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Health Solutions

February 07, 2024

Analysis Methods – Causal Inference

Processes to Evaluate the Safety and Efficacy of Drugs for Rare Diseases or Conditions in the United States and the European Union.

The power of **knowledge.**
The value of **understanding.**

Agenda

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1. Introduction to Target Trial Emulation (5’)
2. Regulatory Application of Target Trial Emulation (4’)
3. Value of Target Trial Emulation on Rare Disease Research (3’)

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1 Introduction to Target Trial Emulation (5’)

Questions in Pharmacoepidemiology

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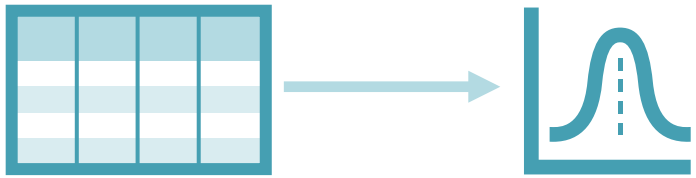
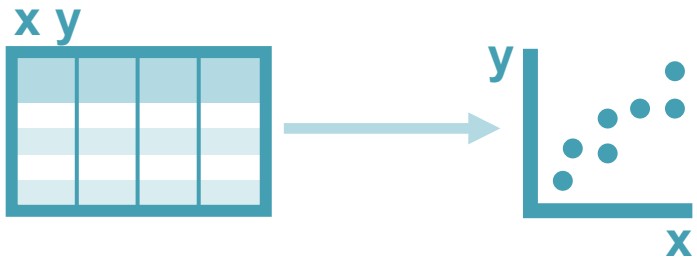
Descriptive questions: answered by using data to provide a quantitative summary of certain features of the world

- E.g., “What are the characteristics of patients diagnosed with rare disease X?”



Predictive questions: answered by using data to map some features of the world to other features of the world

- E.g., “Is the percentage of the population with rare disease X diagnosis the same in men and in women?”

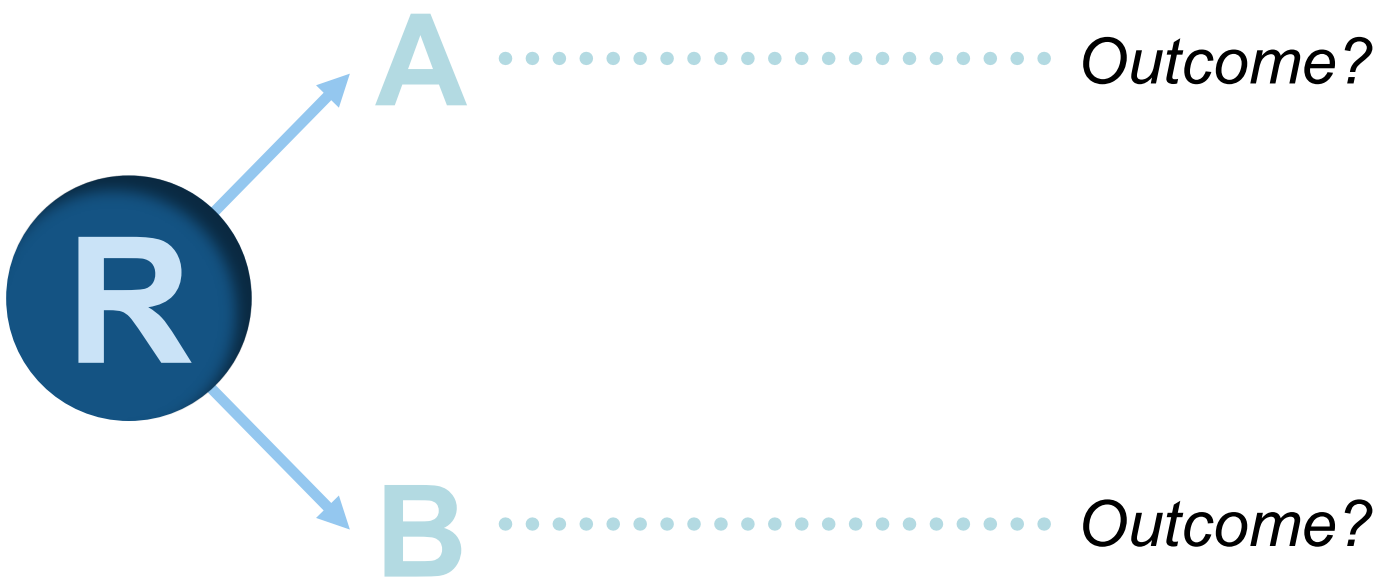


Causal inference questions: answered by using data to predict certain features of the world, as if the world had been different

- E.g., “What is the effect of drug A on the incidence of adverse events compared with drug B in patients with rare disease X?”

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.

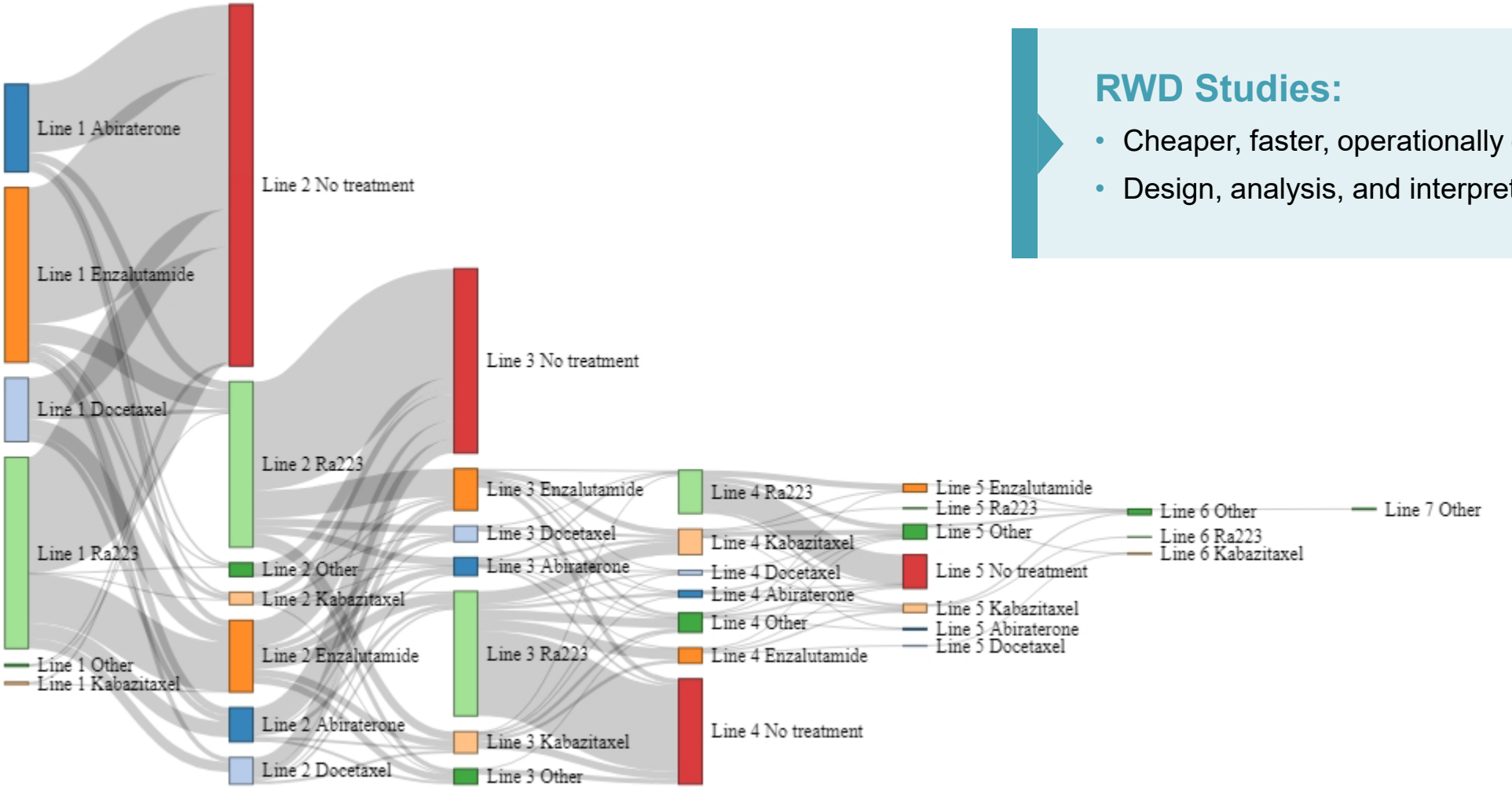
The Randomized Trial



Randomized trials:

- Expensive, lengthy, operationally challenging
- Straightforward to design, analyze, and interpret

Real-World Data Studies



RWD Studies:

- Cheaper, faster, operationally easier
- Design, analysis, and interpretation can be challenging

Pär Stattin P, et al. Real-world outcomes in patients with metastatic, castration-resistant prostate cancer treated with radium-223 in routine clinical practice in Sweden. Clinical Genitourinary Cancer. 2022 Sep 9. In press.

Science thrives under challenging times

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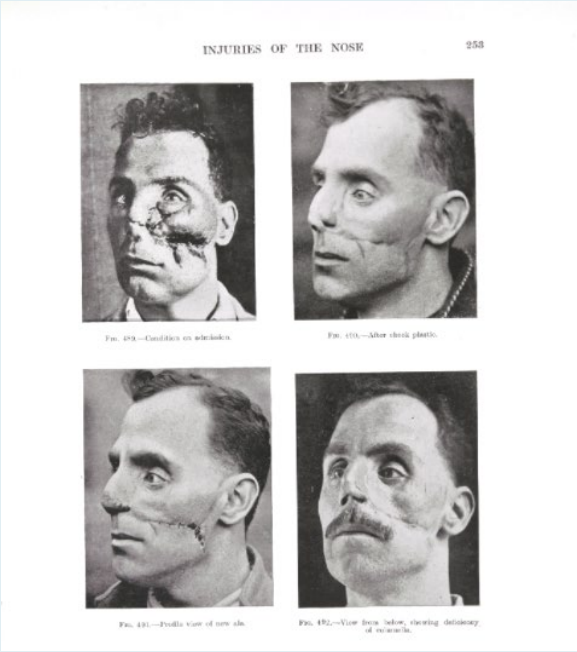
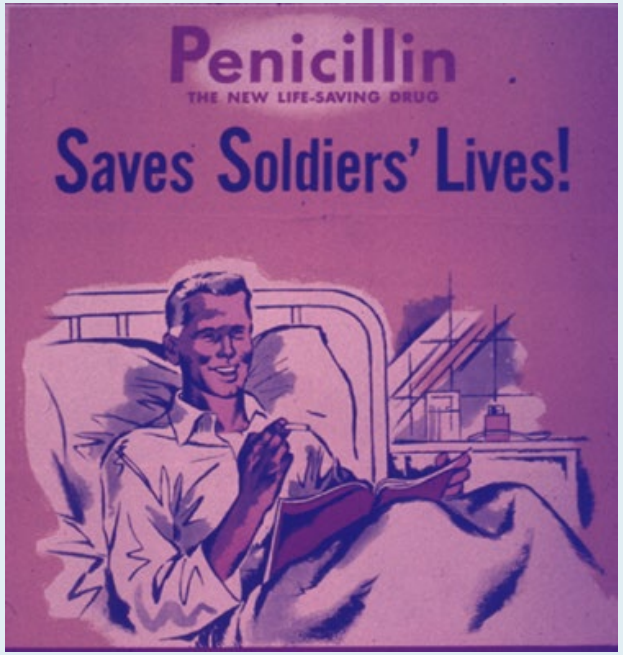
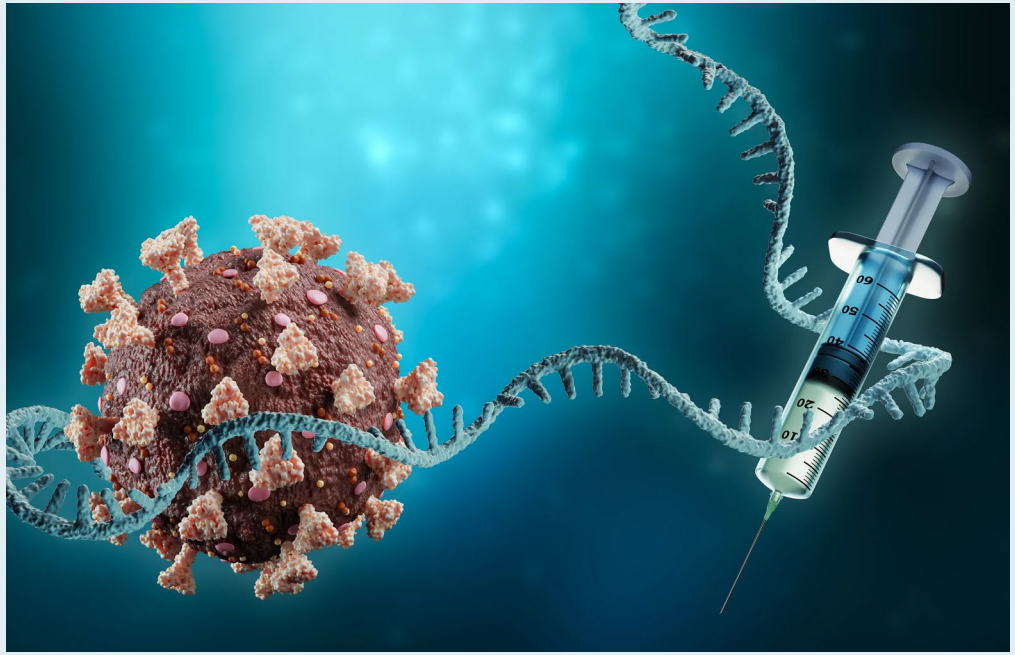
WWI:



WWII:



SARS-CoV-2 pandemic:



Plastic Surgery of the Face. Harold Gillies; Sidney Walbridge [photographer]: Public Domain.
https://www.nationalww2museum.org/war/articles/scientific-and-technological-advances-world-war-ii
https://news.mit.edu/2020/rna-vaccines-explained-covid-19-1211

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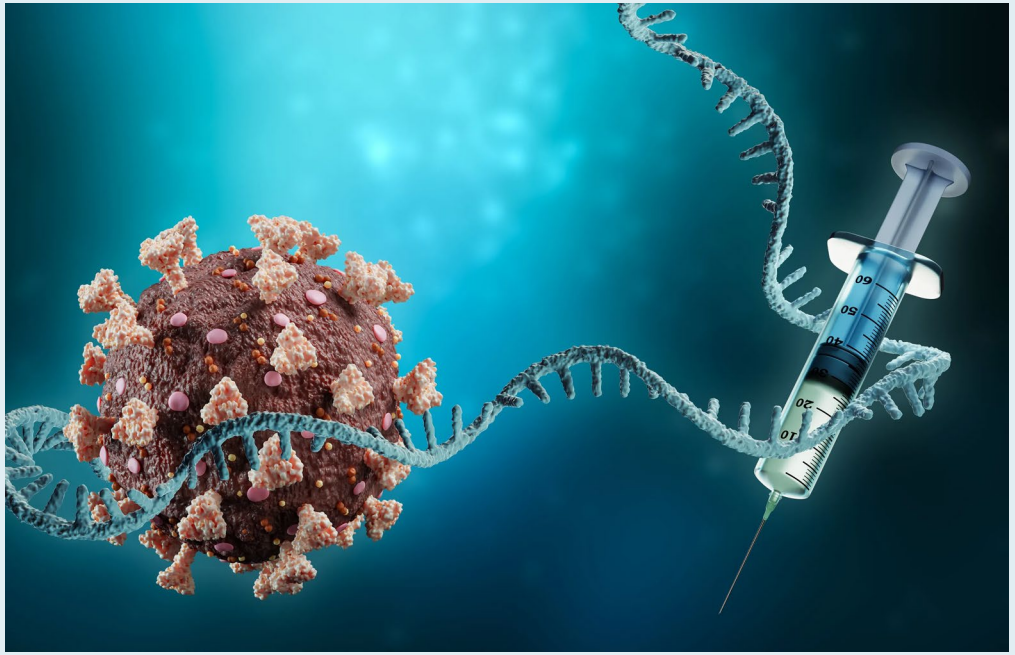
SARS-CoV-2 pandemic:



- Randomized clinical trials (RCTs) were key to prove mRNA vaccines efficacy
- Yet, **unanswered questions** by RCTs:
  - Safety regarding rare events
  - Safety in special populations (e.g. pregnant women)
  - Efficacy and safety in large-scale settings
  - Head-to-head comparisons

https://news.mit.edu/2020/rna-vaccines-explained-covid-19-1211

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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.

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

Head-to-head comparisons

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

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.

Vaccination Effectiveness: Target Trial Emulation

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

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-

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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 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 11)

"ENCePP recommends that, unless an alternative strategy is justified, **target trial emulation** should be considered for non-interventional causal inference studies to improve internal validity and increase transparency on definitions and assumptions"

National Institute for Health and Care Excellence Real-World Evidence Framework (23 June 2022)

"Non-randomised studies should be designed to mimic the randomised trial that would ideally have been performed unconstrained by ethical or feasibility challenges"

https://www.encepp.eu/standards_and_guidances/documents/01.ENCePPMethodsGuideRev.11.pdf
https://www.nice.org.uk/corporate/ecd9/chapter/overview

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

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.

RWD = real-world data.

Target Trial Emulation Framework for Causal Inference

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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 (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**

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2 Regulatory Application of Target Trial Emulation (4')

PRECISE/Rates of bone fractures and survival in metastatic castration-resistant prostate cancer patients treated with Ra-223 in routine clinical practice in Sweden (EUPAS33448)

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- **Ra-223** is a life-prolonging, systemic, targeted alpha therapy indicated for adults with metastatic castration-resistant prostate cancer (mCRPC) who have symptomatic bone metastases and no visceral metastases.
- In the pivotal **ALSYMPCA** clinical trial, Ra-223 prolonged overall survival (OS) and time to first symptomatic skeletal event, increased quality of life or delayed its decline, and had a good safety profile.
- In the subsequent **ERA 223** trial, Ra-223 in combination with abiraterone acetate plus prednisone and/or prednisolone (AAP) was found to increase the **risk of bone fractures** and deaths in the treatment arm, leading to unblinding.
- This safety signal triggered a regulatory procedure by the European Medicines Agency (EMA) that included a change to the label in the European Union
- The aim of the **noninterventional PASS PRECISE** was to estimate the effect of Ra-223 on the incidence of fractures and death compared with the standard of care in a real-world setting.

Stattin P, Westerberg M, Lissbrant IF, Eriksson MH, Kjellman A, Ullén A, Vassilev Z, Sandstrom P, Weinrib R, Martinez D, Garcia-Albeniz X. Real World Outcomes in Patients With Metastatic, Castration-Resistant Prostate Cancer Treated With Radium-223 in Routine Clinical Practice in Sweden. Clin Genitourin Cancer. 2023 Feb;21(1):107.e1-107.e9.

https://www.encepp.eu/encepp/viewResource.htm?id=42249

RWD for PRECISE PASS

Swedish PCBaSe

National Prostate Cancer Register of Sweden

- Since 1998, the primary registry of the NPCR has captured >96% of all men with incident prostate cancer compared with the Swedish National Cancer Register
- Registration is mandated by law
- The primary registration in the NPCR captures **data around the date of diagnosis** regarding cancer characteristics, diagnostic work-up, and primary treatment.
- **Treatments** that are initiated at a **later** stage of the disease, such as mCRPC treatments, are **not captured** in this primary registration

RWD for PRECISE PASS

Swedish PCBaSe

- The PPC was created in 2014 to overcome the lack of data of **follow-up data** in the primary registration of the NPCR .
- Patient-overview prostate cancer is a longitudinal registration of treatments, laboratory values, clinical data, etc. from initiation of ADT to death.
- In April 2021, the PPC contained data on approximately 12,000 patients from 33 healthcare providers
- The PPC has almost complete capture of treatment with Ra-223 in Sweden because contributing centers cover almost all sites at which Ra-223 is administered in Sweden

Target trial emulation

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Protocol component	Target trial specification	Target trial emulation using PCBaSe
Eligibility criteria	• Histologically confirmed adenocarcinoma of the prostate • Tumor is castration-resistant • Initiation of a systemic therapy for mCRPC as a nth line of treatment, where n goes from 1 to 4 • ECOG PS 0-2 • Presence of bone metastases • No prior use of Ra-223 • No prior participation in a blinded RCT	• Same as for the target trial • The initiation of a systemic therapy for mCRPC was used as surrogate for castration resistance and for ECOG PS 0-2 • We assumed all patients initiating Ra-223 have bone metastasis, only patients with recorded bone metastasis were chosen for the comparator
Treatment strategies	**1. 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 *never at the same time of Ra-223*. **2. 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. In both strategies ADT with first-generation antiandrogens can be used at any time.	Same as for the target trial

Target trial emulation

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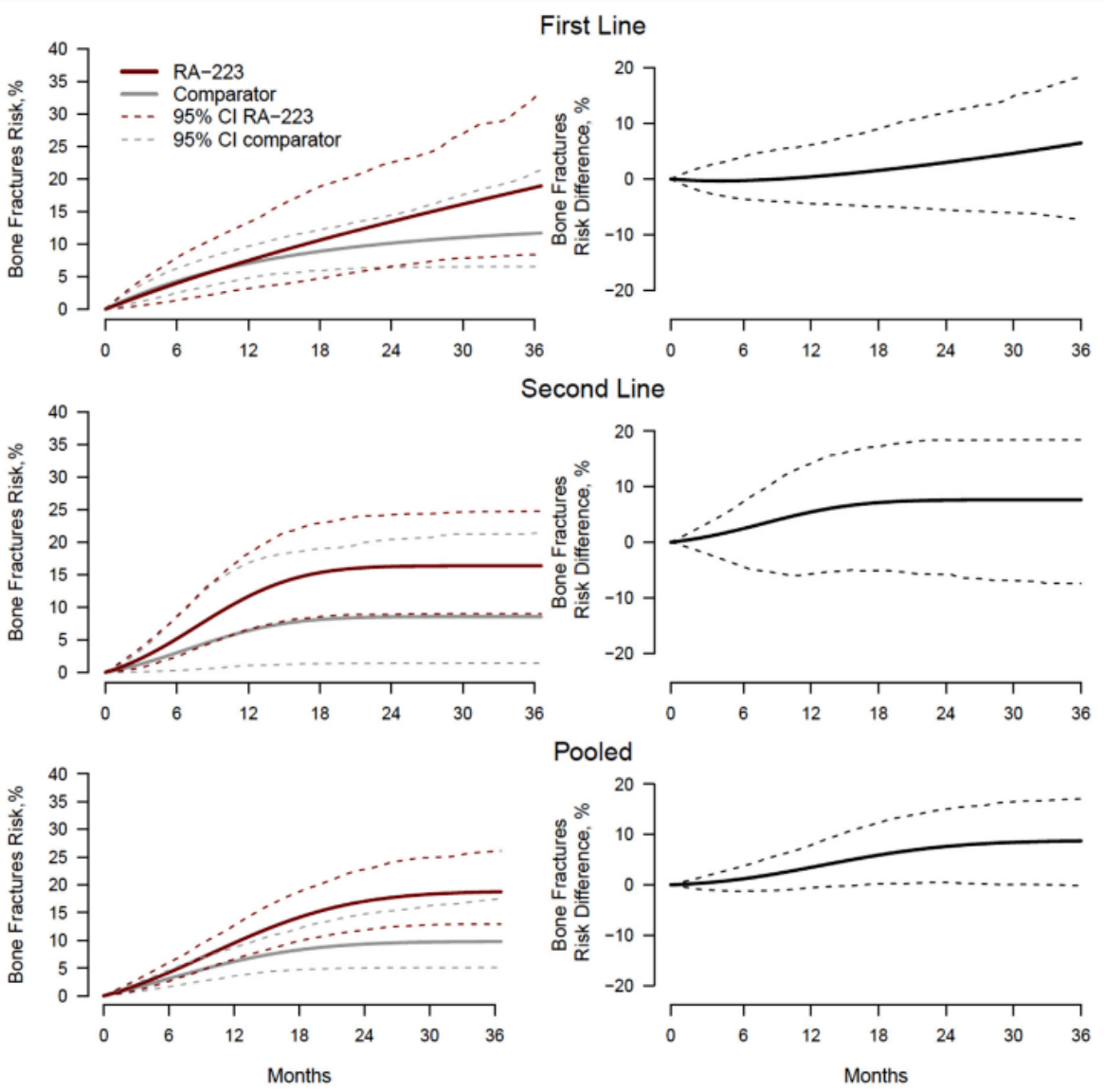
Protocol component	Target trial specification	Target trial emulation using PCBaSe
Treatment assignment	Individuals are randomly assigned to a strategy at baseline and will be aware of the strategy to which they have been assigned	Individuals are classified according to the strategy that their data were compatible with at baseline and randomization is emulated by adjusting for baseline confounders
Outcomes	Fractures, death, prostate cancer-specific death	Same as for the target trial
Follow-up	Starts at baseline and ends at the time of fracture, death, lost to follow-up, 36 months after baseline or administrative end of follow-up	Same as for the target trial
Causal contrast	Per-protocol effect	Observational analogue of the per-protocol effect
Statistical analysis	• Censor participants if and when they deviate from their assigned treatment strategy (Ra-223 group: combination of Ra-223 with other drug; SoC group: initiation of Ra-223) and apply inverse-probability weights to adjust for pre- and post-baseline prognostic factors associated with adherence • Results presented as time-to-event curves, 6 months interval-specific risk and risk differences, and as hazard ratios • Missing values dealt with inverse probability weighting	Same per-protocol analysis with sequential emulation and additional adjustment for baseline covariates

Figure 1:

Standardised cumulative incidence curves for bone fractures, by treatment group, first and second lines, and all the lines of treatment-specific cohorts.

CI = confidence interval;
Ra-223 = radium-223.



CI = confidence interval; Ra-223 = radium-223.

Stattin P, Westerberg M, Lissbrant IF, Eriksson MH, Kjellman A, Ullén A, Vassilev Z, Sandstrom P, Weinrib R, Martinez D, Garcia-Albeniz X. Real World Outcomes in Patients With Metastatic, Castration-Resistant Prostate Cancer Treated With Radium-223 in Routine Clinical Practice in Sweden. Clin Genitourin Cancer. 2023 Feb;21(1):107.e1-107.e9.

Conclusions in PRECISE

- Using real-world data, we estimated that the risk of fractures in patients receiving Ra-223 is similar to the risk observed in RCTs
- The effect estimates of Ra-223 on the 36-month risk of bone fractures compared with other standard of care in first- and second-line treatments were of small magnitude, with 95% CIs that were compatible with both a slightly protective and a mildly deleterious effect
- Patients in the Ra-223 group using concomitant bone-health agents had a lower risk of fracture than those not using them

3 Value of Target Trial Emulation for Rare Disease Research (3')

A. Design of studies using an external comparator

B. Design approaches to maximize the use of information contained in the data

1. Sequential emulation
2. Cloning

Value of Target Trial Emulation for Rare Disease Research

- Rare disease research is characterized by:
  - Difficult patient recruitment
  - Alternative treatments are scarce
  - Randomization may not be ethical
  - Available data on efficacy (either from RCT or from RWD) is limited
- A useful study design: Externally Controlled Trials (FDA, 2023)
  - Study where outcomes in participants receiving the test treatment according to a protocol are compared to outcomes in a group of people external to the trial who had note received the same treatment.
  - The external control arm can be a group of people, treated or untreated, from an earlier time (historical control) or from the same time period (concurrent control) but in another setting

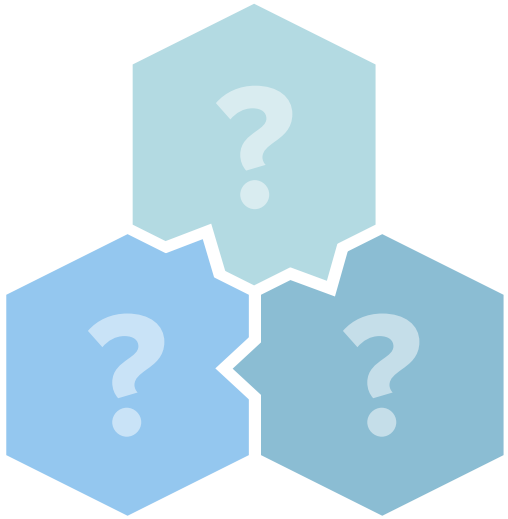
Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (fda.gov)

Challenges of using an external cohort

- Potential for confounding
  - Because of the lack of randomization between the clinical trial and the external cohort, baseline differences can bias the results
- Potential for selection bias
  - Can occur when participation in the study (either initial participation or continued participation) is affected by some of the variables under study
- Potential for measurement bias
  - Measurement bias can occur if there are relevant differences between the clinical trial and the external cohort in the following:
    - Criteria used to establish a diagnosis
    - Capture of treatments
    - Evaluation of the outcomes

How is TTE related to the use of RWE external comparators?

- Use of external controls for causal inference from single-arm or extension trials is plain observational/epidemiological research
- Thus the principles of target trial emulation also apply here:
  - Outline the protocol of the trial you seek to emulate (easy here)
  - Definition of time zero
  - Synchronization of time zero and the start of follow-up
    - No prevalent users
    - No “ever” users
  - Adjustment for baseline confounders
  - Adjustment for time-varying confounders, if interested in the observational analogue of the per-protocol effect



Framework to incorporate TTE into the design and analysis of studies using external comparator arms

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- Engage the regulator early in the process
- Ideally, design the external comparison concomitantly with the clinical trial

Step 1:
Specify the target trial

- Design a hypothetical target trial and specify all the study design and data elements to be emulated
- Many elements already defined by the single-arm study

Step 2: Obtaining external data sources to emulate the trial

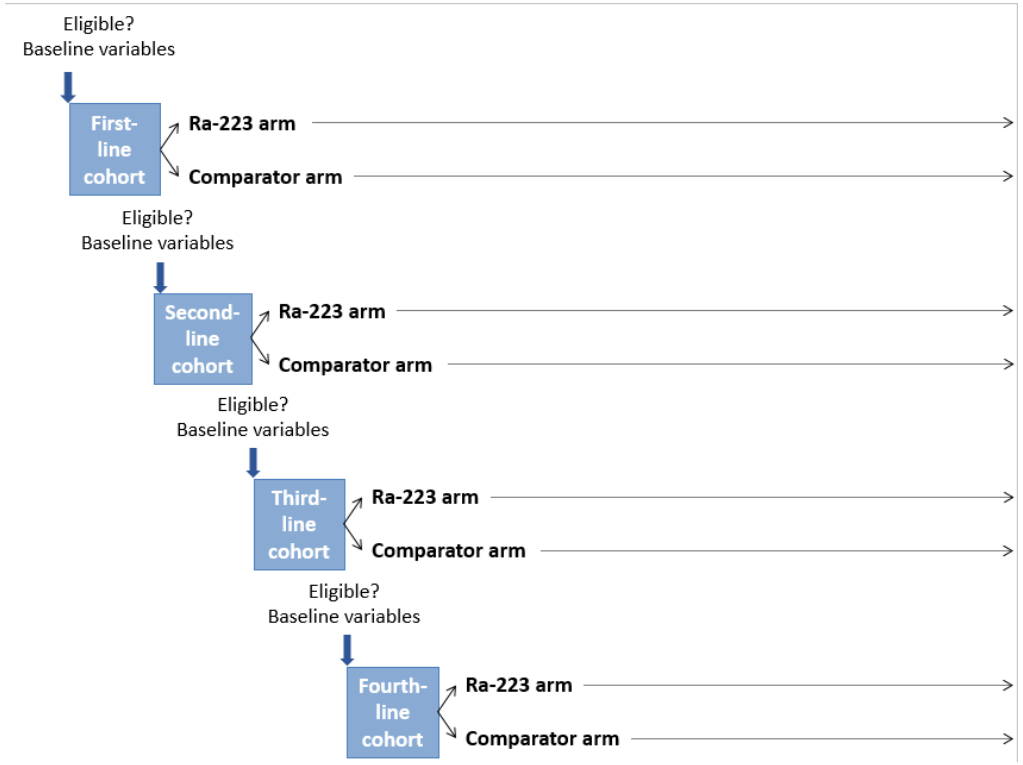
- Find or create data to generate an appropriate external cohort
- If using existing data, query whether the data elements required to emulate the target trial are available and assess their suitability to form a comparator arm
- Obtain clinical input on the assumptions used to emulate the trial

Step 3:
Emulating the target trial

- Estimate treatment effects of the experimental drug in the emulated target trial using epidemiological methods that minimise common biases of non-randomised studies

TTE framework has tools to improve efficiency

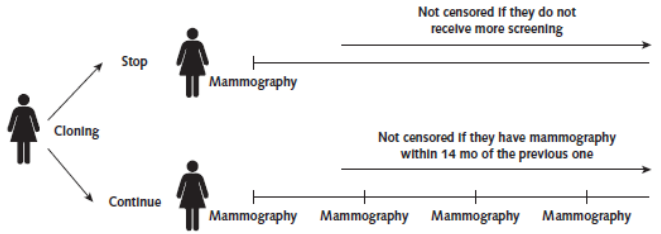
- Sequential emulation
  - Useful when patients meet the eligibility criteria more than once.



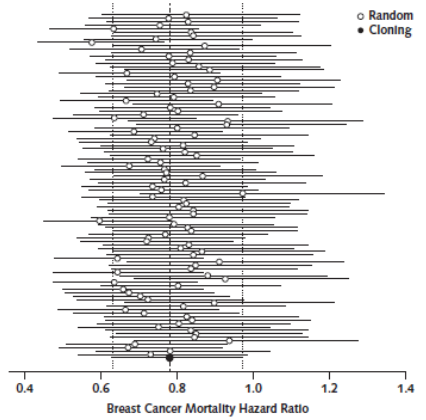
https://www.encepp.eu/encepp/viewResource.htm?id=42249

- Cloning into treatment strategies
  - Useful when patients' data are compatible with more than one treatment strategy at baseline

Appendix Figure 1. Schematic representation of the process of cloning and censoring.



Appendix Figure 2. Hazard ratios for breast cancer mortality using different approaches of baseline treatment assignment in women aged 70 to 74 y.



Horizontal lines represent 95% CIs.

García-Albéniz X, Hernán MA, Logan RW, Price M, Armstrong K, Hsu J. Continuation of Annual Screening Mammography and Breast Canacer Mortality in Women Older Than 70 Years. Ann Intern Med. 2020 Mar 17;172(6):381-389.

Thank You

Questions?