Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment

Tuesday, May 21st, 2026
11:00 AM - 12:00 PM ET

Co-Moderators:

- **Leanne Goldstein, Amgen**
- **Beilei He, Bristol Myers Squibb**

PHUSE Estimands for RWD/RWE Project Team:
https://advance.hub.phuse.global/wiki/spaces/WEL/pages/26816358/Estimands+for+RWD+RWE

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

Subteam 1: White paper development

- Co-leads: Ksenia Titorenko (ICON) and Paramita Chakraborty (IQVIA / Gilead)
- *Establishing Robust Estimands in Real-World Evidence*
  - Literature review
  - Gap analysis
  - Combining frameworks
  - Example use cases
  - Regulatory submission aspects
  - etc
- Preparing for internal PHUSE project team review
- Future public review before published

Subteam 2: At the Intersection of Estimands and Target Trial Emulation (TTE) for RWE webinar series

Project Lead: Matt Baldwin

- **Webinar 1 (22 Apr 2025):** An Introduction to the Estimands and Target Trial Emulation (TTE) Frameworks (recording, slides, additional info)
- **Webinar 2 (05 Jun 2025):** Estimands in Real-World Evidence Studies (recording, slides, additional info)
- **PHUSE Blog:** "*What's the Hype About? PHUSE's Record-Breaking Webinars Explore Estimands and Target Trial Emulation for RWE*"
- **Webinar 3 (24 Feb 2026):** Implementing Estimands & Target Trial Emulation (TTE) in Real-World Evidence: Case Studies & Perspectives (recording, slides, additional info)
- **Webinar 4 (21 May 2026):** Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment

Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment

Today, our speakers examine the key biostatistical challenges and methodologies associated with leveraging RWE for clinical trials and medical product development, drawing on two companion articles. The first article provides an overview of the current landscape of using RWE to inform clinical study design and analysis, while the second article focuses on the practical challenges in the design and analysis of studies employing RWE.

- Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment
- Comment on "Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment"

GUEST SPEAKERS

Chantal Quinten
EMA

Evgeny Degtyarev
Novartis

Yixin Fang
AbbVie

MODERATORS

Leanne Goldstein
Amgen

Beilei He
Bristol Myers Squibb

Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment

Webinar 4 Outline

- (5 min) Leanne Goldstein, *Amgen*

  Introduction
- (10 min) Yixin Fang, *AbbVie*

  Present Paper
- (15 min) Evgeny Degtyarev, *Novartis*

  Present Commentary
- (10 min) Yixin Fang, *AbbVie*

  Respond to commentary & updates from 2021-2026
- (20 min) Chantal Quinten, *EMA*

  Regulatory Reflections and Panel Discussion moderated by Beilei He, Bristol Myers Squibb

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

GUEST SPEAKERS

Chantal Quinten
EMA

Evgeny Degtyarev
Novartis

Yixin Fang
AbbVie

MODERATORS

Leanne Goldstein
Amgen

Beilei He
Bristol Myers Squibb

connect·share·advance

THANK YOU!

Data & Statistical Sciences

Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment

Yixin Fang

Data and Statistical Sciences, AbbVie

May 21st, 2026

abbvie

Disclaimer

The comments provided here are solely those of the author and are not necessarily reflective of the positions, policies or practices of author's employer.

The support of this presentation was provided by AbbVie. AbbVie participated in the review and approval of the content.

Yixin Fang is employee of AbbVie Inc. and may own AbbVie stock.

Outline

- **Introduction**
- Estimand Framework and PICOTS Framework
- Addressing Three Major Comments

Our 2021 Paper

STATISTICS IN BIOPHARMACEUTICAL RESEARCH
2023, VOL. 15, NO. 1, 3–13
https://doi.org/10.1080/19466315.2021.1883473

Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment

Mark Levenson[a], Weili He[b], Jie Chen[c], Yixin Fang[b], Douglas Faries[d], Benjamin A. Goldstein[e,f], Martin Ho[g], Kwan Lee[h], Pallavi Mishra-Kalyani[a], Frank Rockhold[e,f], Hongwei Wang[b], and Richard C. Zink[i]

[a]CDER, FDA, Silver Spring, MD; [b]Global Medical Affairs Statistics, Data and Statistical Sciences, AbbVie, North Chicago, IL; [c]Overland Pharmaceuticals, Dover, DE; [d]Global Statistical Sciences, Eli Lilly & Company, Indianapolis, IN; [e]Department of Biostatistics & Bioinformatics, Duke University, Durham, NC; [f]Duke Clinical Research Institute, Duke University, Durham, NC; [g]CBER, FDA, Silver Spring, MD; [h]Statistics and Decision Sciences, Janssen Research and Development (retired), Spring House, PA; [i]Lexitas Pharma Services, Inc., Durham, NC

ARTICLE HISTORY
Received May 2020
Accepted January 2021

Table of Contents

Section 5 and Section 7 in Particular

- **Section 5. Real World Study Estimand**
  - The ICH E9(R1)'s estimand framework is helpful for real-world studies
  - Discussion of five attributes (treatment, population, variable, methods for intercurrent events, population-level summary) in real-world settings
  - The discussion is "focusing on the development of estimands for RWE that can differ from RCTs"
- **Section 7. Addressing Biases**
  - Biases are classified into three broad categories: selection bias, information bias, and confounding bias
  - Summary of methods for confounding in the design of study
  - Summary of methods for control of confounding using analytical methods

Summary of the 2021 Paper

Two excerpts from the abstract of the following commentary paper:

Comment on "Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment"

ARTICLE HISTORY
Received September 2021
Accepted October 2021

Lisa V. Hampson[a], Evgeny Degtyarev[a], Rui (Sammi) Tang[b], Jianchang Lin[c], Kaspar Rufibach[d], and Cheng Zheng[e]

[a]Novartis Pharma AG, Basel, Switzerland; [b]Servier Pharmaceuticals, Boston, MA; [c]Takeda Pharmaceuticals, Cambridge, MA; [d]Hoffmann-La Roche Ltd, Basel, Switzerland; [e]Zentalis Pharmaceuticals, New York, NY

- "[…] this landscape assessment […] reviews many important biostatistical issues related to the use of real-world data (RWD) to support medicine development."
- "[…], the authors highlight the value of the estimand framework for studies using RWD."

From 2021 to Now


GUIDANCE DOCUMENT

E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials

Guidance for Industry

MAY 2021

Download the Final Guidance Document

Read the Federal Register Notice

Many things have happened since 2021; to name just three

1. One Pivotal Trial, the new default option for FDA approval, ending the two-trial dogma
2. The fusion of two data sources: Clinical data and Real-world data
3. The emerging EU HTA new process: Joint Clinical Assessment

One Pivotal Trial, the New Default Option for FDA Approval — Ending the Two-Trial Dogma

1

Authors: Vinay Prasad, M.D., M.P.H., and Martin A. Makary, M.D., M.P.H. Author Info & Affiliations

Published February 18, 2026 | N Engl J Med 2026;394:815-817 | DOI: 10.1056/NEJMsb2517623 | VOL. 394 NO. 8

- "Going forward, the FDA's default position is that one adequate and well-controlled study, combined with confirmatory evidence, will serve as the basis of marketing authorization of novel products"
- "Confirmative evidence can include mechanistic science, data from a related indication, animal models, information from other drugs of the same class, real-world evidence, or a second adequate and well-controlled study"

The Fusion of Clinical-Trial Data and Real-World Data

2

- External Controlled Trials (ECTs)
  - Single-arm trial (SAT) + External control arm (ECA)
- Hybrid Clinical Trials (HCTs)
  1. Randomized Controlled Trial (RCT) with external covariates
  2. RCT augmented with external controls (Hybrid controlled trial – HCT)
  3. RCT combined with RWD under both treatment and control conditions
  4. Other hybrid designs …
- Decentralized Clinical Trials (DCTs)

EU Health Technology Assessment (HTA) – A New Process

- Legislation passed in 2021 – numerous concessions to get the bill passed following 10+ years of debate
- Original proposal to **accelerate access for patients**
- Regulation is mandatory – no way around it
- Our ability to demonstrate the clinical value of our assets will drive Access
- The scope of the regulation has 4 buckets, and the most relevant to DSS is **Joint Clinical Assessment (JCA)**

JCA **Joint Clinical Assessment** **(Mandatory)**	**EU HTA REGULATION**	JSC Joint Scientific Consultation (Optional)
Emerging Health Technologies		Voluntary Cooperation on HTA

Outline

- Introduction
- **PICO Framework and Estimand Framework**
- Addressing Three Major Comments

Clinical Question

The commentary paper starts with the following:

> Levenson et al. (2021; who we subsequently refer to as LHC) consider challenges for specifying the attributes of an estimand in a study using RWD. However, often the estimand thinking process (Phillips et al. 2017) starts even earlier than this with defining the study objectives, or more precisely the question of interest.

Then how to form a sound clinical question? This is why the PICO framework was proposed:

The well-built clinical question: a key to evidence-based decisions.

Richardson WS , Wilson MC , Nishikawa J , Hayward RS

Author information

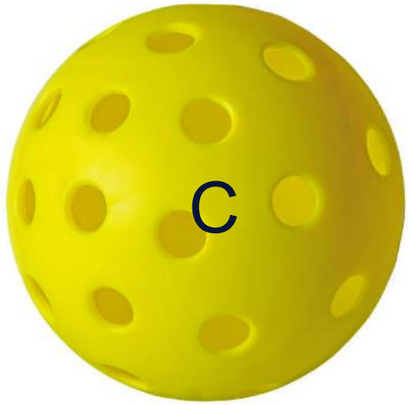
ACP Journal Club, 01 Nov 1995, 123(3):A12-3

PICO Framework

Population:
Who are the patients or population being studied?

Intervention:
What is the intervention or treatment being considered?

Let A denote the investigational drug



Comparator:
What is the alternative intervention or treatment?

Let C denote the comparator

Outcome:
What are the expected outcomes or measures of effectiveness?

Let Y denote the outcome variable

1. Continuous
2. Binary
3. Time-to-event

Multiple PICOs (e.g., there are four in one HTA submission)

Research Question 1

to be answered by

Randomized Controlled Trial (RCT)

Research Question 2

to be answered by

Non-Interventional Study (NIS)

Research Question 3

to be answered by

Externally Controlled Trial (ECT)

Research Question 4

to be answered by

Indirect Treatment Comparison (ITC)

From PICO to PICOTS

- **Time:** Study duration, treatment duration, time zero, baseline, endpoints (e.g., measure time points of outcome variables), retrospective, prospective, historical control, concurrent control
- **Setting:** It refers to the context or environment in which the study or research takes place, such as the type of facility (hospital, clinic), geographic location, or care setting. In this talk, it may refer to either clinical trial setting or real-world setting

ICH E9(R1)’s Estimand Framework

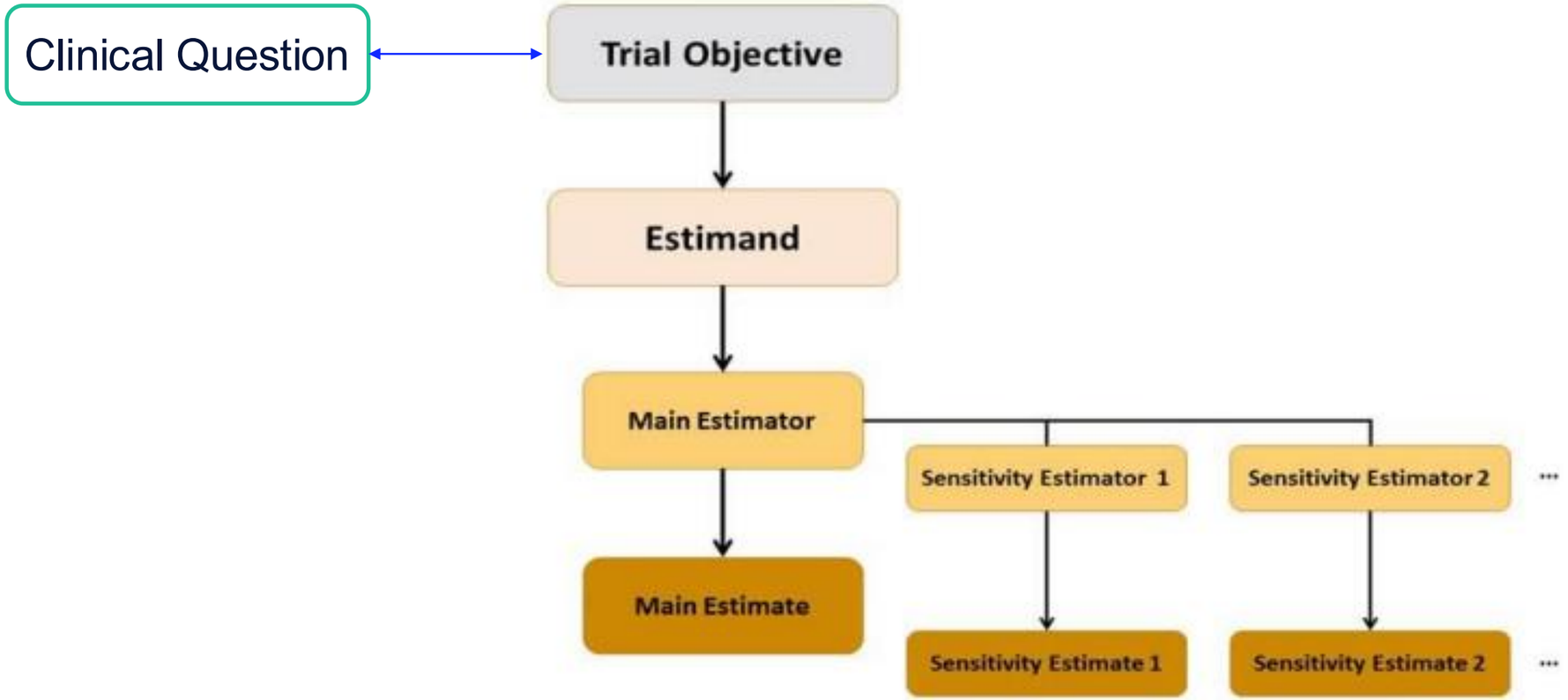
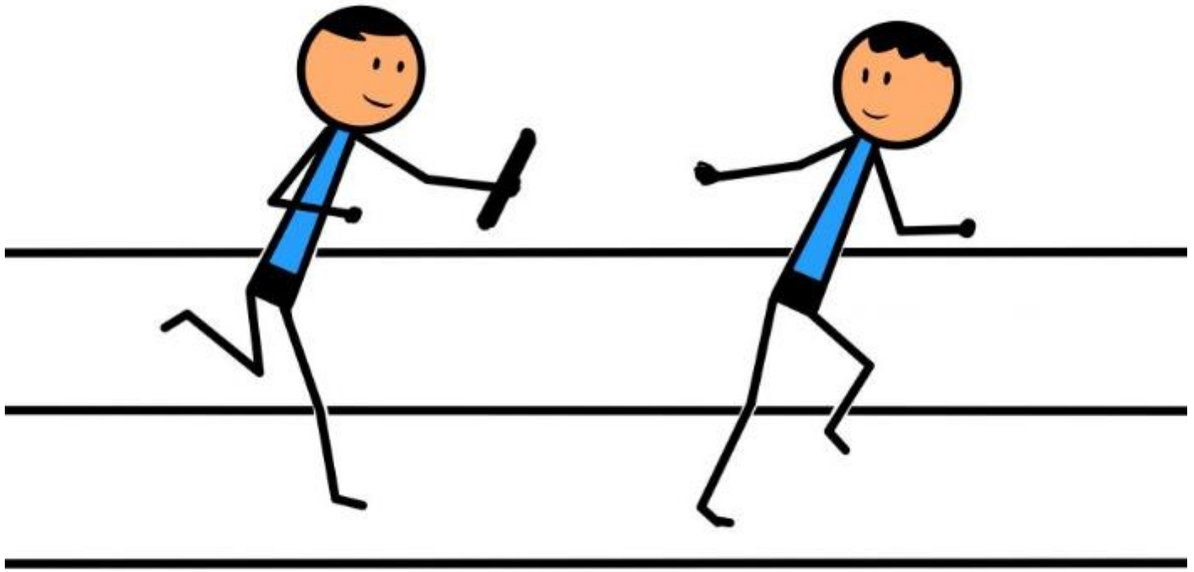


Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

Presenter Switching



Outline

- Introduction
- PICOTS Framework and Estimand Framework
- **Addressing Three Major Comments**
  1. Distinguishing between estimands defined according to ICH E9 and causal estimands?
  2. Is there a reason why target trial framework (target trial emulation –TTE) was excluded from the original paper?
  3. Expand on focus areas of data quality when incorporating RWD into clinical trial design

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Comment 1: Causal Estimand

An excerpt from the first paragraph of the commentary paper:

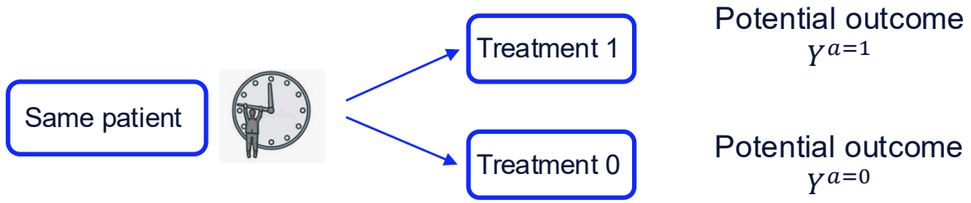
> We assume that when designing comparative studies using RWD, this question will usually be one targeting a causal estimand. Interestingly Ho et al. (2021) distinguish between estimands defined according to the ICH E9(R1) addendum (2019) and "causal estimands," and we would welcome a clarification of this. While formulating a well-posed causal question can be challenging (Goetghebeur et al. 2020), we would argue that it is essential to have one as a point of reference before selecting the estimand attributes.

Estimand: Causal Estimand vs. Statistical Estimand

ICH E9(R1) Guideline

GLOSSARY

Estimand:
A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared.



Causal Estimand

The estimand defined in terms of potential outcomes

For example, $\theta^* = E(Y^{a=1}) - E(Y^{a=0})$

Identifiability Assumptions

Identification

Statistical Estimand

The estimand defined in terms of observed outcomes

For example, $\theta = E[E(Y|X, A = 1) - E(Y|X, A = 0)]$

Outline

- ❑ Introduction
- ❑ PICOTS Framework and Estimand Framework
- ❑ Addressing Three Major Comments

1. Distinguishing between estimands defined according to ICH E9 and causal estimands?
2. **Is there a reason why target trial framework (target trial emulation) was excluded from the original paper?**
3. Expand on focus areas of data quality when incorporating RWD into clinical trial design

Comment 2: Target Trial Framework

An excerpt from the second paragraph of the commentary paper:

Goodman, Schneeweiss, and Baiocchi (2017) comment that the "hallmark of a well-posed causal question is that one can describe the RCT (randomized controlled trial) that would answer it". In this spirit, the target trial framework asks the investigator to specify key elements of the protocol of the RCT that would ideally be run to address the question of interest.

▸ Am J Epidemiol. 2016 Mar 18;183(8):758–764. doi: 10.1093/aje/kwv254

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

Miguel A Hernán*, James M Robins

Target Trial Framework vs. Causal Inference Framework

- We totally agree that we should apply target trial framework in the design and conduct of real-world studies when RCT is not available
- The reason why the target trial framework was excluded from the original paper is that we believed that the causal inference framework (or the potential outcome framework) is **more fundamental**
- The target trial thinking process is one realization of the **what if** thinking process

Spoiler Alert: Same authors for *targeted trial emulation* paper and *what if causal inference* (book): Hernan and Robins

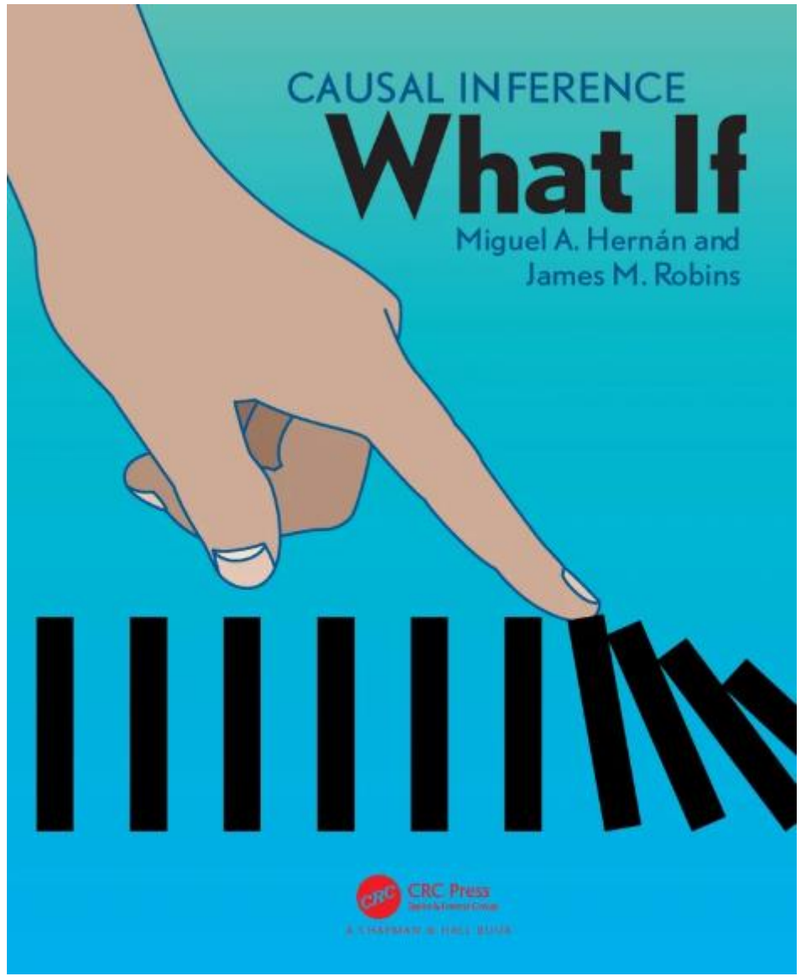
What-If Thinking

ICH E9(R1) Guideline

A.3. ESTIMANDS

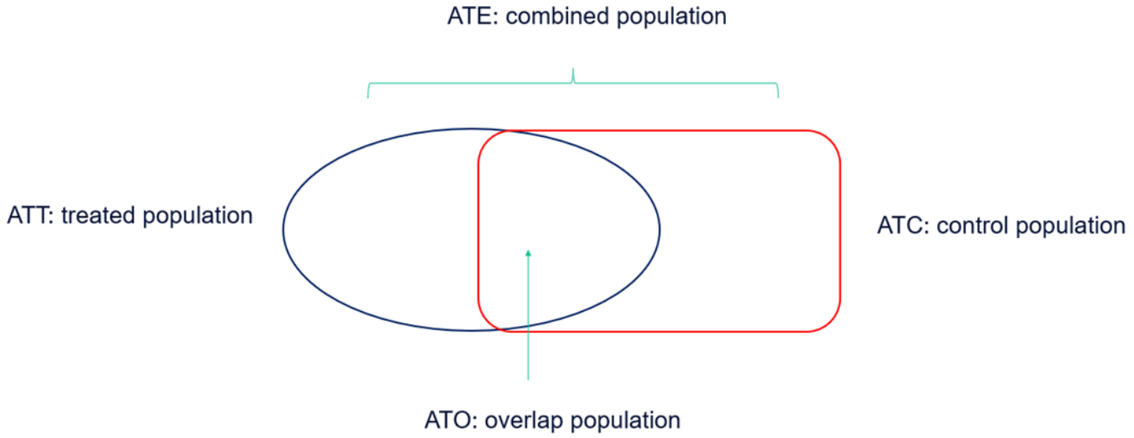
Central questions for drug development and licensing are to establish the existence, and to estimate the magnitude, of treatment effects: how the outcome of treatment compares to what would have happened to the same subjects under alternative treatment (i.e. had they not received the treatment, or had they received a different treatment). An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. It summarises at a population level what the outcomes would be in the same patients under different treatment conditions being compared.

What-IF thinking



Let’s Apply What-IF Thinking to Externally Controlled Trial (ECT)

- In the commentary paper, the section 2 is titled “Applying the target trial framework to a single-arm trial with an external control arm”
- Here, let’s apply what-if thinking to an ECT
- Four populations and four estimands: ATE, ATT, ATC, and ATO
  - What if every subjects in the population were treated by treatment 1
  - What if every subjects in the population were treated by treatment 0



Let's Apply What-IF Thinking to Hybrid controlled Trial (HCT)

- Let's apply what-if thinking to a hybrid controlled trial (HCT)—an RCT augmented with external controls
- Two population and two estimands ($S = 1$ means "is sampled to RCT")
  - covariate-pooled ATE: $\theta_1^* = E[E(Y^{a=1} - Y^{a=0}|X, S = 1)]$
  - Trial-only ATE: $\theta_2^* = E[E(Y^{a=1} - Y^{a=0}|X, S = 1)|S = 1]$

Adaptive-TMLE for the Average Treatment Effect based on Randomized Controlled Trial Augmented with Real-World Data

Mark van der Laan[1], Sky Qiu[1]*, Jens Magelund Tarp[2], Lars van der Laan[3]

[1]Division of Biostatistics, University of California, Berkeley
[2]Novo Nordisk, Søborg, Denmark
[3]Department of Statistics, University of Washington, Seattle

January 22, 2025

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  1. Distinguishing between estimands defined according to ICH E9 and causal estimands?
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  3. **Expand on focus areas of data quality when incorporating RWD into clinical trial design**

Data Quality

- We agree all the points raised in Section 3 of the commentary paper
- Here an excerpt from the commentary paper

> LHC briefly touch on the issue of data quality when using RWD, highlighting it as a very important topic. We would like to expand on this topic further in this section, to highlight what points researchers should pay extra attention to when incorporating RWD into the clinical study trial design. A well-structured guidance would be useful to illustrate the principles for a systematic end-to-end workflow covering: dataset selection; assessment of whether the data are fit-for-purpose; pre-specification of analyses; and how to report results in a transparent and reproducible way.

FDA’s Guidance Documents on RWD, ECT, and HCT

FDA’s Guidance Documents on **RWD**

- Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products (September 2021)
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products (November 2021)
- Data Standards for Drug and Biological Product Submissions Containing Real-World Data (October 2021)

FDA’s Guidance Document on **ECT**

- Considerations for Design and Conduct of Externally Controlled Trials for Drug and Biological Products (February 2024)

FDA’s Guidance Document on **HCT**

Table. Summary of Considerations for Assessing Comparability of Data[29]

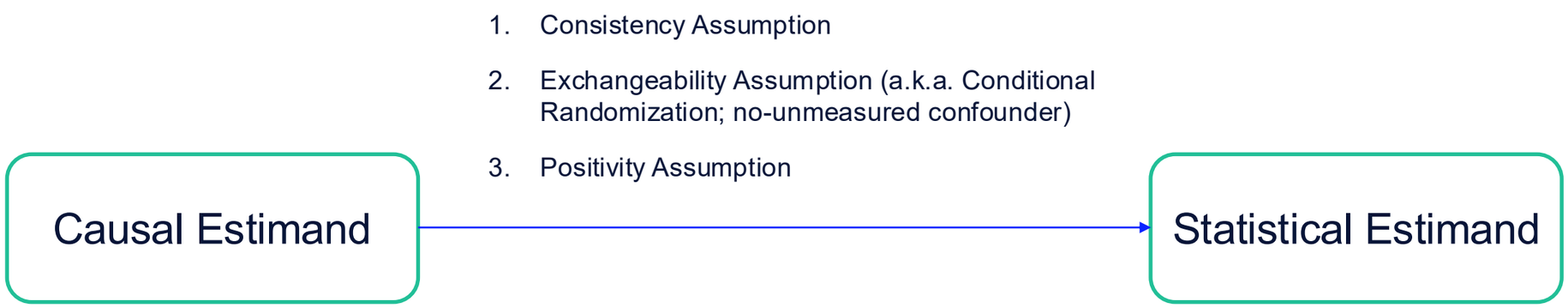
Focus of Comparison	Considerations for Data Comparability
Time periods	Various aspects of clinical care may change over time, such as the standard of care for the condition of interest, types of treatments, supportive care regimens, and criteria for determining disease response or progression. Such temporal differences are difficult to address using statistical analyses alone. It is important to consider whether and how different time frames in the treatment arm and the external control arm impact the interpretability of study findings.

Focus of Comparison:

1. Time periods
2. Geographic region
3. Diagnosis
4. Prognosis
5. Treatments
6. Other treatment-related factors
7. Follow-up periods
8. Intercurrent events
9. Outcomes
10. Missing data

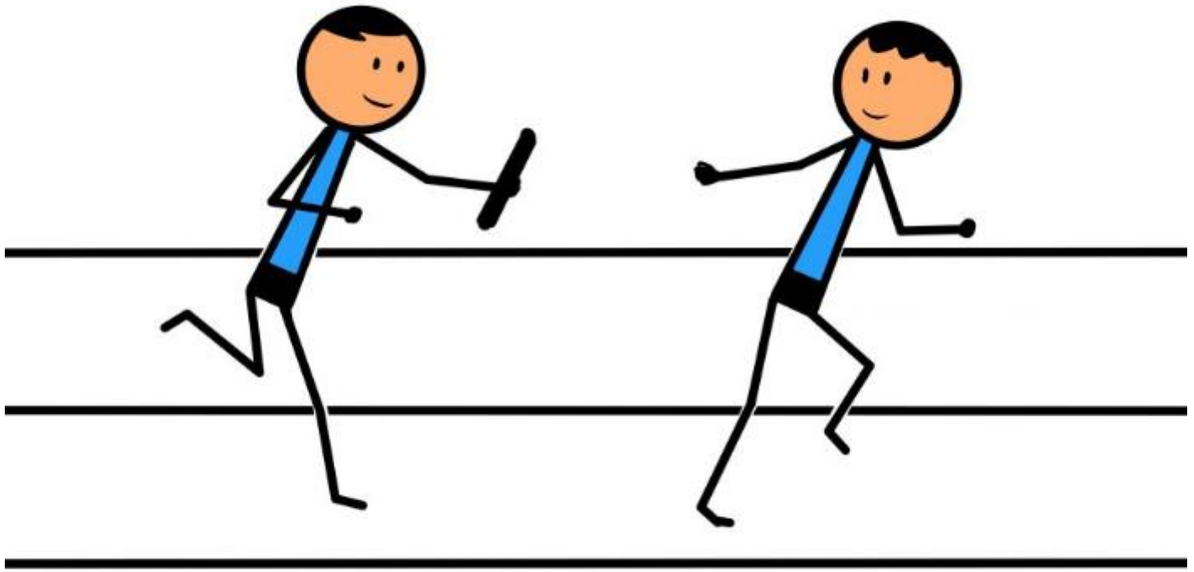
Principles on Data Quality Assessment

- Identifiability assumptions



- Principles of data quality assessment should be to ensure, as far as possible, that the three identifiability assumptions above are satisfied
- The table provided in the FDA's guidance on ECT is to ensure that the exchangeability assumption is satisfied as far as possible

Presenter Switching



Comment on "Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment"

Lisa V. Hampson[a], Evgeny Degtyarev[a], Rui (Sammi) Tang[b], Jianchang Lin[c], Kaspar Rufibach[d], and Cheng Zheng[e]

[a]Novartis Pharma AG, Basel, Switzerland; [b]Servier Pharmaceuticals, Boston, MA; [c]Takeda Pharmaceuticals, Cambridge, MA; [d]Hoffmann-La Roche Ltd, Basel, Switzerland; [e]Zentalis Pharmaceuticals, New York, NY

Evgeny Degtyarev

Advanced Quantitative Sciences, Novartis

May 21, 2026

Why this commentary?

STATISTICS IN BIOPHARMACEUTICAL RESEARCH
2023, VOL. 15, NO. 1, 23–26
https://doi.org/10.1080/19466315.2021.1994459

Taylor & Francis
Taylor & Francis Group

Check for updates

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ABSTRACT
We congratulate the authors of this landscape assessment on a comprehensive and stimulating article which carefully reviews many important biostatistical issues related to the use of real-world data (RWD) to

ARTICLE HISTORY
Received September 2021
Accepted October 2021

Oncology Estimand WG (2018-2024, EFSPI SIG and ASA BIOP SWG): http://www.oncoestimand.org

Real-world and Estimands Taskforce: Illustrate the value and promote the use of target trial framework and estimand framework for design of comparisons including real-world data

Webinar on Estimands and Target Trial Framework in 2022

ASA NJ Chapter Webinar Series:

Getting the question right: Applying the Estimand and Target Trial Frameworks with External Controls

Dec 2, 2022, 10:00 am-12:20 pm (EST) 16:00-18:20 pm (CET)

Jointly by

New Jersey Chapter of the American Statistical Association

Oncology Estimand Working Group of ASA BIOP & PSI/EFSPI

I'll refer to some of the presentations in my talk

All slides available on http://www.oncoestimand.org

Speaker	Institution	Title	Download slides
Pallavi Mishra-Kalyani	FDA	External control arms in oncology: current use and future directions?	link
Xabier Garcia de Albeniz Martinez & Lisa Hampson	RTH Health Solutions & Novartis	Introduction to the ICH E9(R1) estimand and target trial emulation frameworks, and their role in the design and analysis of RWE studies	link
Jufen Chu	Novartis	Combining the target trial and estimand frameworks to define the causal estimand: an application using real-world data to contextualize a single-arm trial	link
Letizia Polito	Roche	Applying the Estimand and Target Trial frameworks to external control analyses using observational data: a case study in the solid tumor setting	link
Stephen Duffield	NICE	Benefits of target trial and estimand frameworks in real-world evidence of treatment effects for supporting health technology assessment	link

Target trial framework

Not mentioned in Levenson et al

One of the main tools of causal inference in observational research

Useful to apply the estimand thinking process to studies using RWD and to evaluate the fitness-for-purpose of the available data

> "hallmark of a well-posed causal question is that one can describe the RCT (randomized controlled trial) that would answer it" (Goodman et al)

Goodman, S. N., Schneeweiss. S., and Baiocchi, M. (2017), "Using Design Thinking to Differentiate Useful From Misleading Evidence in Observational Research," Journal of the American Medical Association, 317, 705–707.

Target Trial Framework

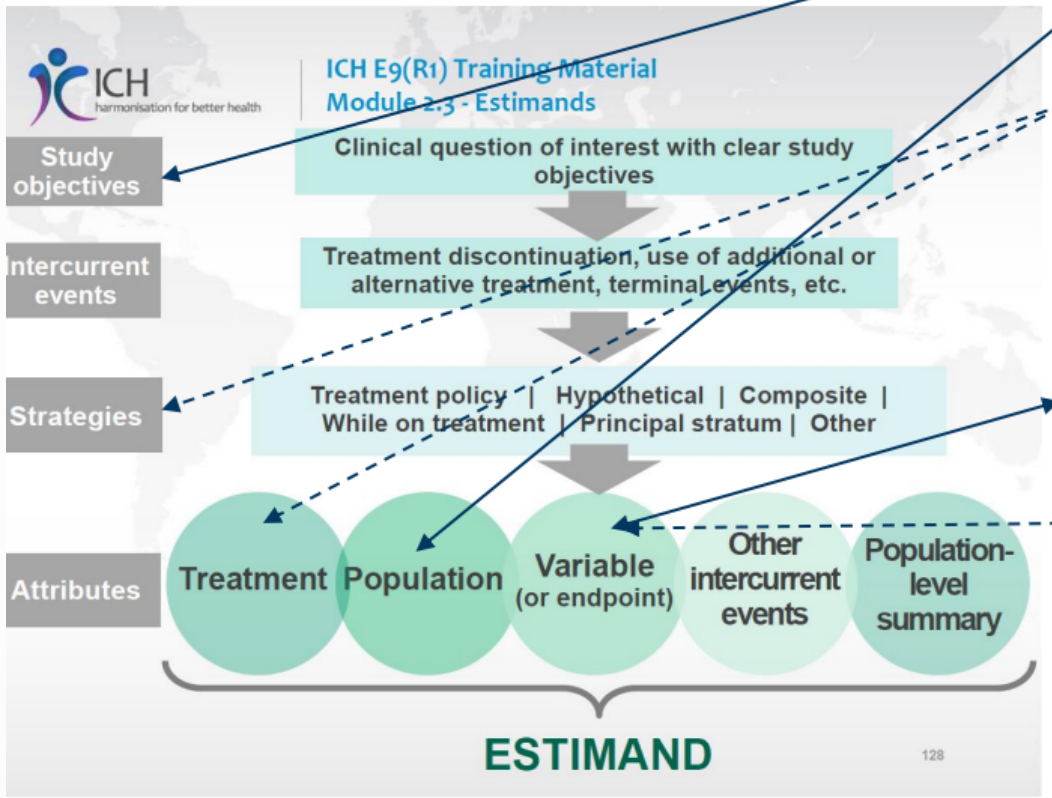
Protocol component	Target trial specification	Target trial emulation
Aim	What is the study objective?	
Eligibility criteria	Who will be included in the study?	
Treatment strategies	What interventions will eligible persons receive?	
Treatment assignment	How will eligible persons be assigned to interventions?	
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.

NOVARTIS | Reimagining Medicine

From Xabier Garcia de Albeniz Martinez & Lisa Hampson talk at the webinar "Getting the question right – Applying the Estimand and Target Trial Frameworks with External Controls" (2022, organized by ASA NJ Chapter and Onco Estimand WG) Link to all presentations

Target trial framework and Estimands



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Causal contrast (or estimand)	Which counterfactual contrast will be estimated using the above data?
Statistical analysis	How will the counterfactual contrasts be estimated?

From Xabier Garcia de Albeniz Martinez & Lisa Hampson talk at the webinar "Getting the question right – Applying the Estimand and Target Trial Frameworks with External Controls" (2022, organized by ASA NJ Chapter and Onco Estimand WG) Link to all presentations

Applying TTE to a single arm trial with external control

Population: same target population, but likely not all eligibility criteria can be implemented in RWD → transparent assessment of bias and fitness-for-purpose

Treatment: no difference between target RCT vs SAT and RWD expected

Treatment assignment: Stratification in target RCT challenging to emulate

Endpoint and intercurrent events: retrospective RWD may constrain endpoint choice, while prospective RWD enable pre-specified, question-driven endpoints

Start of follow-up: in Target trial/SAT at randomization/enrollment, in RWD ideally at prescription

Applying TTE to a single arm trial with external control: Example

Applying target trial & estimand frameworks

Question: What's the treatment effect of prescribing tisagenlecleucel vs SoC in the patient population who participated in the ELARA trial? - ATT

Component	Target RCT trial	Emulated trial		Our strategy
		ELARA	ReCORD	
Population /Eligibility criteria	ELARA inclusion/exclusion (I/E) criteria	**Same as target RCT**	ELARA I/E criteria that are feasible to apply retrospectively	Sensitivity analysis based on worst-case scenario for prognostic factors in ReCORD
Treatment/ Treatment strategy	**CAR-T treatment strategy** vs **Current SoC**	**CAR-T treatment strategy as target RCT**	Current SoC	✓
Treatment assignment	Block randomized to either CAR-T arm or SoC arm	**Emulate simple randomization**		Propensity score weighting method to mitigate confounding bias
Variables	OS is time to death from any cause	**Same as in target RCT**		✓
	CR best overall response of complete remission per Lugano criteria	**Same as target RCT**	CR and progression based on real-world response criteria	Subgroup analysis ≥ 2014 was conducted as year of introduction of Lugano response criteria
	PFS is time to first progression or death from any cause	**Same as target RCT**	Progression dates unavailable for many patients	**To consider new anticancer therapy as PFS event**

- makes limitations of RWD sources and RWE analyses more explicit
- helps to choose appropriate data sources and avoid common methodological pitfalls

Applying target trial & estimand frameworks

Component	Target RCT trial	Emulated trial		Our strategy
		ELARA	ReCORD	
Start of follow-up	Start: date of randomization	Start: enrollment, regarded as prescription date	Start: start date of SoC treatment • Multiple line of therapy	One eligible LoT per patient in ReCORD is systematically selected based on the highest propensity score to be in ELARA
Intercurrent event(s)	**IE: new anti-cancer therapy** OS: Treatment policy strategy CR: ICE reflected in Variable PFS: Hypothetical strategy	Same as target RCT for OS and CR PFS: Composite strategy		✓
Causal effect	**ATT:** Effect of prescribing tisagenlecleucel vs SoC in patients meeting ELARA inclusion/exclusion criteria	Same as in target RCT		✓
Summary measure	Binary endpoints: Difference in marginal response probabilities on CAR-T vs SoC Time-to-event (TTE) endpoints: Marginal HR	Same as in target RCT		✓
Analysis	Binary: Difference in response rates TTE: Cox regression	Binary: Difference in weighted proportions of responders TTE: HR obtained from a weighted Cox regression		✓

From J.Chu talk at the webinar "Getting the question right – Applying the Estimand and Target Trial Frameworks with External Controls" (2022, organized by ASA NJ Chapter and Onco Estimand WG) Link to all presentations

Practical Considerations

End-to-end workflow

- dataset selection
- fit-for-purpose assessment
- pre-specification of analyses
- transparent reporting

Missing data

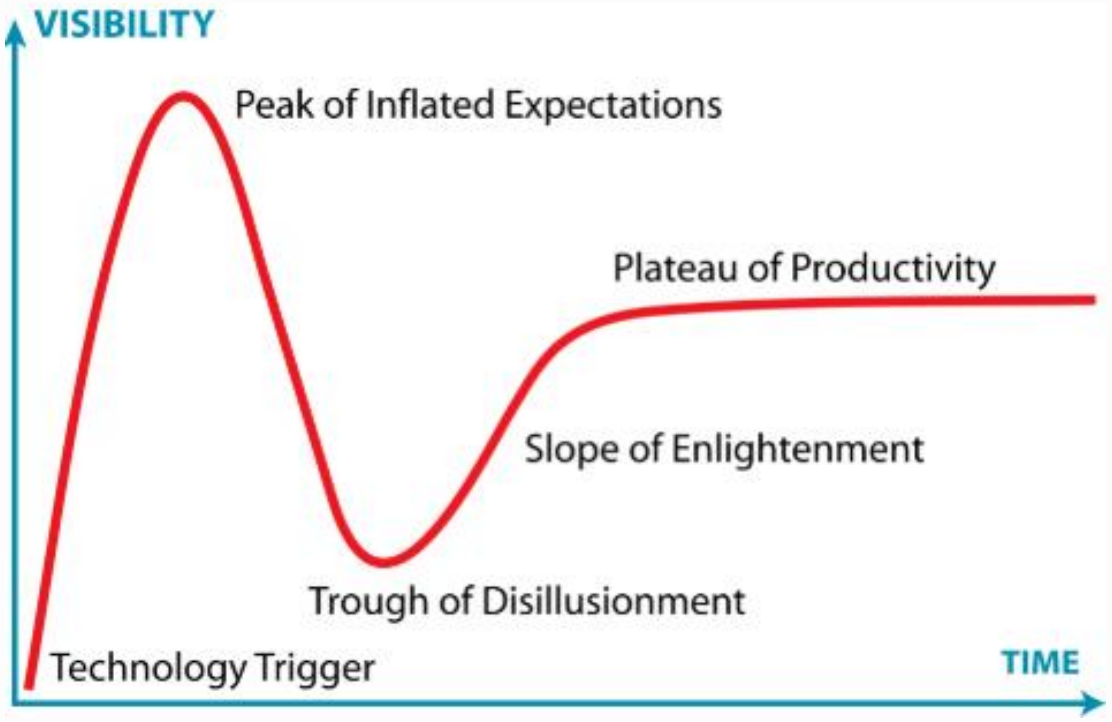
- Proactive mitigation to avoid or minimize missing data essential
- Additional practical examples for selecting missing-data strategies aligned with the target estimand would be valuable

Choice of Methodology

- Access to patient-level data
- Identifying confounders and baseline covariates for propensity score adjustment: DAG graphs!
- Different methods may target different causal effects*
- Choice depends on clinical context and study objectives
  - Conditional vs Marginal
  - ATT vs ATE
    - if single-arm trial is contextualized by RWD, ATT preferred as the estimand targets the trial population rather than a pooled RWD-trial population

*Williamson et al (2011), "Propensity Scores: From Naive Enthusiasm to Intuitive Understanding," Statistical Methods in Medical Research, 21, 273–293. Desai, R. J., and Franklin, J. M. (2019), "Alternative Approaches for Con founding Adjustment in Observational Studies Using Weighting Based on the Propensity Score: A Primer for Practitioners," BMJ, 367, 15657 ; Chen et al (2021), "The Current Landscape in Biostatistics of Real-World Data and Evidence: Clinical Study Design and Analysis," Statistics in Biopharmaceutical Research. DOI:10.1080/19466315.2021.1883474
DAG: Directed Acyclic Graphs; ATT=Average Effect on the Treated; ATE: Average Treatment Effect;

Personal reflections on RWE



Gartner Hype Cycle

Trigger: 21st Century Cures Act (2016) mandating FDA to establish a program for evaluating RWE

Peak of Inflated Expectations (2018-2020): big acquisitions and major investments

Trough of Disillusionment: (2020-2022): Regulatory reality and boundary setting

Slope of Enlightenment (2023-now): selective use if fit for purpose

RWE strengthened statistical thinking

- Created opportunities to learn from observational research (e.g. target trial framework)
- Supported increase in causal inference discussions in biostats community
  - “For objective causal inference, design trumps analysis” (D.Rubin) – fully applicable for RWE!
- Facilitated exchange between all stakeholders on best practices for design, analysis and communication
- Set durable ground rules as AI enters RWD

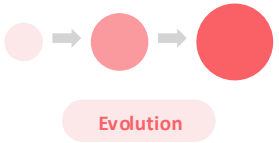
PANEL DISCUSSION

PHUSE Estimands for RWD/RWE: Webinar 4 – Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes

May 2026

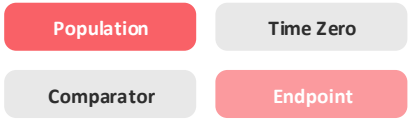
01

What is the change you have seen in estimands and target trial emulation moved from methodological frameworks to practical tools used in regulatory evaluation of RWE studies? (Chantal)



02

Both papers suggest that many important biases should be prevented by design rather than adjusted away analytically. In today's RWE practice, which design decision has the biggest impact on credibility for regulatory? [possibilities include study population, time zero, comparator choice, intercurrent event strategy, endpoint definition, other?] (Evgeny)



03

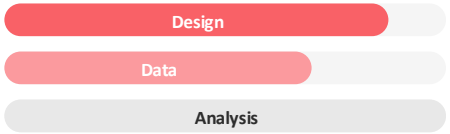
How should one balance methodological rigor with feasibility in distributed TTE studies using real-world data? (Chantal)

04

In what situations is targeting the ATT more defensible than the ATE in regulatory RWE? And can that choice meaningfully change the regulatory conclusion? (Fang)

05

What do you currently consider the minimum requirements for a target trial emulation study using real-world data to be considered sufficiently robust for regulatory decision-making? (Chantal)

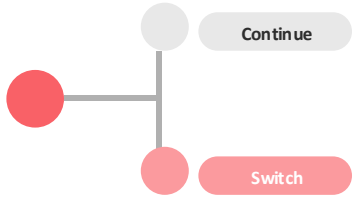


06

What is the one methodological or regulatory question about RWD and estimands that remains genuinely unresolved, where the field still does not know the right answer but most urgently needs one? (All)

07

In RWD settings, intercurrent events like discontinuation and switching are part of routine care rather than protocol deviations. Are hypothetical estimands still defensible in RWE? How can we otherwise handle? (Evgeny , Fang)



Thank You

Open Discussion

We welcome questions, perspectives, and insights from all attendees.