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Landscape of Causal Inference Frameworks of Clinical Studies Using RWD/RWE

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RCT Estimand is Causal in Nature

" Central questions for drug development and licensing are to establish the existence, and to estimate the magnitude, of treatment effects: how the outcome of treatment compares to what would have happened to the same subjects under alternative treatment (i.e. had they not received the treatment, or had they received a different treatment). "

ICH E9 (R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials (2019)
https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

Causal Inference Framework: Scientific Principles that Bridge between What We Can & What We Want

Observed World (Real Study)	Causal World (Ideal Experiment)
What we can learn from obs. data	What we want to know
Compare outcomes between different groups of patients	Compare counterfactual outcomes of the same group of patients
Would the outcomes of the patients who took Drug X be better than those who took Drug Y?*	Would the outcomes be better if *all* patients took Drug X instead of Drug Y?*
Observed variables only	Observed & unobserved variables

* We are interested in the causal effect of the difference between counterfactual outcomes.

RWE Causal Inference Framework: 1/8

1. Setup – *Describe data statistically*

1. Describe Study and Observed Data

- Assume the RWD are evaluated as fit for use for a study
- Study has n subjects randomly and independently drawn from the same population of interest.
- A subject has a set of observed data $O = (W, A, Y)$ where

  W = baseline covariates

  A = a single treatment (0,1) assigned at baseline, and

  Y = an outcome observed at a fixed time point

  $O \sim P_0$ unknown

RWE Causal Inference Framework: 2/8

1. Setup – *Describe data statistically*

2. Target Estimand – *A local attraction*

2. Target Estimand: A Local Attraction (1)

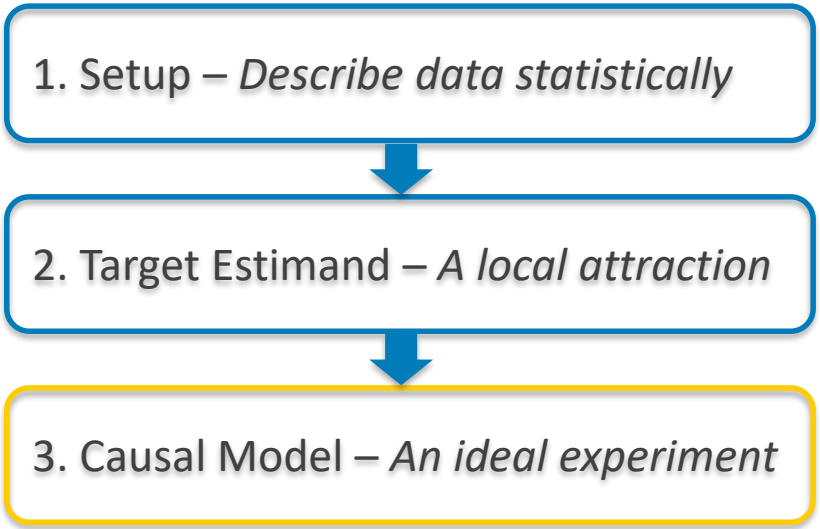
Do the observed data have enough info. to answer the question?

- To define what “enough” is, we need to specify a goal or “destination”.
- Use causal model to define an *ideal experiment* as the destination.
- Figure out what questions we can answer using the observed data only (like a local attraction we *can* go).
- How close is this “local attraction” where we *can* go to the destination where we *want* to go?

2. Target Estimand: A Local Attraction (2)

- A causal estimand Ψ^c is a *causal-model* based estimand that answers the research question, i.e., what we want (details in next step)
- A target estimand Ψ^{obs} is an *observed-data* based estimand that best approximates the Ψ^c.
- How "close" Ψ^{obs} is to Ψ^c?
  1. *Statistical*: If both are equal, then specify criteria (e.g., unbiased, min. variance) for an estimator according to specific needs of the question.
  2. *Causal*: If not, then consider another target estimand or determine what additional assumptions would be required to make both equal.

RWE Causal Inference Framework: 3/8



3. Causal Model: an Ideal Experiment (1)

- Potential outcomes (Y_0, Y_1) of a subject is the subject's outcome when being assigned to receive the control & active treatment, respectively.
- $\Longrightarrow$ An observed outcome of a subject is $Y = AY_1 + (1 - A)Y_0$.
- A causal effect is a comparison of Y_0 and Y_1, e.g., $Y_1 - Y_0$.
- A causal model mathematically represents our knowledge and uncertainty about the data generating process of an ideal experiment, describing the causal relationships between each dependent variable with other variables, measured (observed) or not.

3. Causal Model: An Ideal Experiment (2)

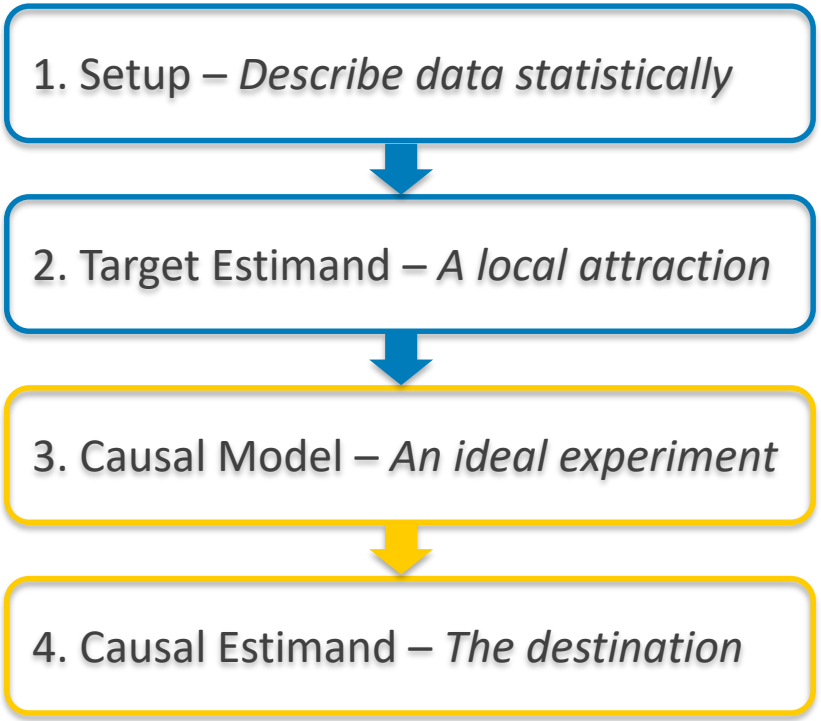
- Incorporate explicit knowledge & uncertainty about the study, e.g.,
  - Sampling scheme
  - Treatment assignment mechanism
  - Censoring mechanism
- Two common classes:
  - Neyman-Rubin causal model (Neyman 1923, Rubin 1973)
  - Structural causal model (Pearl 2000)
  - Fundamentally equivalent using the concept of potential outcomes

Example: Structural Causal Model

- $O =$ (baseline covariates W, assigned treatment A, outcome Y)
- $\{W, A, Y\}$ are driven by deterministic but unknown functions $\{f_w, f_a, f_y\}$
- $U_{\{w,a,y\}}$: unobserved & random; covar. structure reflects causal relationships.

Structural equation	**Our knowledge about the study**
$W = f_w(U_w)$	U_a & U_y do *not* affect W; U_w distribution unknown
$A = f_a(W, U_a)$	W influences treatment assignment
$Y = f_y(W, A, U_y)$	A & W influence outcome

RWE Causal Inference Framework: 4/8



4. Causal Estimand: Our Destination

A *Causal estimand* is a function of the distribution of the counterfactuals, comparing Y_0 and Y_1 (say, $Y_1 - Y_0$) cross all patients or a subgroup, e.g.:

- Average treatment effect (ATE): $\mathbb{E}Y_1 - \mathbb{E}Y_0$
- Average treatment effect on the treated (ATT): $\mathbb{E}[Y_1|A=1] - \mathbb{E}[Y_0|A=1]$

- Suppose one specifies Ψ^c = ATE ($= \mathbb{E}Y_1 - \mathbb{E}Y_0$)
- A Ψ^{obs} candidate that approximates Ψ^c:

$$\Psi^{obs} = \mathbb{E}_{w,0}[\mathbb{E}_0(Y|A=1,W) - \mathbb{E}_0(Y|A=0,W)]$$

- What assumptions do we need to make $\Psi^c = \Psi^{obs}$?

Example: Causal Estimand

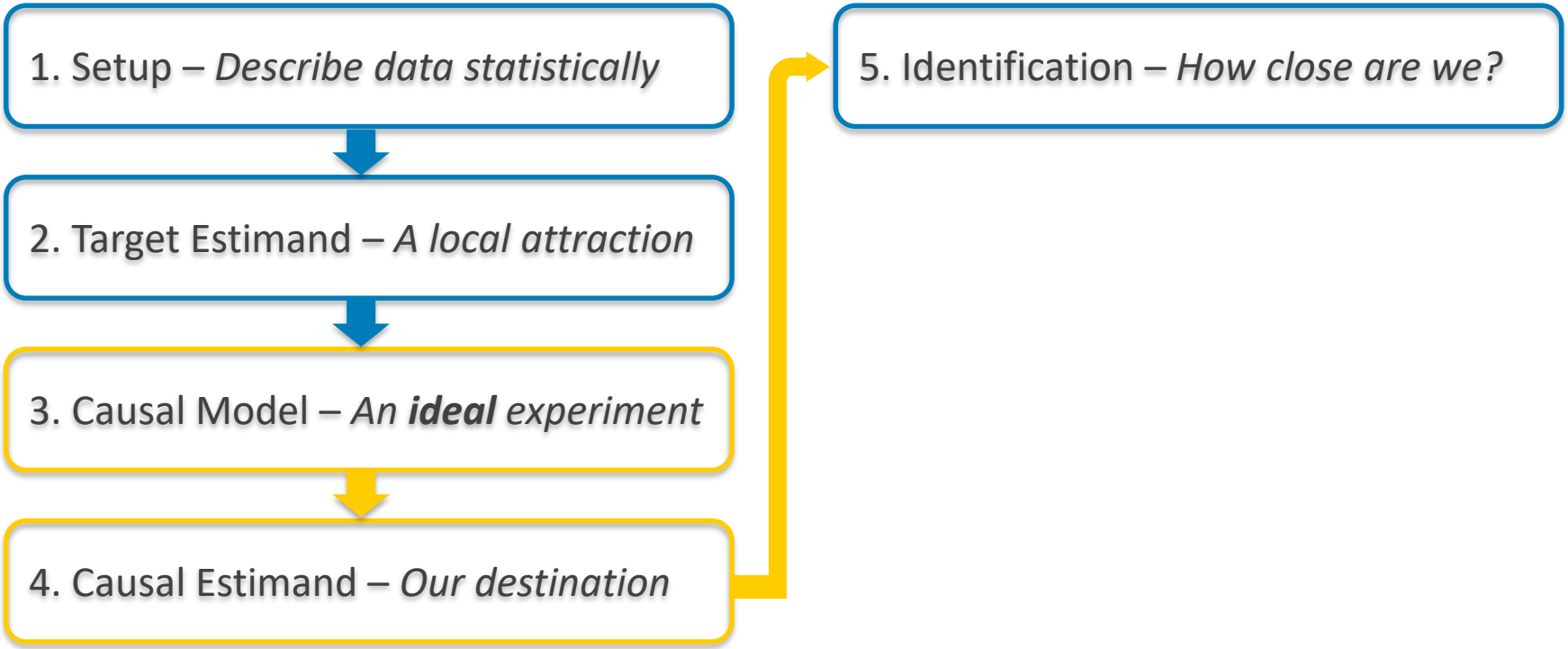
Recall: Subject has baseline covariates W, assigned treatment A, obs. outcome Y

Structural equation	*Our knowledge about study's data generating process*
$W = f_w(U_w)$	U_a & U_y do *not* affect W; U_w distribution unknown
$A = f_a(W, U_a)$	W influences treatment assignment
$Y = f_y(W, A, U_y)$	A & W influence outcome

Describe a research question precisely using a well-defined ideal experiment

- A subject's potential outcomes: $Y_1 = f_y(W, 1, U_y)$ and $Y_0 = f_y(W, 0, U_y)$
- A subject's causal effect: $Y_1 - Y_0 = f_y(W, 1, U_y) - f_y(W, 0, U_y)$
- A population's causal estimand $\Psi^c = \mathbb{E}Y_1 - \mathbb{E}Y_0$

RWE Causal Inference Framework: 5/8



5. Identification: How Close Are We?

- Definition: If Ψ^c can be written as some function of the observed data distribution (e.g., Ψ^{obs}), then it is identified.
- If $\Psi^c = \Psi^{obs}$, then Ψ^c is identifiable.

What additional causal assumptions would make $\Psi^c = \Psi^{obs}$?

By g-computation identifiability result (Robins 1986), $\Psi^c = \Psi^{obs}$ if:

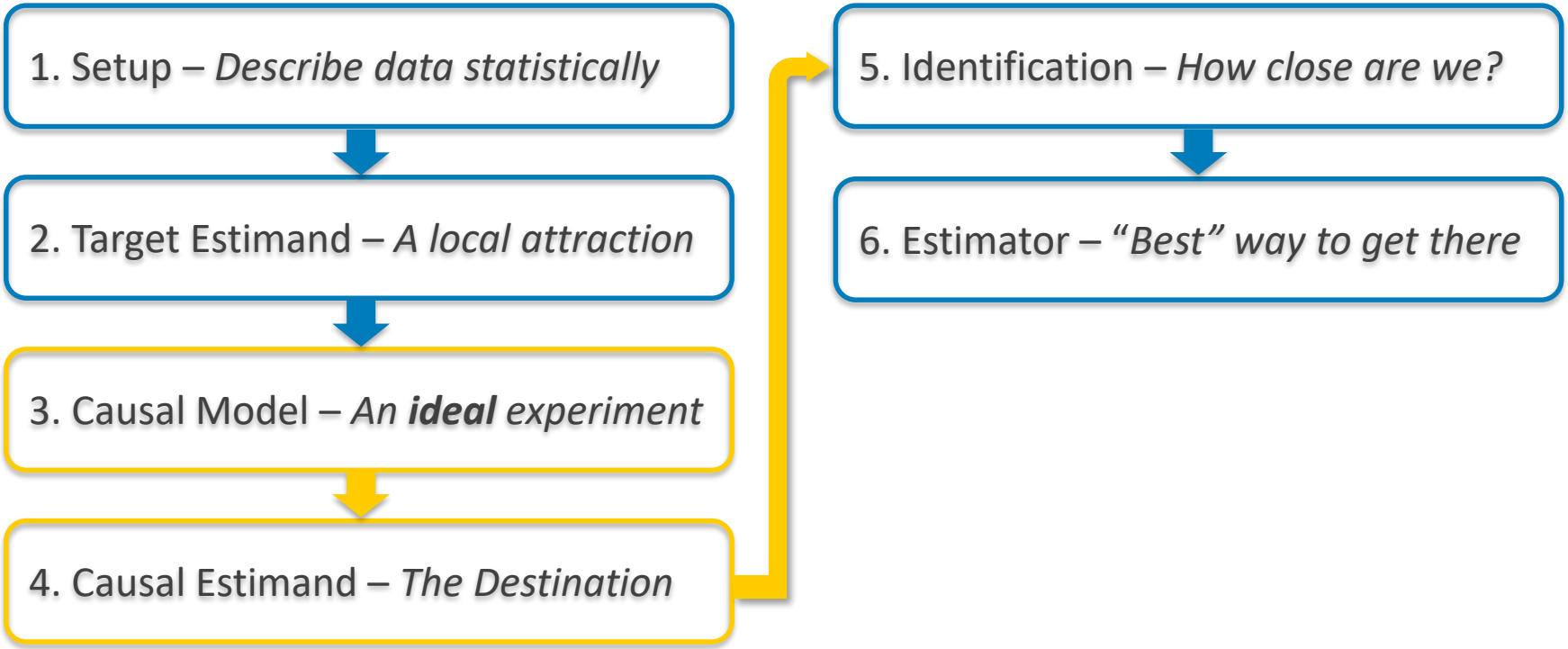
I. U_a is independent of U_y, conditional on W — Cond. Randomization

II. $0 < P(A = 1 \mid W) < 1$ — Positivity

Then,

$$\Psi^{obs} = \mathbb{E}_{w,0}[\mathbb{E}_0(Y|A=1,W) - \mathbb{E}_0(Y|A=0,W)] \text{ on obs. data only}$$
$$= \mathbb{E}_0(Y \mid A=1) - \mathbb{E}_0(Y \mid A=0) = \Psi^c$$

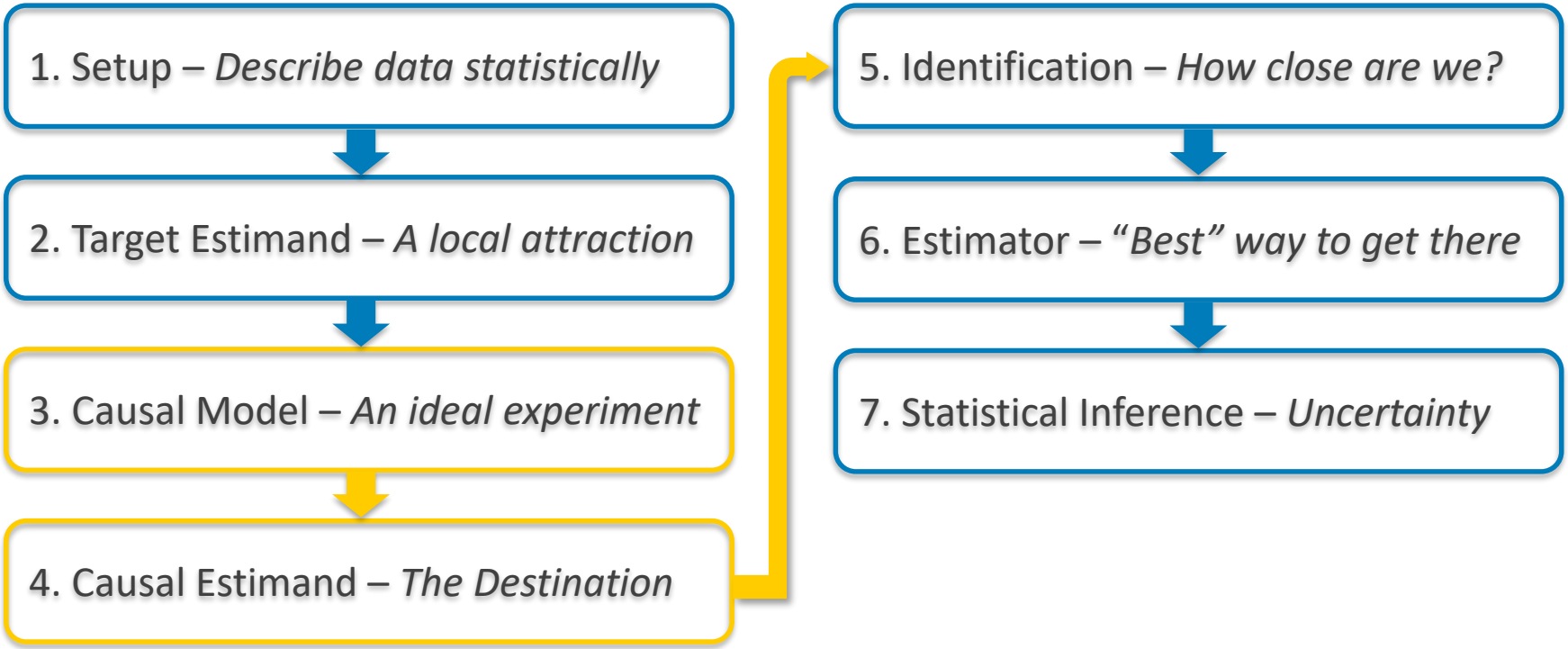
RWE Causal Inference Framework: 6/8



6. Estimator – “Best” Way to Get There

- An estimator is defined as an *a priori* algorithm.
- Decouple the estimator from the causal estimand
- Choose estimators based on statistical properties (e.g., bias, variances)
- Popular estimators include:
  - Parametric g-computation (Robins 1986)
  - Doubly robust estimation (Bang and Robins 2005)
  - Matching estimators (Stuart 2010)
  - Inverse probability of treatment weighting (Rotnitzky and Robins 2014)
  - Target maximum likelihood estimation with machine learning methods (van der Laan and Rose 2011)

RWE Causal Inference Framework: 7/8



7. Statistical Inference – Uncertainty

- One can use various methods based on an estimator of the sampling distribution of the estimator chosen at #6.
  - Normal approximation, e.g., Wald-type confidence interval
  - Resampling, e.g., bootstrap
- Proposed confidence interval requires:
  - Asymptotic linearity and normality for validity
  - Simulation studies for finite sample coverage

RWE Causal Inference Framework

1. Setup – *Describe data statistically*
2. Target Estimand – *A spot we can go*
3. Causal Model – *An **ideal** experiment*
4. Causal Estimand – *The destination*
5. Identification – *How close are we?*
6. Estimator – *"Best" way to get there*
7. Statistical Inference – *Uncertainty*
8. Sensitivity Analysis – *Robustness*

8. Interpretation and Sensitivity Analysis

- Robustness against violating the assumptions that bridge the identification gap between the target & casual estimand
- A lot of these identification assumptions are non-testable.
- Evaluate a hierarchy of result interpretation with increasing strength of assumptions for a causal interpretation (Petersen and van der Laan 2014)
- Sensitivity analysis assesses the impacts of each level of assumption violations in the hierarchy on the statistical results

Next Steps: RWE SWG Phase II Topics

	Team and Co-leads	Topic
I	Jie Chen (Overland Pharma) Hana Lee (CDER)	Estimands: From concepts to applications in real-world setting
II	Weili He (Abbvie) * Mark Levenson (CDER)	Principles and approaches for the use and evaluation of fit-for-purpose data sources
III	Yixin Fang (Abbvie) Martin Ho (CBER) *	Illustrative examples of applying the RWE causal inference roadmap to clinical studies

* Co-chair of the ASA BIOP RWE SWG

Concluding Remarks

- A good RWE Causal Inference Framework should be:
  - Rigorous enough to meet the evidentiary standards for regulators, and
  - Flexible enough to accommodate the evolving sources of RWD
- Decoupling estimation method & causal modeling: makes statisticians to explicitly state the research question (as a causal estimand) first.
- Specified causal estimand can guide statisticians to develop causally interpretable statistical estimators that are closer to their destinations.
- Examples of applying the RWE Causal Inference Framework to clinical trials can promote these scientific principles among statisticians.

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