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Introduction to Regulatory-Grade Causal Inference

Joint HMA/EMA Big Data Steering Group Workshop on RWE methods: Harnessing Real-World Data for Regulatory Use

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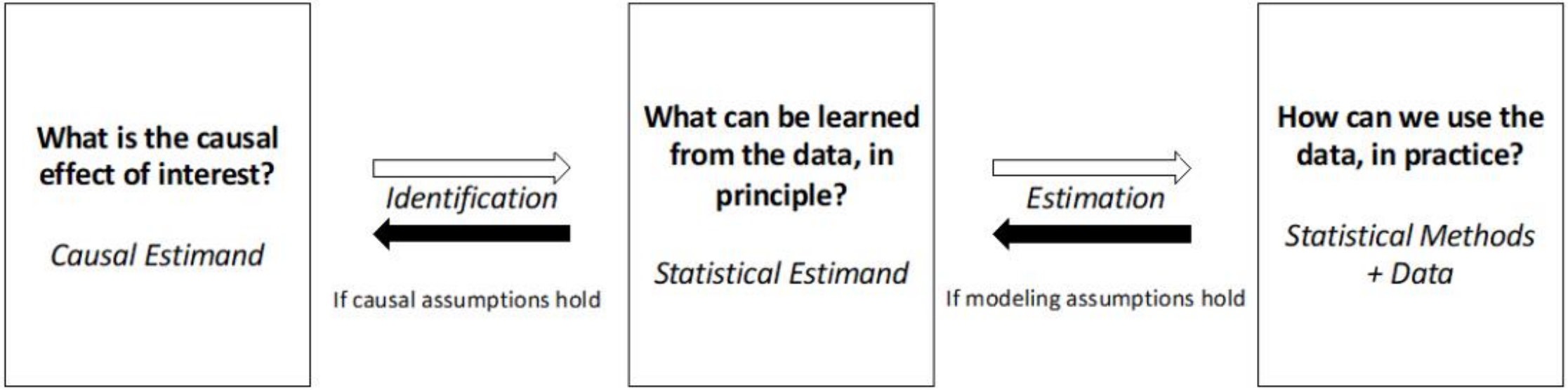
The power of knowledge.
The value of understanding.

Causal Inference Framework

eFigure 1: Schematic of the Relationship Between Causal Estimands, Statistical Estimands, and Statistical Analysis Methods Applied to Data



Dahabreh IJ, Bibbins-Domingo K. Causal Inference About the Effects of Interventions From Observational Studies in Medical Journals. JAMA. 2024 May 9. doi: 10.1001/jama.2024.7741. Epub ahead of print. PMID: 38722735.

What is emulating a target trial?

- Target trial emulation is a framework to articulate causal questions when using real-world data.
- Concept used by Dorn (1953), Wold (1954), Cochran (1972), Rubin (1974), Feinstein (1971), Dawid (2000). Generalized to time-varying treatments by Robins (1986).
- 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
- Motto: “don’t do with observational data anything you would not do in a trial”

RWD = real-world data.

Target Trial Emulation Framework for Causal Inference

Protocol component	Target trial specification	Target trial emulation
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	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.

Target Trial Emulation Framework for Causal Inference

CAUSAL ESTIMAND

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Two Important Components of the TTE framework

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1. Use of TTE to address a problem present in **RWD** analyses, **but not** in **RCTs**: alignment of time zero, exposure assignment and start of follow-up

2. Use of TTE to address a problem present in **RWD** analyses **and** in **RCTs**: the effect under complete adherence to treatment strategies

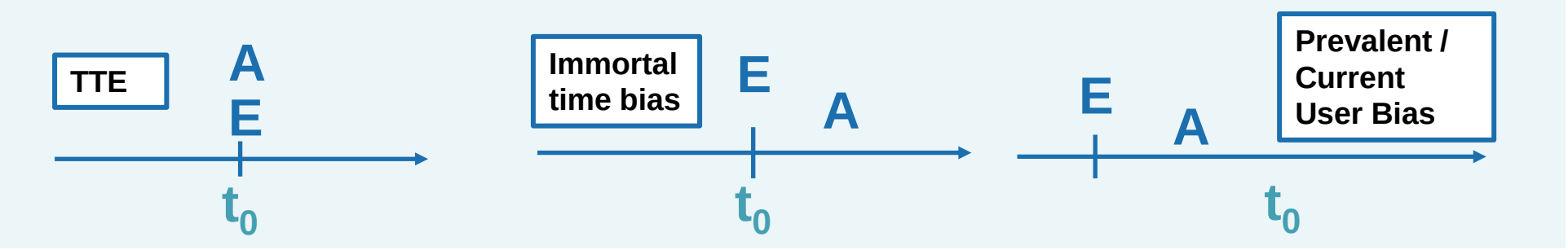
1 Alignment of time zero, eligibility and treatment assignment

Defining Time Zero

- Time zero refers to the point in time when we start counting the outcomes
- A proper specification of time zero is key for a successful emulation of a target trial (many emulation failures stem from errors in time zero identification)
- We must align the following three components:
  - **Time zero**
  - **Application of eligibility criteria**
  - **Exposure assignment**
- Sometimes this is intuitive and straightforward (e.g., in RCTs); others, not.

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
   - 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

Defining Time Zero – eligibility criteria are met a single time

- Simple scenario, usually “active vs. active” comparisons
- Examples include:
- Comparison of primo vaccination with vaccine A vs. vaccine B for COVID-19
  - Time zero is the time of vaccination
- Comparison of Ra-223 vs standard of care in patients with metastatic prostate cancer candidate to start a first line therapy (EUPAS33448).
  - Time zero is the time of therapy initiation

Defining Time Zero – eligibility criteria are met more than once

- Can be more complex
- Initiation vs. no initiation of statins in individuals over 30 years
- Individuals who meet the eligibility criteria continuously after age 30 would be eligible for the target trial at multiple times
- When should we assign time zero? There are two options:
  - Choose a single eligible time (e.g., the first eligible time, or a random eligible time)
  - Choose all eligible times

Hernán MA, Robins JM. 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.

Classifying individuals into treatment strategies

- There are situations when treatment strategies are not defined at baseline:

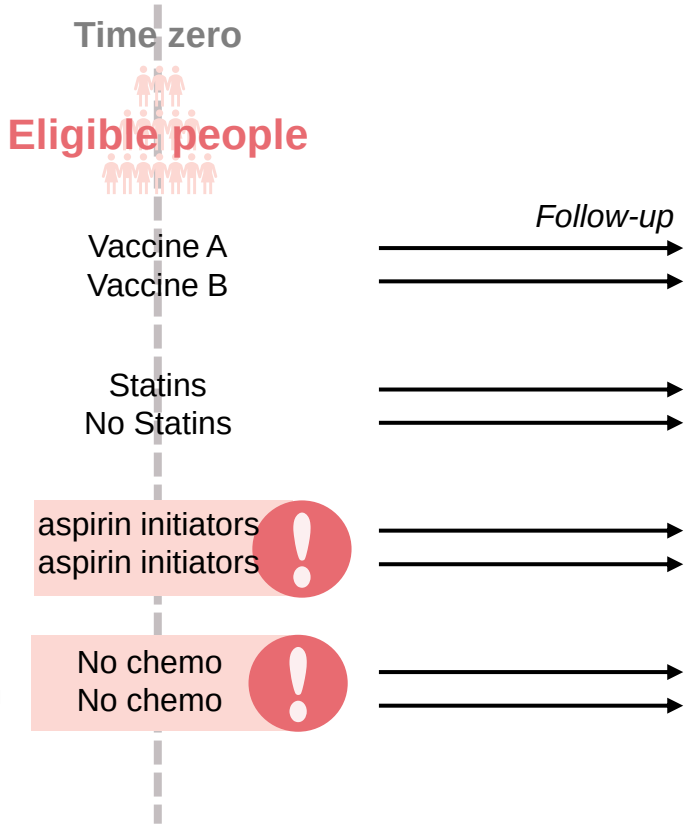
1. When using a grace period
   - Treatments do not happen immediately in real life
   - Extra diagnostics
   - Reimbursement approvals
2. When studying duration of treatment
   - At baseline, everybody starts, but they will continue for different times
3. Whey studying some dynamic strategies of treatment
   - A dynamic strategy of treatment is defined by the occurrence of a post-baseline event
   - E.g., Initiate antiretroviral therapy when the CD4 counts goes below 300 vs. below 100

Options: cloning or random assignment.

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

Classify individuals into exposure strategies their baseline data are compatible with

Treatment strategy defined at time zero?	Time zero easily identifiable?	
Yes	Yes	**Intervention A vs. Intervention B**
Yes	No	**Intervention vs. No Intervention**
No	Yes	**Intervention 3y vs. Intervention 6y**
No	No	**Intervention in a grace period vs. No intervention**



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2 Effect under complete adherence to treatment strategies

Causal Contrast

- Which counterfactual contrast will be estimated?
- Usually two options:
  - The **effect under initiation** of the treatment strategies.
    - Observational analogue of the intention to treat effect
  - The **effect under complete adherence** to the treatment strategies.
    - Observational analogue of the per protocol effect.
- The causal contrast will drive the type of statistical analysis
  - The observational analogue of the **intention to treat effect** requires adjustment for **baseline** variables (under complete follow-up)
  - The observational analogue of the **per protocol effect** requires adjustment for **baseline** variables and for **time-varying** variables that can affect adherence (under complete follow-up)

Treatment Strategies

- A treatment strategy (also referred as plan, policy, protocol or regime) is a set of rules to assign treatment at each time *k* of follow-up
- Defining the exposures as treatment strategies is one of the main attributes of target trial emulation
- It entails specifying
  - Treatment initiation
  - Valid reasons for treatment discontinuation
  - Use of concomitant therapies
  - Monitoring
- This will be the foundation of subsequent analytic decisions

Examples of treatment strategies

Reference	Experimental strategy	Control strategy
Effectiveness of Screening Colonoscopy to Prevent Colorectal Cancer Among Medicare Beneficiaries Aged 70 to 79 Years: A Prospective Observational Study. García-Albéniz et al. Ann Intern Med 166:18	Screening colonoscopy at baseline	No screening at baseline
Real World Outcomes in Patients With Metastatic, Castration-Resistant Prostate Cancer Treated With Radium-223 in Routine Clinical Practice in Sweden. Stattin et al.Clin Genitourin Cancer 21:107 (EUPAS33448)	Initiate Ra-223. Patients can stop Ra-223 after 6 cycles or earlier in the event of toxicity, cancer progression, or worsening of the overall health status. Patients can start other systemic drugs for mCRPC after the initiation of Ra-223, when clinically indicated, but they can never be used while taking Ra-223.	Initiate other standard of care (docetaxel, cabazitaxel, enzalutamide, abiraterone, others). Patients are allowed to stop the standard of care and continue with other lines of treatment, with the exception of Ra-223, when clinically indicated.
	ADT with first-generation antiandrogens can be used at any time	

Handling of post-baseline events

Treatment change
(stop/addition/switch)

- What is the causal contrast?
- Adhering to strategy despite change (e.g., treatment change was due to toxicity)?

Competing event
(e.g. because of death in the absence of the outcome of interest)

Choose your causal estimand (i.e., research question)

- Effect on the composite outcome
- Effect on the outcome through all causal pathways (*total effect*)
- Effect on the outcome in absence of the competing event (*direct effect*)
- Effect on the outcome not mediated by its effect on the competing event (*separable direct effect*)
- Effect on the outcome only through its effect on the competing event (*separable indirect effect*)

Loss to follow-up

Estimate the effect had everyone been under complete follow-up

Conclusion

- **To inform patients, clinicians, policy makers and regulators, we need to:**
  - Evaluate populations who are identifiable at the time of decision making.
  - Compare treatment strategies, not treatments.
  - Estimate effects under complete adherence, especially in safety studies
  - Choose relevant causal estimands (i.e., research questions)
  - Avoid “self-inflicted” design biases by aligning time zero, exposure assignment and eligibility
  - Outline identifying assumptions

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- **The target trial emulation framework does exactly that**

Thank You

Questions?