
2	~~0~~	0	0	0	1
3	~~0~~	0	1		1
4	~~0~~	0	1		1
5	~~1~~	1	0	0	0
6	~~1~~	1	0	0	1
7	~~1~~	1	1		1
8	~~1~~	1	1		1
9	~~2~~	1	0	1	0
10	~~2~~	1	0	1	1
11	~~2~~	1	1		1
12	~~2~~	1	1		1

- Causal risk ratio of mortality at year 2 for "2 years of aspirin" vs. "no aspirin"?
  - $\frac{\Pr[D_2=1|durA=2)}{\Pr[D_2=1|durA=0)}$
- What's the problem?
  - No *durA*? Make it!
  - Emulate target trial

Assigning individuals to a treatment duration strategy at time zero

Individual	durA	A_0	D_1	A_1	D_2
1	0	0	0	0	0
2	0	0	0	0	1
3	0	0	1		1
4	0	0	1		1
5	?	1	0	0	0
6	?	1	0	0	1
7	?	1	1		1
8	?	1	1		1
9	?	1	0	1	0
10	?	1	0	1	1
11	?	1	1		1
12	?	1	1		1

- #1, #2, #3, and #4 are assigned to durA=0
- And the others?
- Take #7
  - durA=1 or durA=2?
- Some individuals have data consistent with >1 strategy

Individual/Clone	durA	A_0	D_1	A_1	D_2
1	0	0	0	0	0
2	0	0	0	0	1
3	0	0	1		1
4	0	0	1		1
5a	1	1	0	0	0
6a	1	1	0	0	1
7a	1	1	1		1
8a	1	1	1		1
9a	1	1	0	1	0
10a	1	1	0	1	1
11a	1	1	1		1
12a	1	1	1		1
5b	2	1	0	0	0
6b	2	1	0	0	1
7b	2	1	1		1
8b	2	1	1		1
9b	2	1	0	1	0
10b	2	1	0	1	1
11b	2	1	1		1
12b	2	1	1		1

1. Cloning

- Clone individuals with data consistent with >1 strategy at baseline
- Assign each clone to a different strategy
- Cloning prevents immortal time bias

Individual/Clone	durA	A_0	D_1	A_1	D_2
1	0	0	0	0	0
2	0	0	0	0	1
3	0	0	1		1
4	0	0	1		1
5a	1	1	0	0	0
6a	1	1	0	0	1
7a	1	1	1		1
8a	1	1	1		1
9a	1	1	0	1	0
10a	1	1	0	1	1
11a	1	1	1		1
12a	1	1	1		1
5b	2	1	0	0	0
6b	2	1	0	0	1
7b	2	1	1		1
8b	2	1	1		1
9b	2	1	0	1	0
10b	2	1	0	1	1
11b	2	1	1		1
12b	2	1	1		1

1. Cloning

- Causal risk ratio?
  - $\frac{\Pr[D_2=1|\text{durA}=2)}{\Pr[D_2=1|\text{durA}=0)}$
- Correct analysis

  (6/8) / (3/4) =1
- This is ITT effect but, unlike in the trial, not all clones adhered
  - Per-protocol effect?

Individual/Clone	durA	A_0	D_1	A_1	D_2
1	0	0	0	0	0
2	0	0	0	0	1
3	0	0	1		1
4	0	0	1		1
5a	1	1	0	0	0
6a	1	1	0	0	1
7a	1	1	1		1
8a	1	1	1		1
9a	1	1	0	1	Censored
10a	1	1	0	1	Censored
11a	1	1	1		1
12a	1	1	1		1
5b	2	1	0	0	Censored
6b	2	1	0	0	Censored
7b	2	1	1		1
8b	2	1	1		1
9b	2	1	0	1	0
10b	2	1	0	1	1
11b	2	1	1		1
12b	2	1	1		1

2. Censoring

- To estimate per-protocol effect, censor clones when they "deviate" from their strategy
- What's the causal risk ratio now?

Individual/Clone	durA	A_0	D_1	A_1	D_2
1	0	0	0	0	0
2	0	0	0	0	1
3	0	0	1		1
4	0	0	1		1
5a	1	1	0	0	0
6a	1	1	0	0	1
7a	1	1	1		1
8a	1	1	1		1
9a	1	1	0	1	Censored
10a	1	1	0	1	Censored
11a	1	1	1		1
12a	1	1	1		1
5b	2	1	0	0	Censored
6b	2	1	0	0	Censored
7b	2	1	1		1
8b	2	1	1		1
9b	2	1	0	1	0
10b	2	1	0	1	1
11b	2	1	1		1
12b	2	1	1		1

2. Censoring

- Ignoring the censored people,

  (5/6)/(3/4)=1.11
  Biased!

- Censoring induces selection bias
  - Need to adjust

Individual/Clone	durA	A_0	D_1	A_1	D_2	IP weight
1	0	0	0	0	0	1
2	0	0	0	0	1	1
3	0	0	1		1	1
4	0	0	1		1	1
5a	1	1	0	0	0	2
6a	1	1	0	0	1	2
7a	1	1	1		1	1
8a	1	1	1		1	1
9a	1	1	0	1	Cens	0
10a	1	1	0	1	Cens	0
11a	1	1	1		1	1
12a	1	1	1		1	1
5b	2	1	0	0	Cens	0
6b	2	1	0	0	Cens	0
7b	2	1	1		1	1
8b	2	1	1		1	1
9b	2	1	0	1	0	2
10b	2	1	0	1	1	2
11b	2	1	1		1	1
12b	2	1	1		1	1

3. IP weighting

- Informally, each uncensored individual receives a weight equal to the inverse of his/her probability of being uncensored
  - censored individuals transfer their weight to individuals who remain uncensored

Individual/Clone	durA	A_0	D_1	A_1	D_2	IP weight
1	0	0	0	0	0	1
2	0	0	0	0	1	1
3	0	0	1		1	1
4	0	0	1		1	1
5a	1	1	0	0	0	2
6a	1	1	0	0	1	2
7a	1	1	1		1	1
8a	1	1	1		1	1
9a	1	1	0	1	Cens	0
10a	1	1	0	1	Cens	0
11a	1	1	1		1	1
12a	1	1	1		1	1
5b	2	1	0	0	Cens	0
6b	2	1	0	0	Cens	0
7b	2	1	1		1	1
8b	2	1	1		1	1
9b	2	1	0	1	0	2
10b	2	1	0	1	1	2
11b	2	1	1		1	1
12b	2	1	1		1	1

3. IP weighting

- Causal risk ratio of mortality at year 2 for "2 years of aspirin" vs. "no aspirin"?
  - $\frac{\Pr[D_2=1|durA=2)}{\Pr[D_2=1|durA=0)}$
- Correct analysis

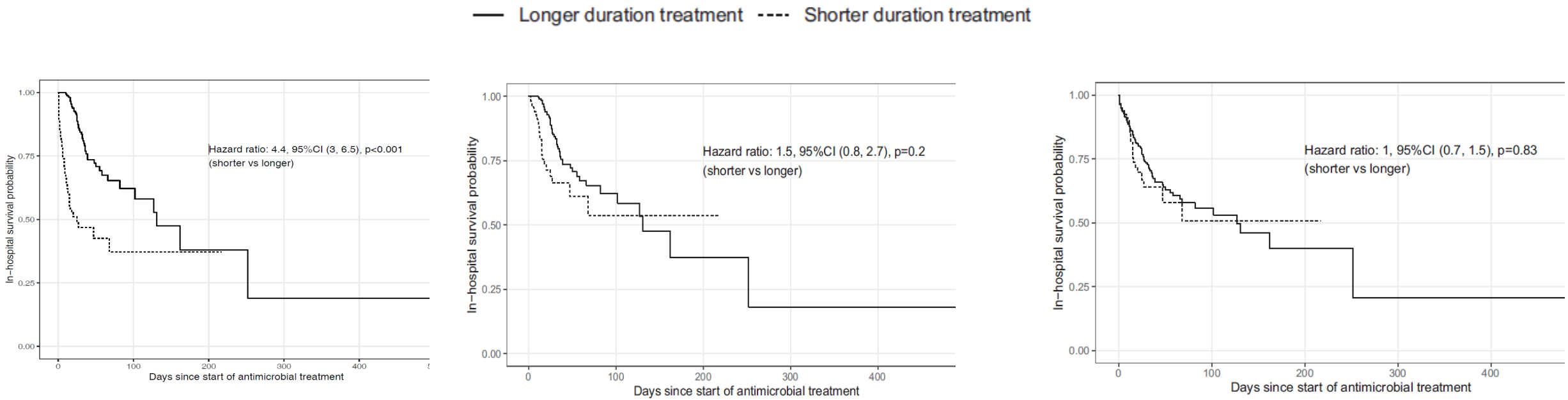
  (6/8) / (3/4) =1

  Unbiased!

3-step process cloning+censoring+weighting

- Cloning
  - to assign individuals to strategies; guarantees assignment is not based on information learned after time zero (never look into the future to group persons now !)
- Censoring
  - to ensure that the clones follow their assigned strategy during the entire follow-up; introduces selection bias
- IP weighting
  - to eliminate the selection bias introduced by censoring

The effect of duration [shorter (≤10 days) vs longer (>10 days)] of antimicrobial treatment for bacteremia in critically ill patients on in-hospital mortality



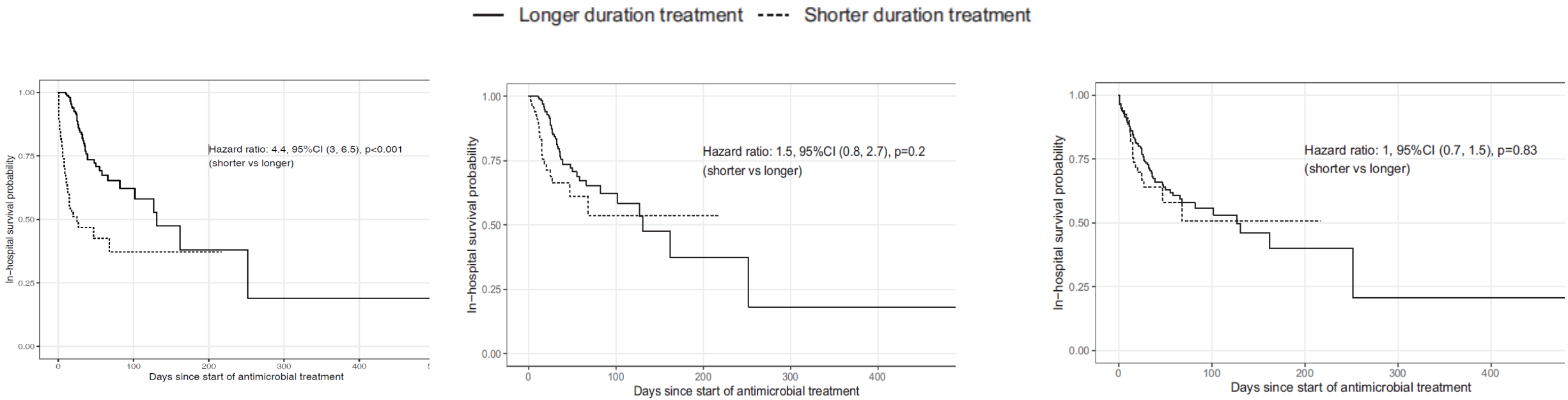
Naïve analysis

Cox: time dependent analysis

Cloning approach

Zuercher P, Moser A, Frey MC, et al. Journal of Critical Care 2023;74:154257

The effect of duration [shorter (≤10 days) vs longer (>10 days)] of antimicrobial treatment for bacteremia in critically ill patients on in-hospital mortality



Naïve analysis

Cox: time dependent analysis

Cloning approach

Zuercher P, Moser A, Frey MC, et al. Journal of Critical Care 2023;74:154257

Immortal Bias : Recognized as a widespread problem in …

- Pharmaco-Epidemiology
- Transplantation Medicine
- Emergency medicine

Levesque LE, Hanley JA, Kezouh A, Suissa S: Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ 2010, 340:b5087

The target trial approach: A recipe how to use RWD in an appropriate

- For a given question
  - What would be the ideal randomized randomized trial to answer the quesion ?
  - Is it possible to use the observational data to emulate a hypothetical RCT?
  - If successfull → an emulated trial and a real trial would give the same answer (effect estimate)

Procedure to answer the clinical / policy question

- Step 1
  - Define traget trial : Describe the protocol of the RCT that would answer the question
- Step 2
  - Option A: conduct the trial
  - Option B:
    - Use observational data to explicitely emulate the target trial
    - Apply appropriate inference techniques to obtain causal effect estimates

The obsverational study needs to emulate

- Eligibility criteria
- Start/End of follow-up
- Interventions
  - As if randomly assinged at start of follow-up
- Outcomes
- Causal contrast(s) of interest
- Analysis plan

Article

SMMR
STATISTICAL METHODS IN MEDICAL RESEARCH

Statistical Methods in Medical Research
22(1) 70–96

DOI: 10.1177/0962280211403603
smm.sagepub.com
SAGE

Observational data for comparative effectiveness research: An emulation of randomised trials of statins and primary prevention of coronary heart disease

Goodarz Danaei,[1] Luis A García Rodríguez,[2]
Oscar Fernández Cantero,[2] Roger Logan[1] and Miguel A Hernán[1,3]

Tutorial on how to emulate such a trial

Software implementation (SAS) available on
http://www.hsph.harvard.edu/causal/software/

American Journal of Epidemiology

Vol. 183, No. 8
DOI: 10.1093/aje/kwv254
Advance Access publication
March 18, 2016

Practice of Epidemiology

Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

Miguel A. Hernán* and James M. Robins

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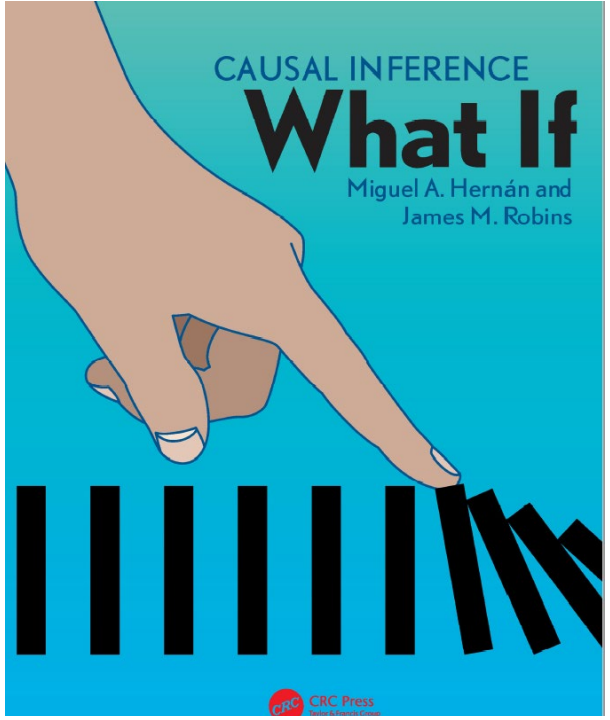
Initially submitted December 9, 2014; accepted for publication September 8, 2015.

Or read here Chapter 22



https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/

To cite the book, please use "Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC."

This book is only available online. You can download it for free from this page. A print version (for purchase) is expected to become available soon. The components of the book can be accessed by clicking on the links below:

- Causal Inference: What If (preprint, 2020; revised 2024)

Three important uses of RWD in health-related research

- Description
- Clinical prediction

} "Seeing "
"Predicting / diagnosing"

- What is the effect of choosing a treatment?

"Doing"

Getting an answer to "Doing" is harder than one to "Seeing"

Hernán MA et al: A Second Chance to Get Causal Inference Right: A Classification of Data Science Tasks. CHANCE 2019, 32:42-9

Acknowledgments

Miguel Hernán

Examples exist using explicit target trial approach

- When to start treatment in HIV infected persons
  - Health records from Europe and the USA
- Hormone replacement therapy and coronary heart disease in postmenopaual women
  - Electronic medical records form the UK / observational cohort study in the US
- Statins vs standard of care and risk of coronary heart disease
  - Electronic medical records form the UK
- By 2024 many more….

Research

JAMA | Original Investigation

Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses
Results of 32 Clinical Trials

Shirley V. Wang, PhD, ScM; Sebastian Schneeweiss, MD, ScD; and the RCT-DUPLICATE Initiative

JAMA. 2023;329(16):1376-1385. doi:10.1001/jama.2023.4221

Individual/Clone	durA	A_0	D_1	A_1	D_2	IP weight
1	0	0	0	0	0	1
2	0	0	0	0	1	1
3	0	0	1		1	1
4	0	0	1		1	1
5a	1	1	0	0	0	2
6a	1	1	0	0	1	2
7a	1	1	1		1	1
8a	1	1	1		1	1
9a	1	1	0	1	Cens	0
10a	1	1	0	1	Cens	0
11a	1	1	1		1	1
12a	1	1	1		1	1
5b	2	1	0	0	Cens	0
6b	2	1	0	0	Cens	0
7b	2	1	1		1	1
8b	2	1	1		1	1
9b	2	1	0	1	0	2
10b	2	1	0	1	1	2
11b	2	1	1		1	1
12b	2	1	1		1	1

3. IP weighting

- Probability of being uncensored
  - durA=0
    - 1 for all
  - durA=2:
    - 1 for those who died during the first year
    - 1/2 for the others

Have we quantified the intention-to-treat effect or the per-protocol effect?

- In this oversimplified example
  - Intention-to-treat effect = Per-protocol effect
  - Because all individuals adhered to their assigned treatment strategies
- If there were incomplete adherence, this correct analysis would quantify the intention-to-treat effect only
  - Quantifying the per-protocol effect would require additional adjustments