An Introduction to the Estimands and Target Trial Emulation (TTE) Frameworks

Tue, Apr 22nd, 2025
10:00-11:00am ET

Moderator:
Matt Baldwin, Amgen

PHUSE Estimands for RWD/RWE project team

- PHUSE RWE Working Group (link)
  - PHUSE Estimands for RWD/RWE project team (link)
    - Co-Leads
      - Matt Baldwin, Amgen
      - Ksenia Titorenko, ICON
      - Paramita Chakraborty, IQVIA
    - ~20 active project team members
    - Subteam 1 – White Paper Development
    - Subteam 2 – Webinar Series

At the Intersection of Estimands and Target Trial Emulation (TTE) for RWE webinar series (link)

- **Webinar 1 (Apr 2025):** An Introduction to the Estimands and Target Trial Emulation (TTE) Frameworks
- **Webinar 2 (Jun 2025):** Estimands in Real-World Evidence Studies
- **Webinar 3 (TBD):** Choosing the Right Estimand for a Stakeholder
- **Webinar 4 (TBD):** Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment
- **Webinar 5 (TBD):** Applying and Implementing the Estimand and Target Trial Emulation Frameworks

An Introduction to the Estimands and Target Trial Emulation (TTE) Frameworks

This introductory webinar aims to orient attendees on the intersection of the estimands and target trial emulation (TTE) frameworks, along with a suggested causal roadmap overview. After two presentations from publication authors and regulatory agency reflections, there will be a panel discussion. Attendees should have a basic knowledge of estimands from the ICH E9(R1) Addendum.

Real-World Evidence to Support Causal Inference: Methodological Considerations for Non-Interventional Studies (18Jun2024)

A causal roadmap for generating high-quality real-world evidence (22Sep2023)

ATTENTION – No live Q&A, any questions submitted via the Zoom chat or Q&A or workinggroups@phuse.global will be answered in a published Q&A file with the recording and slide decks

An Introduction to the Estimands and Target Trial Emulation (TTE) Frameworks

Webinar 1 Outline

- (5 min) Introduction
- (15 min) Dr Rachele Hendricks-Sturrup, *Duke-Margolis*
- (15 min) Dr Lauren Eyler Dang, *NIAID*
- (10 min) Dr Juanjo Abellán, *EMA*
- (13 min) Panel Discussion
- (2 min) Closing

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An Introduction to the Estimands and Target Trial Emulation (TTE) Frameworks

Panel Discussion

- Can you briefly share concerns from the causal inference / epidemiology perspective on the estimands framework?
- How can we navigate these concerns as RWD/RWE is increasingly appearing in study designs for regulatory submission?
- What are challenges to increased adoption of the frameworks you have outlined today?

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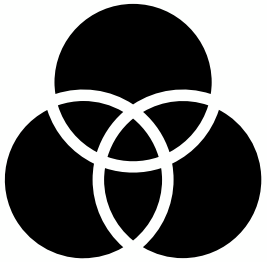
Generating and Leveraging RWE for Causal Inference

Duke | MARGOLIS INSTITUTE *for* Health Policy

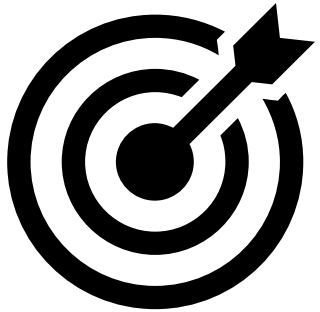
Non-Interventional, Observational Studies



- Non-interventional studies can be a mechanism to generate insights that may be otherwise inaccessible via randomized controlled trials.
  - Ex. Stronger subgroup analyses, as RWE studies typically comprise larger sample sizes.
- Results from non-interventional studies can be useful to inform health care decisions by capturing real-world outcomes, patient variability, and long-term effects of interventions.
- When intentionally designed, non-interventional or observational study designs that involve fit-for-purpose real-world data (RWD) and real-world evidence (RWE) can help researchers assess treatment effectiveness and measure causality in real-world settings.

Fit-for-Purpose Real-World Data for Causal Inference

- Ensuring the credibility of RWE for causal inference purposes requires clear design, fit-for-purpose RWD, communication, and rigorous statistical analysis.
- Establishing acceptable causal inferences in observational studies will rely foundationally on:
  - Clear and iterative study design.
  - Assumption formulation.
  - Precise communication of limitations and biases, and specification of research parameters.
  - Careful application of statistical methods to bridge the gap between causal and statistical estimands.



Background & Overview, cont.

- To reliably estimate the estimand from observational data and avoid design-related mistakes, there are multiple frameworks to assess causality using RWD:
  - ✓ **Estimand framework**
  - ✓ **Target trial framework**
  - ✓ **Causal roadmap framework**
- These three causal inference frameworks complement one another, are highly interrelated, and are aligned with foundational assumptions.

Framework for Causal Inference Studies Using Observational RWD	Key Features & Considerations
Estimand	• Structured approach to clarify study objectives and address uncertainties, particularly in the presence of deviations—including intercurrent events like treatment discontinuation or emergency medication use. • Consists of five key attributes: treatment, population, outcome variable, population-level summary, and handling intercurrent events.
Target Trial	• Grounded in counterfactual theory and offers a structured process for evaluating observational RWD. • Involves specifying a hypothetical RCT's protocol (defining eligibility, treatment/treatment regimen, follow-up periods, outcomes, etc.) and mimicking these components using observational data.
Combined Target Trial and Estimand	• Using target trial and the estimand framework in tandem leads to early internal alignment on study objectives, common understanding of potential sources of bias, and an early assessment of the quality and relevance of external controls. • This combined approach also can help researchers clarify the target trial design, improve the transparency of assumptions needed to emulate the target trial, and help facilitate choices around the best estimand.
Causal Roadmap	• Explicit, itemized, and iterative process that guides investigators to prespecify study design and analysis plans and addresses a wide range of guidance within a single framework. • Involves seven steps to help investigators prespecify design and analysis plans for studies that utilize RWD.

Framework for Causal Inference Studies Using Observational RWD	Key Limitations to Address
Estimand	• As observational data can be incomplete and contain measurement errors and biases: ✓ Conduct a series of analyses with the intent to explore the robustness of inferences from the main estimator to deviations from its underlying modeling assumptions and limitations in the data. ✓ Ensure research questions are clearly described to ensure that the estimand framework can be useful to assess treatment effects and avoid methodological challenges or shortcomings.
Target Trial	• When conducting an observational study to using retrospective claims data: ✓ Closely emulate an ongoing randomized controlled trial to compare the effectiveness of treatments, ✓ Identify patients who met the study's eligibility criteria, and ✓ Compare the risk of major adverse events between treatment groups, • Address any issues associated incomplete data used to replicate inclusion/exclusion criteria and endpoints, as well as potential residual confounding (see the PRONOUNCE study as an example).

Framework for Causal Inference Studies Using Observational RWD	Key Limitations to Address, cont.
Combined Target Trial and Estimand	• A limited number of studies (n= 1) have used this approach. • Future studies can consider current approaches: ✓ When comparing long-term survival outcomes within a pooled set of multiple previously reported randomized phase 3 trials, clearly define the hypothetical target trial structured according to the estimand framework.
Causal Roadmap	• Limitations are similar to data limitations of other frameworks using observational data. For example: ✓ Selection bias ✓ Bias due to baseline confounding ✓ Ability to correctly define the index date for comparison • Apply best practices that aim to produce high-quality estimates of causal effects using RWD.

Summary

- Causal inference using RWE is an approach aimed at identifying causal relationships between treatments or exposures and outcomes by analyzing observational data from RWD sources, such as electronic health records, insurance claims, and patient registries.
- Causal frameworks (estimand, target trial, causal roadmap) combine theory with practice in a structured approach to help researchers:
  - Translate complex theoretical constructs (like causal models and assumptions) into concrete analytical steps.
  - Ensure those constructs are appropriately reflected in the data analysis.
- It is important to note that regulators like the FDA either may not or have stated that they do not endorse the use of one causal framework over another.
- Sponsors are encouraged to describe their proposed approach to support causal inference and mitigate bias and confounding.

Contact Me!

Email: Rachele.hendricks.sturrup@duke.edu

A Causal Roadmap for Generating High-Quality Real-World Evidence

PHUSE Webinar: An Introduction to the Estimands and Target Trial Emulation Frameworks

04.22.2025

Lauren Dang, MD, PhD, MPH
Mathematical Statistician
Biostatistics Research Branch
National Institute for Allergy and Infectious Diseases

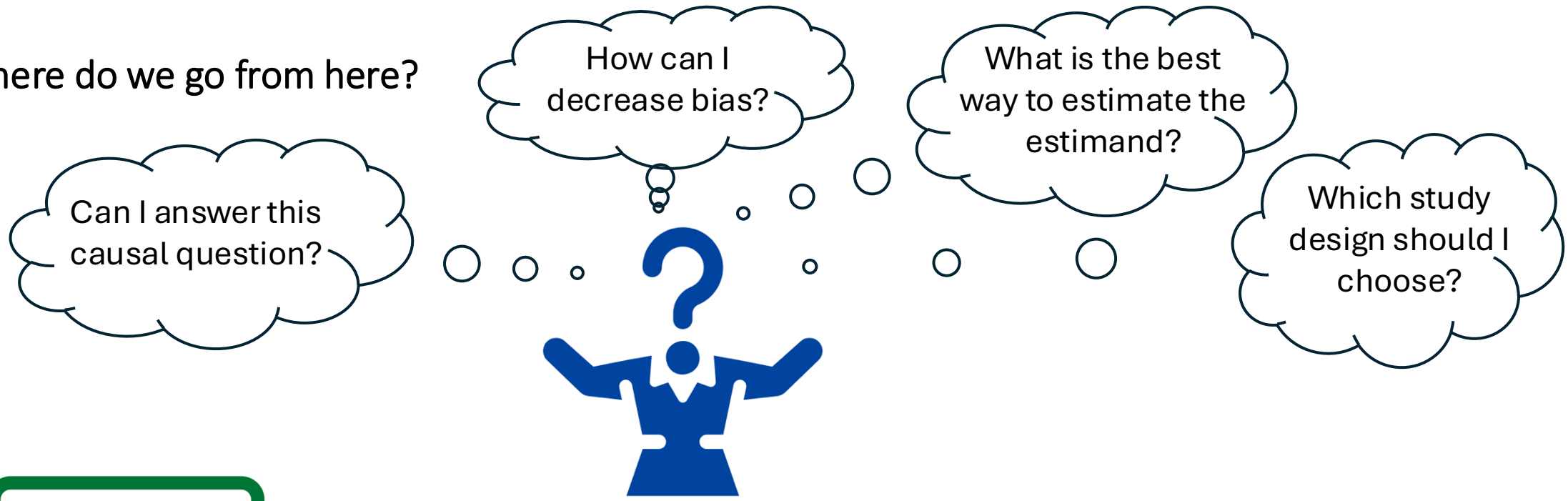
Re-Cap of ICH E9(R1) and TTE

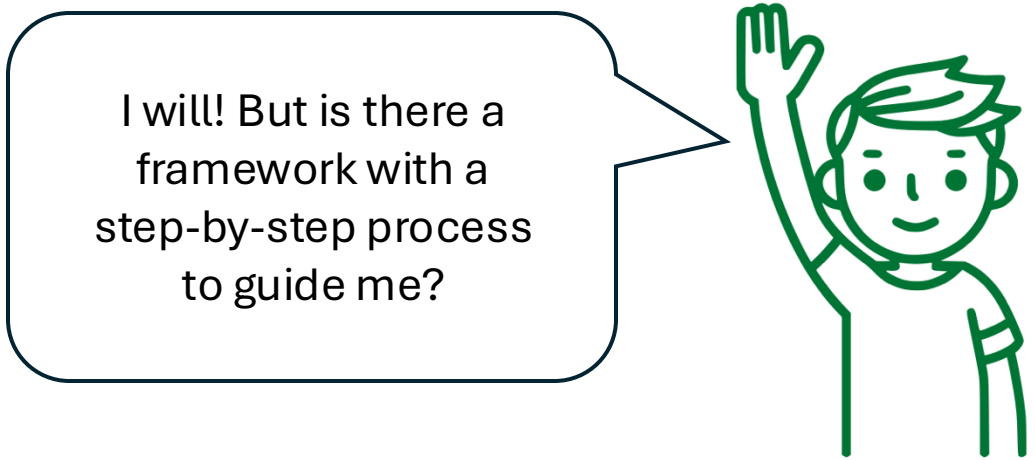
ICH E9(R1) Attribute (ICH, 2021)	Target Trial Emulation Protocol Component (Hernán & Robins, 2016)
Population	Eligibility Criteria
Treatment	Treatment Strategies
	Follow-up Period
Variable or Endpoint	Outcome
Population Summary	Causal Contrasts of Interest

- **Goal:** Preliminary query → research question (specific, interpretable, reproducible)
  - Estimand answers that question

We have specified an estimand…

- Where do we go from here?

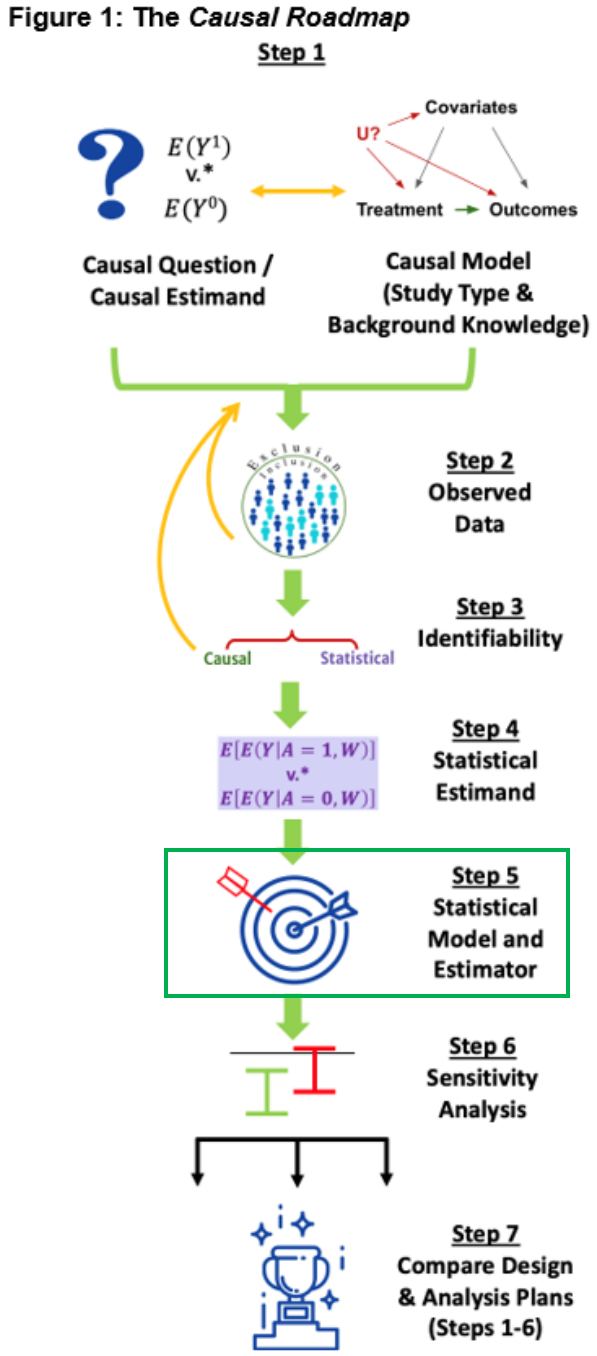




Yes! → The Causal Roadmap

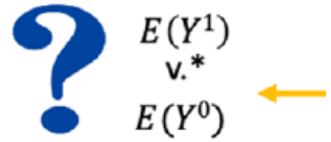
- Originally developed by Petersen & van der Laan (2014)
- Iterative step-by-step process
- Assists with pre-specification of study design/analysis plans
  - Useful for any study (traditional RCT to observational)
- Helps with selection between study designs
- Facilitates transparent evaluation of assumptions
  - Design/analytic modifications to decrease bias
  - Appropriate interpretation of results
- Closely related to the "Targeted Learning" framework (van der Laan & Rose, 2011)
  - Emphasizes TMLE for the estimation step

- Synthesis of decades of causal inference literature
  - For TTE: Many excellent papers, What If? (Hernán and Robins, 2020), …
  - ICH, EMA, FDA…: Many useful sources of guidance
  - Many others: PHUSE working groups, Duke Margolis Center, …
- **In my opinion:** Mostly agree! All are useful!
  - I find the Causal Roadmap to be particularly helpful



Dang et al., 2023

STEP 1A: Causal Question and Estimand



- **Goal:** Preliminary query → research question (specific, interpretable, reproducible)
  - **Causal** estimand answers that question

ICH E9(R1) Attribute (ICH, 2021)	Target Trial Emulation Protocol Component (Hernán & Robins, 2016)
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Ideal causal question may not be answerable from observed data

STEP 1B: Causal Model

- Knowledge about how the data have been/will be generated
- E.g., Directed Acyclic Graph (Pearl, 1995)

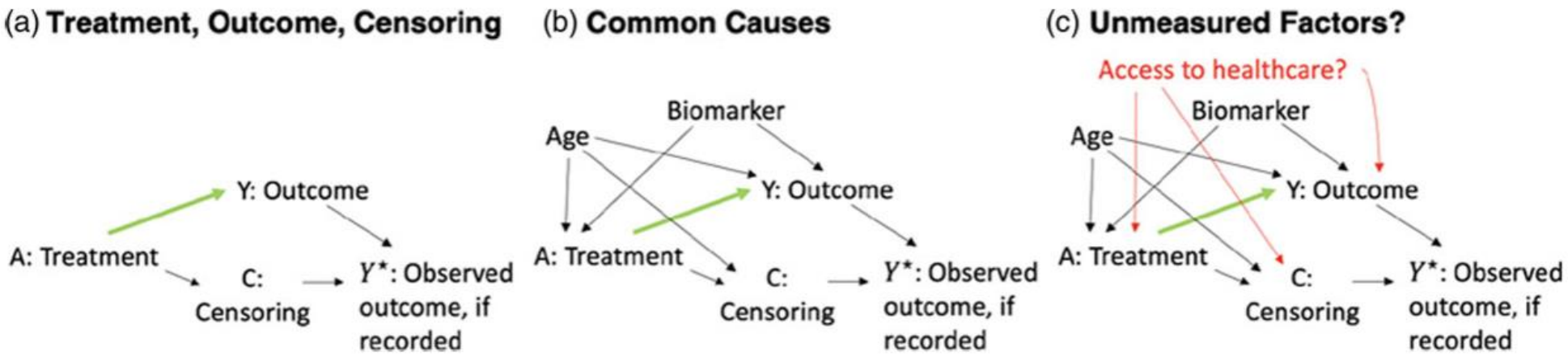
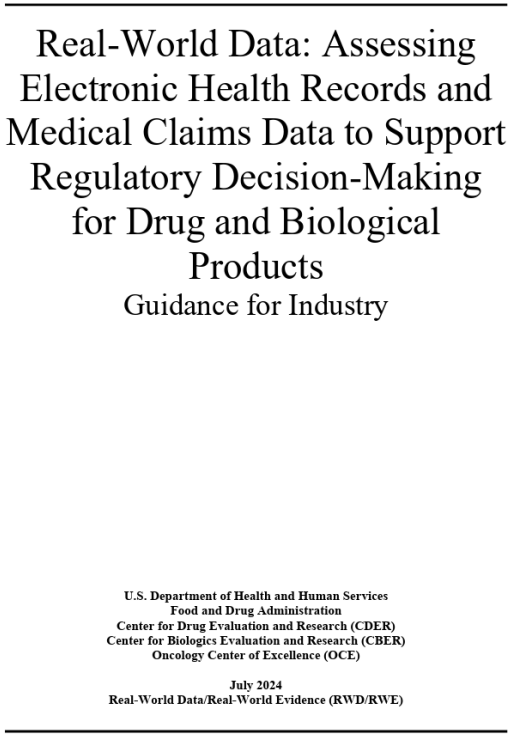


Figure 2. Basic process for generating a causal graph. $Y^{\star}$ is equal to the actual outcome value if it was observed and is missing otherwise.

Dang et al., 2023

STEP 2: Observed Data

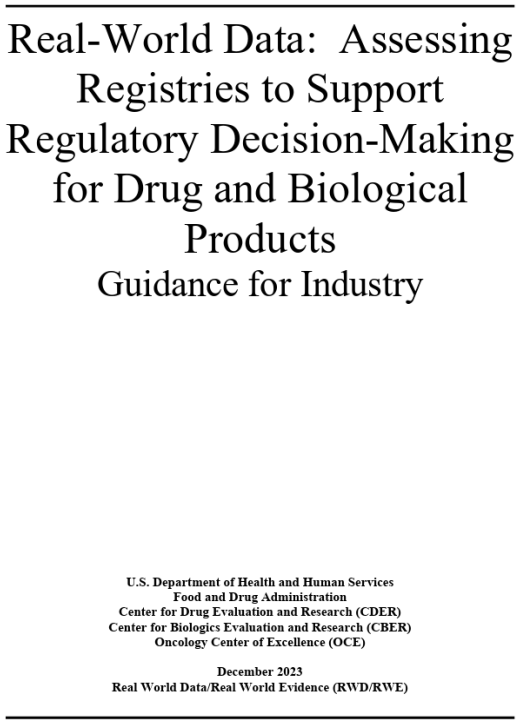
- Are the data “fit-for-purpose”? (FDA, 2018)
  - Relevant variables measured?
  - Reliability of measurements?
  - Different considerations for different data sources


Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

July 2024
Real-World Data/Real-World Evidence (RWD/RWE)

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory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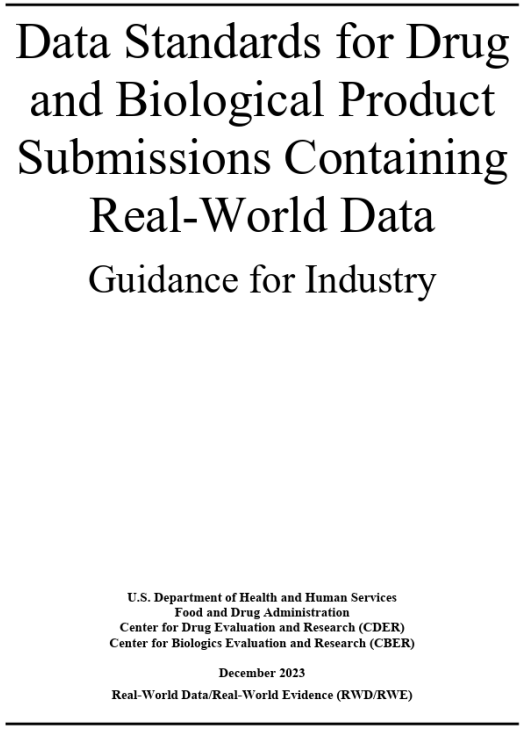
December 2023
Real World Data/Real World Evidence (RWD/RWE)

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-registries-support-regulatory-decision-making-drug-and-biological-products


Data Standards for Drug and Biological Product Submissions Containing Real-World Data
Guidance for Industry

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Real-World Data/Real-World Evidence (RWD/RWE)

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-standards-drug-and-biological-product-submissions-containing-real-world-data

STEP 3: Identifiability

Causal — Statistical

- Assumptions needed to answer ideal question from actual data

Assumption
Exchangeability • a.k.a. no unmeasured confounding, missing at random • More complex if intercurrent events
Positivity • Positive probability of receiving either treatment for all strata of covariates
Consistency**
No interference**
Unbiased measurement

- Consider each assumption
- Discuss plausibility of assumption
- May iterate on question, study design to improve plausibility

STEP 4: Statistical Estimand

$E[E(Y|A=1,W)]$
v.*
$E[E(Y|A=0,W)]$

- In Step 1, we defined the Causal Estimand
  - Cannot directly estimate this
- Statistical Estimand: Quantity that we will estimate from the data
  - E.g., difference in adjusted mean outcomes, relative risk, odds ratio…
- Causal Estimand = Statistical Estimand under assumptions
- Should be as close as possible to the answer to our ideal causal question

- May not be equal to a coefficient in a parametric model
- **Basic ATE:** $E_W[E[Y^*|A=1,W=w] - E[Y^*|A=0,W=w]]$
- ATE with informative dropout

$$\Psi = \sum_{w,l}\Big[E[Y^*|W=w,L=l,A=1,C=0]\Big]P(L=l|A=1,W=w)P(W=w)$$

-

$$\sum_{w,l}\Big[E[Y^*|W=w,L=l,A=0,C=0]\Big]P(L=l|A=0,W=w)P(W=w)$$

STEP 5: Statistical Model and Estimator

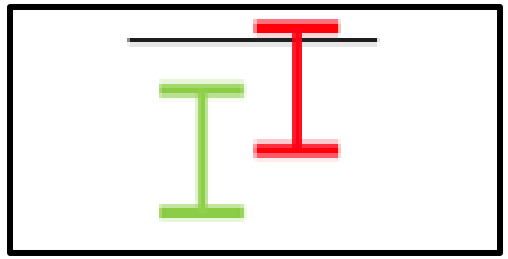
- **Basic ATE:** $E_W[E[Y^\star|A=1,W=w] - E[Y^\star|A=0,W=w]]$
- How should we estimate that?
  - Estimate
    - Outcome regression (e.g., $E[Y|A=a,W=w]$)
    - Propensity score (e.g., $\mathrm{P}(A=1|W)$)
    - Both (i.e. doubly robust (DR) estimators)
  - Goals
    - Fully pre-specified yet flexible
    - Avoid unrealistic assumptions
    - Accurate inference (95% coverage, type 1 error control)
    - Unbiased and efficient
  - TMLE (other DR estimators that incorporate machine learning)
  - Outcome blind simulations helpful in estimator selection

https://www.wordclouds.com/

STEP 6: Sensitivity Analysis / Falsification Tests

- How would results change if assumptions wrong?
- What strength of confounding would be needed to make results null?
- Do we have other evidence of bias?
  - Treatment associated with a negative control outcome?
  - Negative control exposure associated with outcome?
- **Goal:** Facilitate appropriate interpretation of results

"Tipping Point" (e.g., Yan et al. 2009)



I estimated an association!

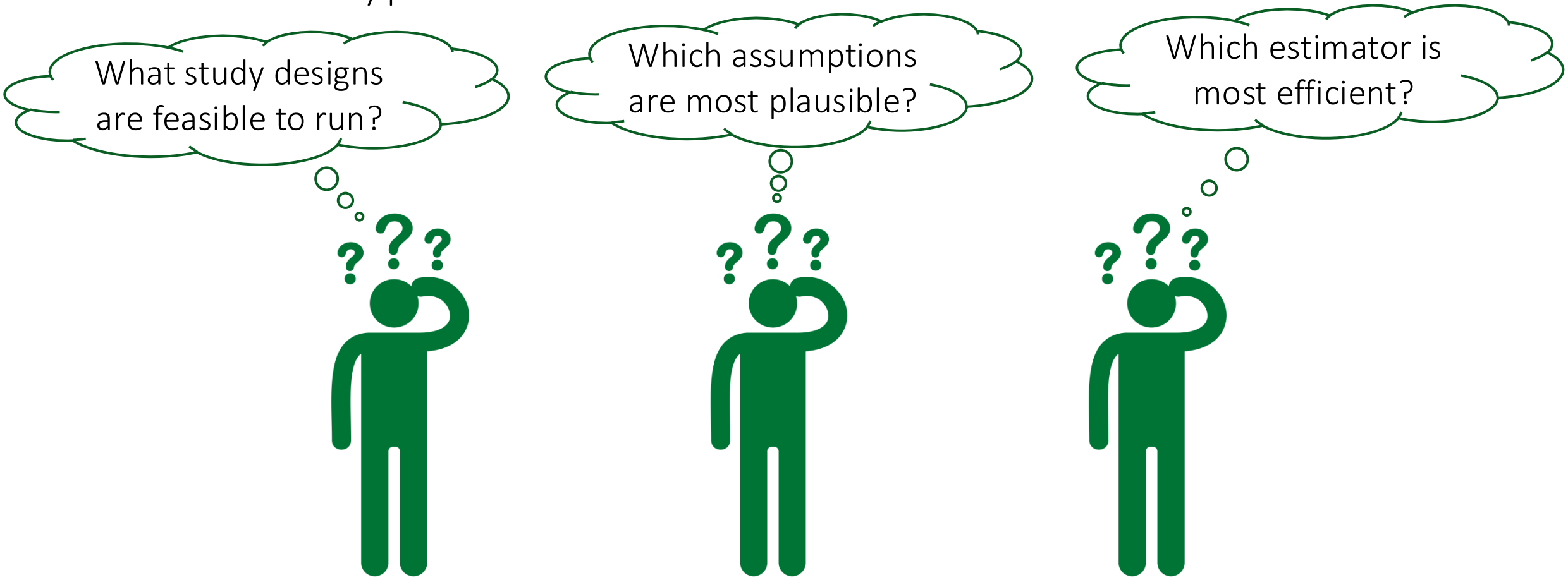
The association was small, and important confounders were unmeasured

Although uncertain, the assumptions are plausible, and the association is large enough to conclude there is a causal effect.

Low-Quality RWE → High-Quality RWE

STEP 7: Compare Design and Analysis Plans

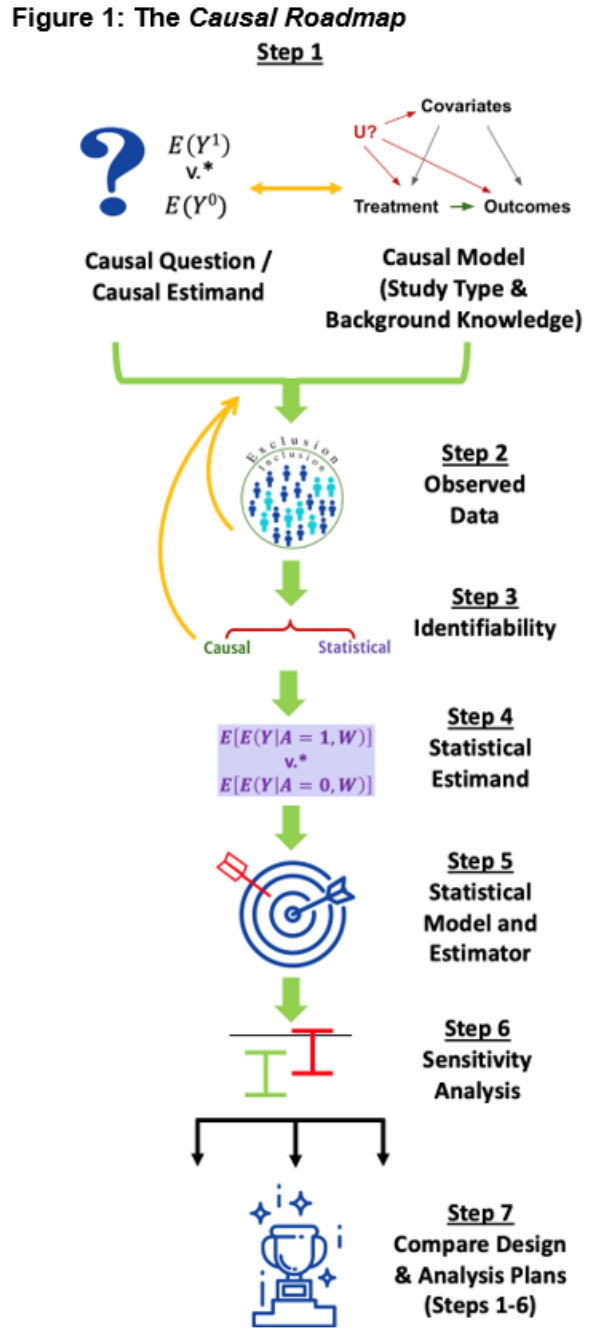
- Pros and cons to different study designs and analytic approaches
- Run the best study possible!



- Work through Roadmap steps for each approach
- Outcome blind simulations often helpful!

Summary

- I follow the Causal Roadmap steps for every study to:
  - Make sure all collaborators on the same page
  - Identify (and sometimes fix) sources of bias
  - Decide whether to pursue a study/alter design
  - Appropriately interpret results
- Multi-disciplinary collaboration is vital at every step!
- Interested in learning more?
  - Estimands involving intercurrent events (e.g., Gruber et al. 2022, 2023)
  - Mediation analysis (e.g., van der Laan and Rose, 2018)
  - Optimal dynamic treatment regimes (e.g., van der Laan and Rose, 2018)
  - TMLE for estimation (e.g., van der Laan and Rose, 2011)
  - References on next slide…



Dang et al., 2023

References

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- Maya Petersen, Mark van der Laan, Susan Gruber, Laura Balzer, and many others for their work on the Roadmap
- Many others for their work on causal inference influencing the Roadmap including James Robins, Donald Rubin, Judea Pearl, Miguel Hernán, and many many more

EMA
EUROPEAN MEDICINES AGENCY

Target trial emulation and estimands for better non-interventional studies with causal objectives

PHUSE Webinar: An Introduction to the Estimands and Target Trial Emulation Frameworks

Juan Jose Abellan, European Medicines Agency

22 April 2025

EMA reflection paper

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 March 2025
EMA/99865/2025
Committee for Human Medicine Products/
Methodology Working Party (CHMP/MWP)

Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence for regulatory purposes

Draft agreed by Methodology Working Party (MWP)	October 2023
Adopted by CHMP PROM for release for consultation	15 April 2024
Start of public consultation	3 May 2024
End of consultation (deadline for comments)	31 August 2024
Agreed by Methodology Working Party (MWP)	March 2025
Adopted by CHMP PROM	17 March 2025

Draft published for public consultation May to August 2024

Final version published in April 2025

Distinguishes between non-interventional studies with descriptive and causal objectives

For studies with causal objectives:

- Recommends considering target trial emulation
- Recommends considering the estimands framework for the target trial

Rationale: Starting from a target trial adds clarity and increases coherence and transparency

EMA

Estimand vs Estimand framework

- Estimand: “a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial” [ICH E9(R1)]
- Estimand framework, a tool to structure the thinking to define an estimand
  - Think of intercurrent events and strategies for handling them
    - Five possible strategies in ICH E9(R1): Treatment policy, hypothetical, composite, while on treatment / while alive, and principal stratum
  - Then define the estimand attributs:
    - Population, for your research question (not to be confused with incl/exlc criteria)
    - Treatments conditions
    - Variable/endpoint, to be collected from every subject
    - Summary measure, at group level and for comparison between treatment groups
- Estimand framework better aligns
  Objective <-> Estimand <-> Study Design <-> Estimation method <-> Sensitivity analyses

Example (inspired in a DARWIN EU study)

- Suppose a NIS to investigate if first-line treatment with immunotherapies in combination with chemotherapies improves survival in non-small cell lung cancer (NSCLC) patients compared to treatment with chemotherapies.
- An estimand of interest could be: What is the hazard ratio of death from any cause in patients with locally advanced or metastatic NSCLC treated with immunotherapies in combination with chemotherapies compared to treatment with chemotherapies alone regardless of treatment discontinuation and in the absence of new anticancer therapy?

Example

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- An estimand of interest could be: What is the hazard ratio of death from any cause in patients with locally advanced or metastatic NSCLC treated with immunotherapies in combination with chemotherapies compared to treatment with chemotherapies alone regardless of treatment discontinuation and in the absence of new anticancer therapy?
- Estimand attributes:
  - Population: patients with locally advanced or metastatic NSCLC
  - Treatments: immunotherapies in combination with chemotherapies; chemotherapies
  - Variable endpoint: overall survival, defined and time from start of therapy to death from any cause
  - Summary measure: hazard ratio
  - Intercurrent events and strategies: treatment discontinuation, handled with a 'treatment policy' strategy; start of a new anti-cancer therapy, handled with a 'hypothetical' strategy

Target trial emulation in combination with the estimand framework

First think of key elements of the target trial that would answer the research question

- Objective
- Estimand
- Key study design elements (e.g. incl/excl criteria, randomization,…)
- Statistical analysis method, including assumptions made
- Sensitivity analysis (to understand impact of assumptions made in the primary analysis)

Then design the non-interventional study to emulate as close as possible the target trial

- Research question (estimand)
- Study design
- Analysis methods: main analysis and sensitivity analysis
- Supplementary analysis, to contextualise results

Emulation

		Target trial	NIS
Research question		Estimand (Population, treatments, endpoint, summary measure, IEs+strategies)	Same research question (ideally)
Design elements	Incl/excl criteria	May involve clinical assessments	Computational phenotypes
	Treatment assignment	e.g. 1:1 randomisation	Addressed at analysis stage with PS matching
	Follow-up	Start/stop of trial participant journey	Start/stop of follow-up
Data analyses	Primary analysis	Data, method and assumptions	Data, methods (may differ from TT) and assumptions
	Sensitivity analyses	Varying assumptions	Same + bias
Supplementary analyses	For context	Possibly targeting other estimands	e.g. varying definition of exposure/outcome

Implementation of TTE+EF

- EMA-funded research project to implement the TTE + EF
  - 10 use-cases of regulatory interest
  - 2 years, started Autumn 2024
  - European academic consortium led by University of Utrecht
- Several EMA studies with causal objectives considering TTE + EF
  - Effectiveness of HPV vaccines to prevent cervical cancer
  - Effectiveness of selected immunotherapies on overall survival in patients with NSCLC
  - A few other safety studies currently in discussion

Summary

- Target Trial Emulation valuable for NIS with causal objectives
  - Makes the target trial explicit
- A clear specification of the target trial is critical for better emulation with the NIS
- Use of the estimands framework to define the target trial helps add clarity
  - Use of estimands in RCT is current practice as per regulatory guidance
- Consideration to other elements of ICH E9(R1) would also be beneficial
  - Estimands and estimation are separate discussions
  - Changes in estimand attributes lead to different estimands, not to sensitivity analyses
  - Set the estimand, then choose the estimation method and then consider sensitivity analyses to assess the robustness of the results to assumptions made in the estimation method

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Thank you

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