Estimands in Real-World Evidence Studies

June 5, 2025

11:00 (EDT)/ 16:00 (BST) / 17:00 (CEST)

Moderator: Ibrahim Turkoz, PhD; Johnson & Johnson

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 (Sep 2025): 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

Estimands in Real-World Evidence Studies

This webinar will explore the pivotal role of estimands in RWE studies, bridging the gap between regulatory guidance and practical implementation. The session will address challenges unique to RWE settings, such as heterogeneous patient populations, complex treatment regimens, and the impact of intercurrent events on study outcomes with a focus on generating RWE that can inform regulatory decision-making. Through practical examples, case studies, and an engaging panel discussion featuring domain experts, this session will highlight best practices for defining estimands that enhance the interpretability and reliability of RWE findings. Participants will leave with a systematic approach to estimand definition, empowering them to conduct RWE studies that are robust, actionable, and aligned with evolving regulatory standards.

https://advance.hub.phuse.global/wiki/spaces/WEL/pages/130285569/Real+World+Evidence+Webinar+Series+2025

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

Estimands in Real-World Evidence Studies

Webinar 2 Outline

- (4 min) Introduction
- (10 min) Dr. Hana Lee, US-FDA
- (25 min) Dr. Hongwei Wang, AbbVie
- (20 min) Panel Discussion
- (1 min) Closing

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Hana Lee Presentation

U.S. FOOD & DRUG ADMINISTRATION

FDA's Definition of Real-World Data and Real-World Evidence for Regulatory Submission

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Office of Biostatistics
Center for Drug Evaluation and Research
US Food and Drug Administration

PHUSE 2025
June 5, 2025

Disclaimer

This presentation reflects the view of the author and should not be construed to represent FDA's views or policies.

FDA's Definition of RWD/E

Real World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

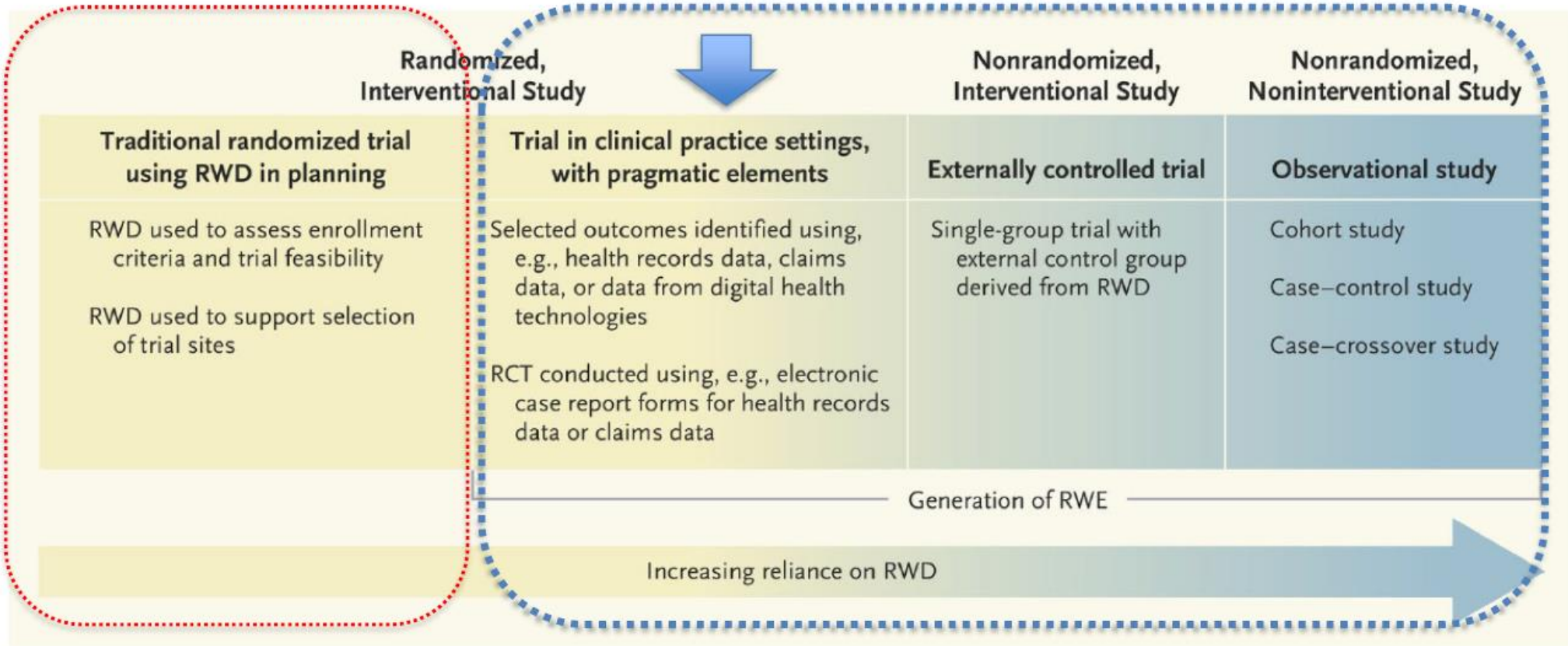
- electronic health records (EHRs)
- claims and billing data
- data from product and disease registries
- patient-generated data including in home-use settings
- data gathered from other sources that can inform on health status, such as mobile devices

Real World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Generated using many different study designs, including but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies.

Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.

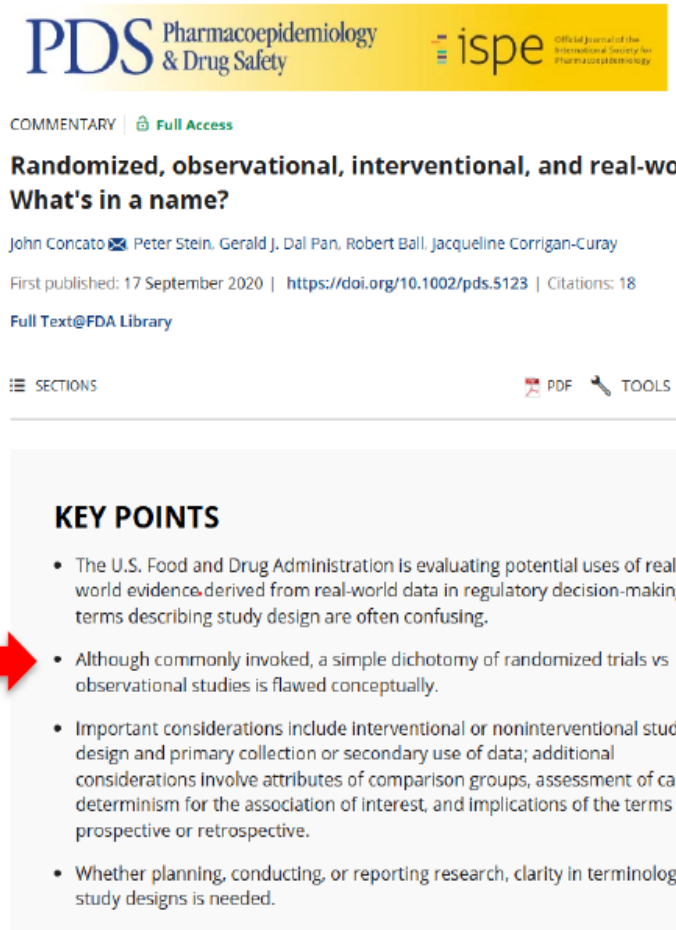


Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

N ENGL J MED 386;18 NEJM.ORG MAY 5, 2022

Nonrandomized vs. Noninterventional Study



PDS Pharmacoepidemiology & Drug Safety | ispe

COMMENTARY | Full Access

Randomized, observational, interventional, and real-world—What's in a name?

John Concato, Peter Stein, Gerald J. Dal Pan, Robert Ball, Jacqueline Corrigan-Curay

First published: 17 September 2020 | https://doi.org/10.1002/pds.5123 | Citations: 18

Full Text@FDA Library

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KEY POINTS

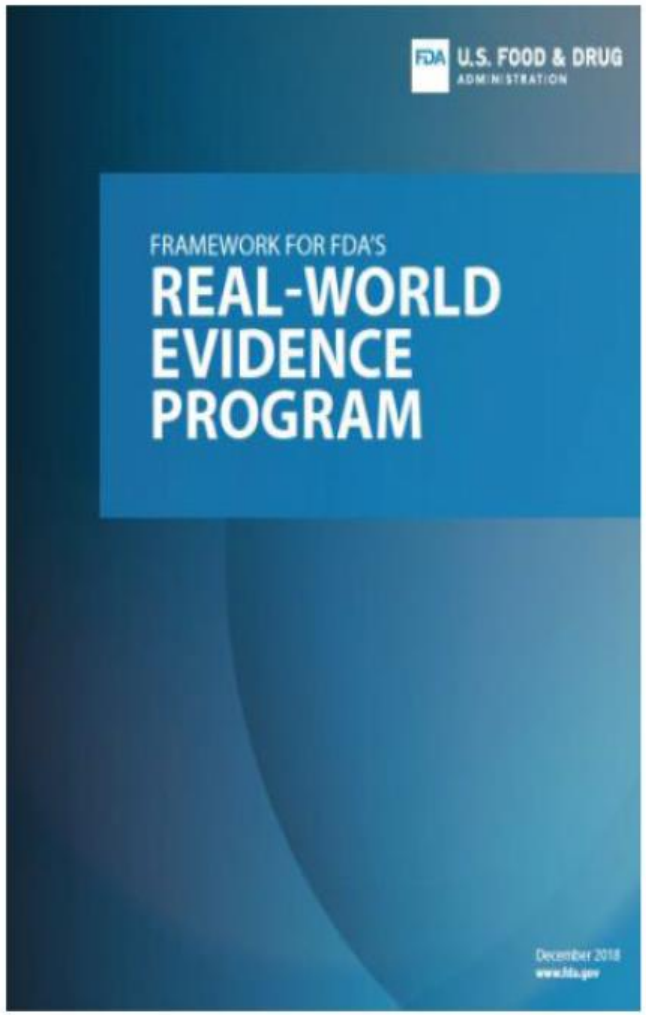
- The U.S. Food and Drug Administration is evaluating potential uses of real-world evidence derived from real-world data in regulatory decision-making, but terms describing study design are often confusing.
- Although commonly invoked, a simple dichotomy of randomized trials vs observational studies is flawed conceptually.
- Important considerations include interventional or noninterventional study design and primary collection or secondary use of data; additional considerations involve attributes of comparison groups, assessment of causal determinism for the association of interest, and implications of the terms prospective or retrospective.
- Whether planning, conducting, or reporting research, clarity in terminology of study designs is needed.

- Defining feature of a clinical trial: Whether Investigator assigns treatment according to an investigational protocol

	Interventional	Non-Interventional
Primary data collection for research	• traditional RCTs • decentralized RCTs	• registry-based analyses*
Secondary use of clinical data	• pragmatic RCTs • cluster RCTs	• health records- or claims-based analyses*

*Non-interventional research designs include observational cohort and case-control studies; RCT = randomized, controlled trial.

FDA RWE Framework (Dec. 2018)

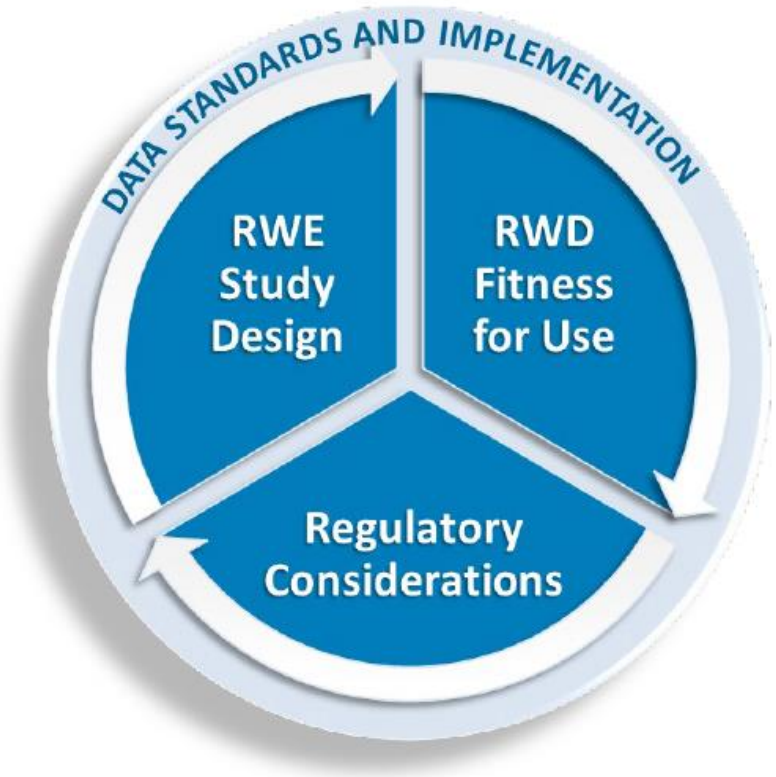


1. Applies to Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)

2. Describes current use of RWD for evidence generation

3. Delineates framework for evaluating RWD/RWE for their use in regulatory decisions – Data, Design, Conduct

Framework for Evaluating RWD/RWE for Use in Regulatory Decisions



FDA's framework:

1. Whether the RWD are fit for use

2. Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question

3. Whether the study conduct meets FDA regulatory requirements

Recent Guidance on RWD/RWE

Considerations	Topic	Status	Date
Data	EHRs and claims data	Final published	July 2024
	Registry data	Final published	Dec 2023
Design	Externally controlled trials	Draft published	Feb 2023
	Non-interventional studies	Draft published	Mar 2024
	Integrating RCTs into routine clinical practice	Draft published	Sep 2024
Regulations &	Regulatory considerations	Final published	Aug 2023
Conduct	Data standards and submission	Final published	Dec 2023
	Submitting documents	Final published	Sep 2022

Regulatory Considerations Guidance: Overview

- Discusses legal requirements for non-interventional studies
- Sponsors should
  - engage with FDA early in the drug development
  - provide protocol/statistical analysis plan
  - document all analyses performed on the data, including feasibility evaluations/exploratory analyses
- Sponsors **must** ensure that they are able to submit **patient-level data** in a marketing application when required

Advancing Real-World Evidence Program

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Development Resources

- Advancing Real-World Evidence Program
- Antibacterial Drug Development Task Force
- BEST Resource Taxonomy
- Clinical Outcome Assessment Compendium

On this page

Content current as of:
01/17/2024

Regulated Product(s)
Drugs

https://www.fda.gov/drugs/development-resources/advancing-real-world-evidence-program

PERSPECTIVE

US Food and Drug Administration's Advancing Real-World Evidence Program: Initial Experience

Kimberly A. Smith[1,*], Yin Huang[2], Theresa Kehoe[1], Stefanie Kraus[1], Mark Levenson[1], Jie Li[1], Kristen Miller[1], Ann Punnoose[1], Donna R. Rivera[3], Yueqin Zhao[1], Richard Forshee[2] and John Concato[4]

Advances in the availability and analysis of real-world data (RWD) have enabled the generation of robust real-world evidence (RWE) to support regulatory decision making by the US Food and Drug Administration. Realizing the full potential of RWE in a regulatory environment requires cross-discipline expertise and collaboration to increase confidence in RWE-based approaches. The FDA's Advancing RWE Program was established to address this need by providing a new option for regulatory interactions on RWE-based approaches.

RATIONALE FOR THE PROGRAM

The FDA regularly engages with sponsors to discuss their development plans, including potential approaches to establish safety and effectiveness that involve the use of RWD.[1] The use of RWD to generate RWE for regulatory decision making can often benefit from additional, early interactions with FDA to address key challenges. This includes, for example, assessing the relevance and reliability of RWD sources; ensuring study designs are appropriate to answer the regulatory question of interest and analytic plans are adequate to mitigate biases; and adhering to regulatory requirements, such as human subject protections, submission of patient-level data to FDA, and the ability of FDA inspectors to access source records.[2,3]

During Prescription Drug User Fee Amendments negotiations for fiscal years 2023 through 2027 (PDUFA VII), FDA and industry sought a mechanism to identify and promote awareness of approaches for generating RWE that could meet regulatory requirements in support of labeling for effectiveness or for meeting post-approval study requirements. In addition, there was a need to develop Agency processes to promote consistent decision making and shared learning regarding RWE. As a result, FDA developed the Advancing RWE Program, which was announced in the Federal Register on October 20, 2022.[4]

PROGRAM OVERVIEW

The Advancing RWE Program is a pathway for sponsors selected into the program to meet with staff from the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Oncology Center of Excellence (OCE) to discuss the use of RWE in medical product development. Sponsors can submit an initial meeting request to the program on a rolling basis through March 31, 2027, and FDA reviews all requests received in the preceding 6-month submission cycle after each submission deadline. FDA may grant up to two initial meeting requests per semi-annual submission cycle during the first two program years (fiscal years 2023 and 2024) and up to four initial meeting requests per cycle in subsequent years (fiscal years 2025–2027). After an initial program meeting, sponsors can request up to three follow-up meetings to continue discussions of their proposed studies.

The Advancing RWE Program is administered by CDER's Office of Medical Policy under the leadership of a team comprised of representatives from CDER's Offices of Medical Policy, New Drugs, Biostatistics, Surveillance and Epidemiology, and Regulatory Policy as well as representatives from CBER's Office of Biostatistics and Pharmacovigilance and the OCE. Meetings with sponsors include relevant review staff and leadership from these groups as well as from primary review divisions with

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- Sharing FDA's initial experience from the The first four semi-annual cycles of the Advancing RWE Program
- FDA received 21 initial meeting requests and accepted four, with one sponsor completing participation
- FDA primarily focused on two areas:
  - Substantial differences between two groups are highly likely
  - Adequacy of endpoints
- More information on selected sponsors and applications, reasons for reasons for denial of meeting requests, etc. are available


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RWE in NDA and BLA Application Approvals During FY 2020-2022

Real-World Evidence in New Drug and Biologics License Application Approvals During Fiscal Years 2020–2022

Gabriel K. Innes[1]*, Kimberly A. Smith[1], Aida Kuzucan[2], Jie Li[2], Donna Rivera[3], Orestis A. Panagiotou[2] and John Concato[4]

Abstract

Improvements in the relevance and reliability of routinely collected clinical data and statistical methods to analyze the available data have enhanced the adoption of real-world data (RWD) to generate real-world evidence (RWE) for regulatory decision making of medical products. As part of the reauthorization of the Prescription Drug User Fee Act (PDUFA VII), the US Food and Drug Administration (FDA) committed to issuing annual reports describing such uses for drugs and biological products. The first report covered fiscal year (FY) 2023 and described two approvals based, at least in part, on RWE: tocilizumab (trade name Actemra) and lacosamide (trade name Vimpat). This article describes New Drug Applications and Biologics Licensing Applications approved by the Center for Drug Evaluation and Research (CDER) in FYs 2020–2022 with RWE that (1) contributed to substantial evidence of effectiveness or (2) provided safety data necessary for approval. RWE contributed to substantial evidence of effectiveness for the approval of applications for fosdenopterin (trade name Nulibry) and tacrolimus (trade name Prograf) in FY 2021 and abatacept (trade name Orencia), vosoritide (trade name Voxzogo), and alpelisib (trade name Vijoice) in FY 2022. No studies provided only safety data necessary for approval. The five approvals included six total studies that provided RWE pivotal for the applications approval. Four studies leveraged registry data, and two leveraged medical record data. In parallel with annual RWE public reporting under PDUFA VII, this report can inform interested parties regarding how RWD are used to generate RWE that can support regulatory decision making for medical products.

Improvements in the reliability (i.e., accuracy, completeness, and traceability) and relevance (i.e., availability of data for key study variables and sufficient numbers of representative patients) of routinely collected clinical data and statistical methods to analyze those data have enhanced the adoption of real-world data (RWD) to generate real-world evidence (RWE) for regulatory decision making for medical products. RWE has an extensive history of use for evaluating the safety of medical products, often in the postmarketing phase of development.[1] On a more limited basis, RWE has also been used to support effectiveness. Following the passage of the 21st Century Cures Act in 2016 to help accelerate medical product development and improve public health, the US Food and Drug Administration (FDA) published a framework for evaluating the potential use of RWE to help support the approval of a new indication for a drug already approved or to help support or satisfy post-approval study requirements.[2] FDA has since published a series of guidance documents to share the agency's current thinking on RWD sources, study design, and regulatory issues. Based on such efforts and the work of the scientific and medical community,[3] there is increased interest by both medical product developers and regulators to incorporate RWD into studies designed to evaluate medical products' safety and effectiveness.[4,5]

As part of the reauthorization of the Prescription Drug User Fee Act (PDUFA VII), the FDA committed to publish annual reports describing drug and biologic product submission documents containing RWD to generate RWE intended to support or that supported regulatory decision making. The first annual report of submissions to CDER and the Center for Biologics Evaluation and Research (CBER) was posted in June 2024 and covered fiscal year (FY) 2023.[6]

The goal of this brief report was to describe applications to CDER for drugs and biological products containing RWD to generate RWE in pivotal studies and that resulted in regulatory approvals in the years immediately preceding the first PDUFA report; thereby, this work provides additional context to inform future efforts in research and medical product development.

METHODS

We reviewed approved original and supplemental Biologics License Applications (BLAs) and New Drug Applications (NDAs) wherein CDER took regulatory action during FYs 2020–2022 (October 1, 2019–September 30, 2022). We identified drug and biological product

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Table 1 Approved CDER product applications during FYs 2020–2022 with studies containing RWE that contributed to substantial evidence of effectiveness

Product	Date of approval	Approved indication		RWE study type	RWD source
Fosdenopterin	2/26/2021	Reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A		Other[a]	Medical records
Tacrolimus	7/16/2021	Prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic liver, kidney, heart, or lung transplants, in combination with other immunosuppressants		Non-interventional (observational) study: cohort	Registry
Vosoritide	11/19/2021	Increase linear growth in pediatric patients with achondroplasia with open epiphyses	(Study 1)	Externally controlled trial	Registry
			(Study 2)	Externally controlled trial	Registry
Abatacept	12/15/2021	Prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor.		Non-interventional (observational) study: cohort	Registry
Alpelisib	4/8/2022	Treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS) who require systemic therapy		Non-interventional (observational) study: cohort	Medical records

[a]Single-arm interventional trial with additional treatment data derived from RWD and comparator data derived from RWD.

Innes GK, Smith KA, Kuzucan A, Li J, Rivera D, Panagiotou OA, Concato J. Real-World Evidence in New Drug and Biologics License Application Approvals During Fiscal Years 2020–2022. Clinical Pharmacology & Therapeutics. 2025 Apr 29.

RWE in FY 2023

Real-World Evidence Submissions to the Center for Drug Evaluation and Research

As part of the reauthorization of the Prescription Drug User Fee Act (PDUFA VII), FDA committed to reporting aggregate and anonymized information on submissions to the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) that contain real-world evidence (RWE).

The tables below describe submissions to CDER containing RWE that meet reporting criteria. This report is not intended to include all submissions to CDER containing analyses of real-world data (RWD). Columns will be added annually to represent submissions by fiscal year (FY) from FYs 2023 through 2027.

Overview

The table below provides an overview of submissions to CDER containing RWE by category. A study that generates RWE may be reflected in more than one category depending on the status of the study.

Category	FY 2023
Protocol[a]	10
New drug application (NDA)/biologics license application (BLA)	4[b]
Final study report to satisfy a postmarketing requirement (PMR) or postmarketing commitment (PMC)	n/a[c]

The first report covered fiscal year (FY) 2023 and described two approvals based, at least in part, on RWE:

- Tocilizumab (trade name Actemra)
- Lacosamide (trade name Vimpat)

Real-World Evidence Submissions to the Center for Drug Evaluation and Research | FDA

BACK UP SLIDES

Background: 21st Century Cures Act (2016)

- FDA shall establish a program to evaluate the potential use of real-world evidence (RWE) to:
  - Support new indication **for a drug approved** under section 505(c)
  - Satisfy post-approval study requirements
- FDA issued a framework document in December 2018
- FDA issued various guidance documents (including draft guidance) for industry since 2021
- Standard for **substantial evidence for effectiveness** remains unchanged; commitments are aligned with Prescription Drug User Fee Act (PDUFA)

Substantial Evidence Efficacy

"**evidence consisting of adequate and well-controlled investigations**, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involve on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." *Federal Food, Drug, and Cosmetic Act 1962*

Drug Regulation History: https://www.fda.gov/about-fda/fda-history/history-drug-regulation

FDA's guidance on substantial evidence: https://www.fda.gov/media/133660/download

Adequate and Well-Controlled Study

1. Clear objectives, summary of methods and results
2. Design permits a valid comparison with a control (concurrent and historical controls)
3. Adequate selection of patients
4. Assigning patients to treatment and control groups minimizes bias
5. Adequate measures to minimize biases on subjects, observers, and analysts
6. Well-defined and reliable assessment of subjects' responses
7. Adequate analysis to assess drug results

Hongwei Wan Presentation

Data & Statistical Sciences

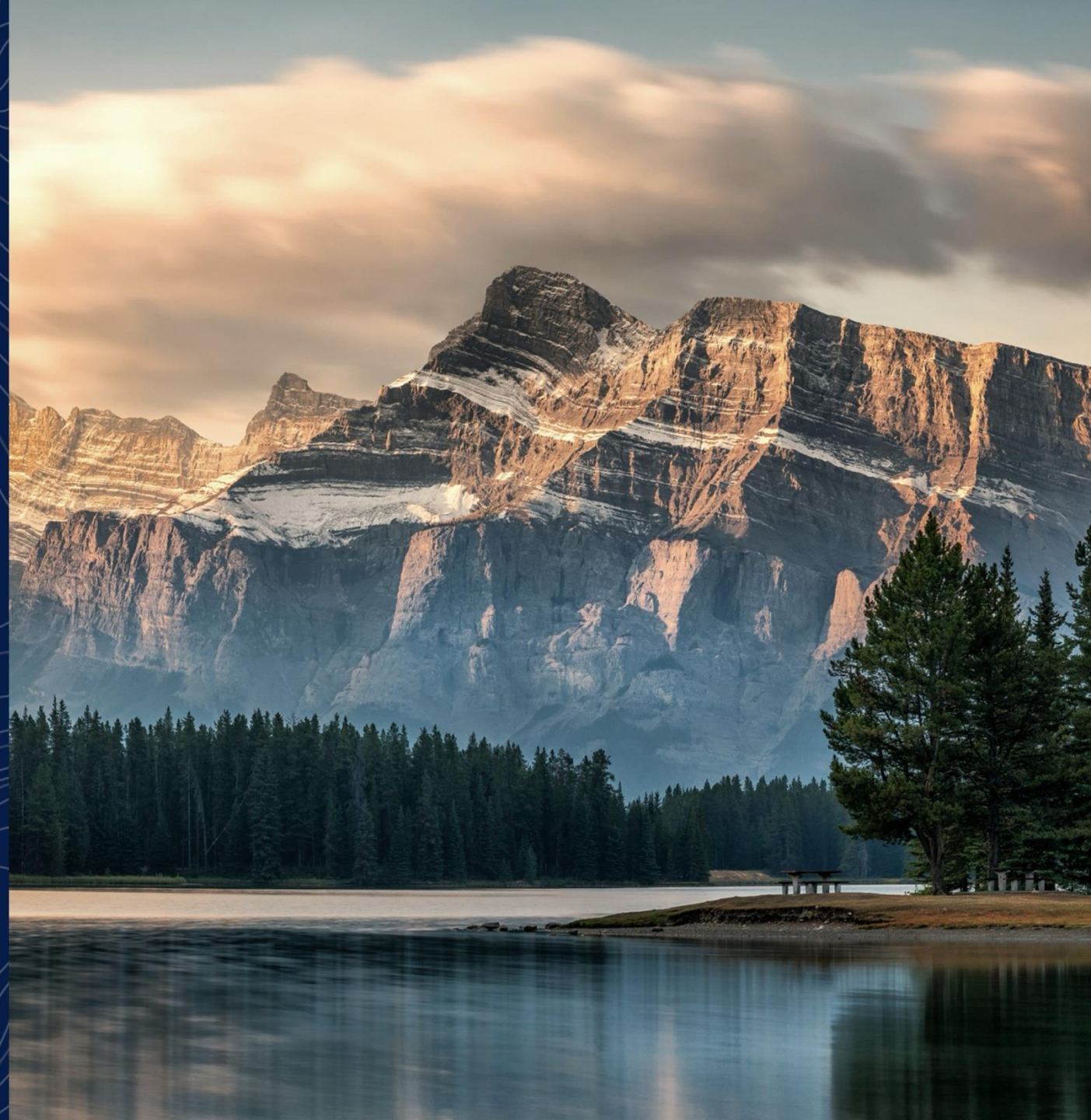
Estimands in Real-World Studies

Hongwei Wang and Weili He

AbbVie

Jun 5, 2025

abbvie



Acknowledgement

- The work presented here is based on an external professional collaboration via the American Statistics Association (ASA) Biopharm section sponsored RWE Scientific working group (SWG)

Industry	Affiliation	Academic/FDA	Affiliation
Jie Chen	Overland	**Hana Lee**	CDER
Weili He	AbbVie	John Scott	CBER
Hongwei Wang	AbbVie	Heng Li	CDRH
Yang Song	Vertex	Daniel Scharfstein	Utah
Binbing Yu	AstraZeneca		
Xiwu Lin	Janssen		
Patricia Luhn	Genentech		

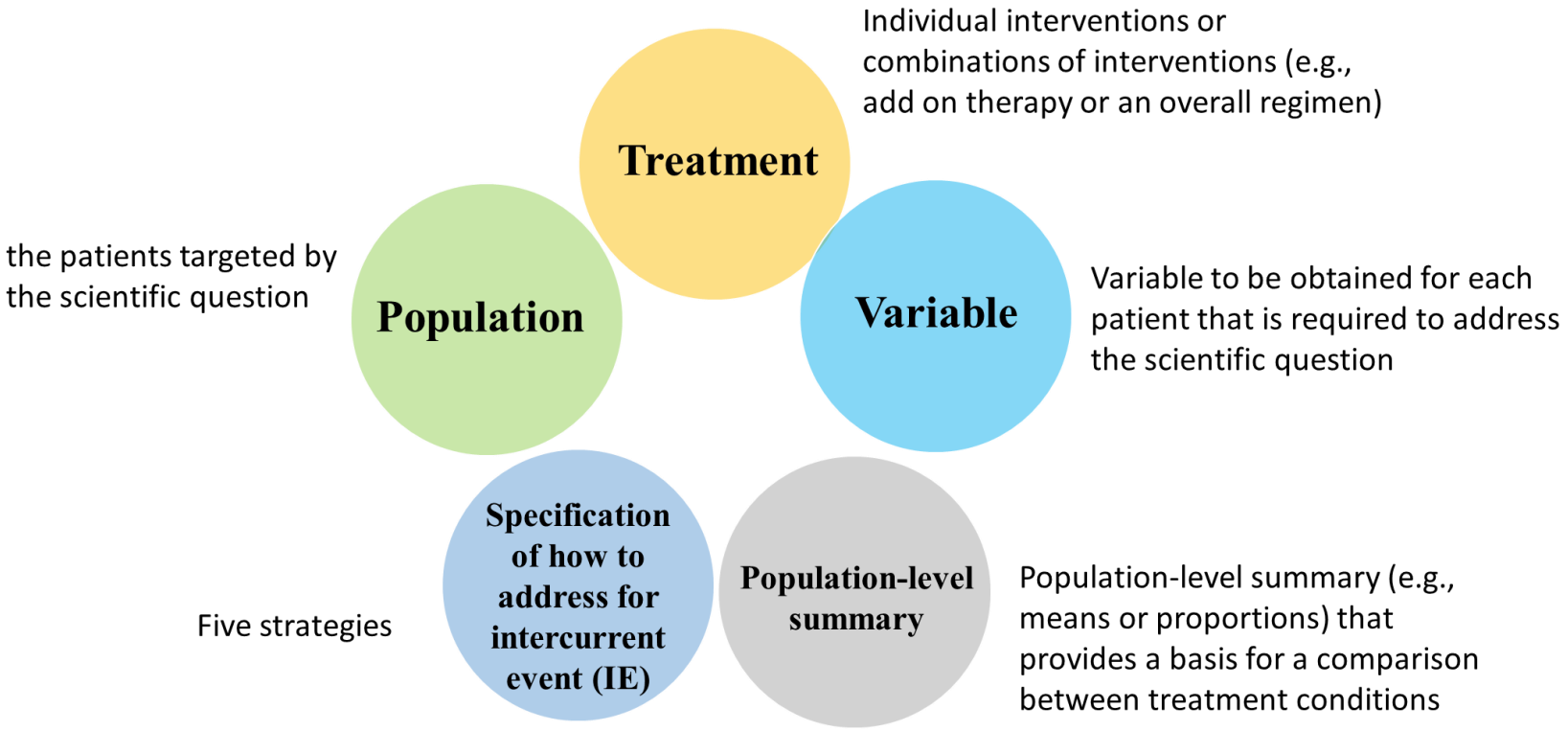
Chen, J., Scharfstein, D., Wang, H., Yu, B., Song, Y., He, W., Scott, J., Lin, X. and Lee, H., 2024. Estimands in real-world evidence studies. *Statistics in Biopharmaceutical Research*, 16(2), pp.257-269.

Outline

- **Introduction**
- **General considerations in defining estimand for RW studies (RWSs)**
  - Similarities and differences between RCT and RWS
  - Roadmap for defining estimand
- Critical assessment of case studies under estimand framework
- Conclusions

Introduction

- ICH E9 (R1) presents statistical principles for constructing estimands in *clinical trials*
  - Focus on **five attributes**
  - Strategies for handling of intercurrent events (**ICEs**)
    - Treatment policy
    - Hypothetical
    - Composite variable
    - While-on-treatment
    - Principal stratum



Mallinckrodt, Craig H., et al. Estimands, Estimators and Sensitivity Analysis in Clinical Trials. CRC Press, 2020.

Estimand in RW Studies – Population

- More ***heterogeneous*** population with less restrictive inclusion /exclusion criteria (IEC) mimicking patients from routine clinical practice
  - Diverse demographic backgrounds and geographical locations
  - Accesses to different healthcare systems
  - Comorbidities and use of concomitant medications
  - Patients who would otherwise not be included in RCTs
- Some RWD may be more selective and hence less representative
  - Commercial insurance claims via employment – healthy worker effect characterized as lower mortality and morbidity
  - Population meeting specific criteria, e.g., Medicare, Medicaid

Population Attribute – Similarities & Differences

Similarities/ differences	TCTs	RWE studies
	Population	
Similarities	• Study populations are clearly defined with a set of inclusion and exclusion criteria (IEC)	
Differences	• Target populations are restricted to those who meet a list of prospectively defined IEC • Patients with comorbidities may be excluded • Some populations such as children and elderly are usually under-represented	• IEC may be less restrictive • IEC are defined based on or limited to available data • Study populations may include those with comorbidities and who are under-represented in TCTs and hence generally more heterogeneous

Estimand in RW Studies – Treatment

- Patients tend to have more ***complex treatment patterns***
  - Availability of multiple treatments
  - Distinct preferences of individual patients and treating physicians
  - Different healthcare systems, e.g., reimbursement policy
  - Different treatment sequence or lines of therapy with initiation, dose adjustment, discontinuation, switch, add-on
  - Suboptimal non-adherence to treatment regimen
  - Polypharmacy and concomitant medications
- What is the primary treatment strategy / regimen for evaluating effect needs to be clearly articulated and reliably captured by RWD

Attribute of Treatment – Similarities & Differences

Similarities/ differences	TCTs	RWE studies
	Treatment	
Similarities	• A treatment or sequence of treatments of interest is pre-specified	
Differences	• A single (or multiple doses of) treatment is often of interest • A single sequence of treatment is often of interest • One alternative treatment or multiple treatments as a whole is specified as a comparison group • Use of rescue treatments may be considered as an ICE	• Various treatment use patterns are observed (nonadherence, switching, concomitant use, etc., are more frequent) • Multiple treatments (some of them may be SoCs) are often involved • Different lines of therapies are usually considered as more relevant (e.g., SoC followed by a new therapy) to obtain optimal dynamic treatment regimes

Estimand in RW Studies – Endpoint

- Choice of endpoints depends on research question and available RWD sources Not all relevant outcomes are captured
  - Often not adjudicated leading to information bias
  - Timing of outcomes depends on the local practice and data capturing mechanism
  - Some outcomes may be over- or under-reported
  - Some outcomes need to be derived, approximated by an algorithm

- Key question is if endpoints (and confounders) are validly measured and meet the criteria for the intended audience

Attribute of Endpoint – Similarities & Differences

Similarities/ differences	TCTs	RWE studies
	Endpoints	
Similarities	• One or more endpoints of primary/secondary interest are defined • A composite endpoint may also be used	
Differences	• Endpoints are usually measured at pre-defined time schedules or visits • Endpoints are often measured blindly • Both surrogate endpoints and clinical outcomes can be used	• Endpoints are measured only when the patient/prescriber reports the outcome • Endpoints are measured without blinding • Clinical outcomes are often used

Estimand in RW Studies – ICEs

- Treatment regimes and the types of ICEs (and their occurrence) are much more complex than in RCTs
- Four classification from patient perspective
  - E1: Discontinuation due to ***safety*** concerns
  - E2: Discontinuation due to ***lack of efficacy/effectiveness***
  - E3: ***Behavior-related*** discontinuation, e.g., patient preference, inconvenience of use, recommendation by a friend, physician-patient relationship
  - E4: ***Non-behavior-related*** discontinuation, e.g., insurance change, related to moving, developing new contradict conditions, improvement of health conditions, participating RCT, death
- Multiple ICEs may occur at different time points and chronological order, exact reasons of occurrence may not be known

Qu et al (2021). Defining estimands using a mix of strategies to handle intercurrent events in clinical trials. Pharmaceutical Statistics 20 (2), 314–323.

Attribute of ICEs – Similarities & Differences

Similarities/ differences	TCTs	RWE studies
Similarities	*Intercurrent events (ICEs)* • ICEs and strategies to handle them are pre-specified	
Differences	• Product-induced ICEs are generally of more interest in product development • Five strategies to handle ICEs as described in E9(R1)	• More diversified ICEs (than those in TCT) may occur and they can be part of treatment strategies • Pattern of ICE occurrence may be more complex • Patient behaviors may impact the use of a product

Estimand in RW Studies – Summary

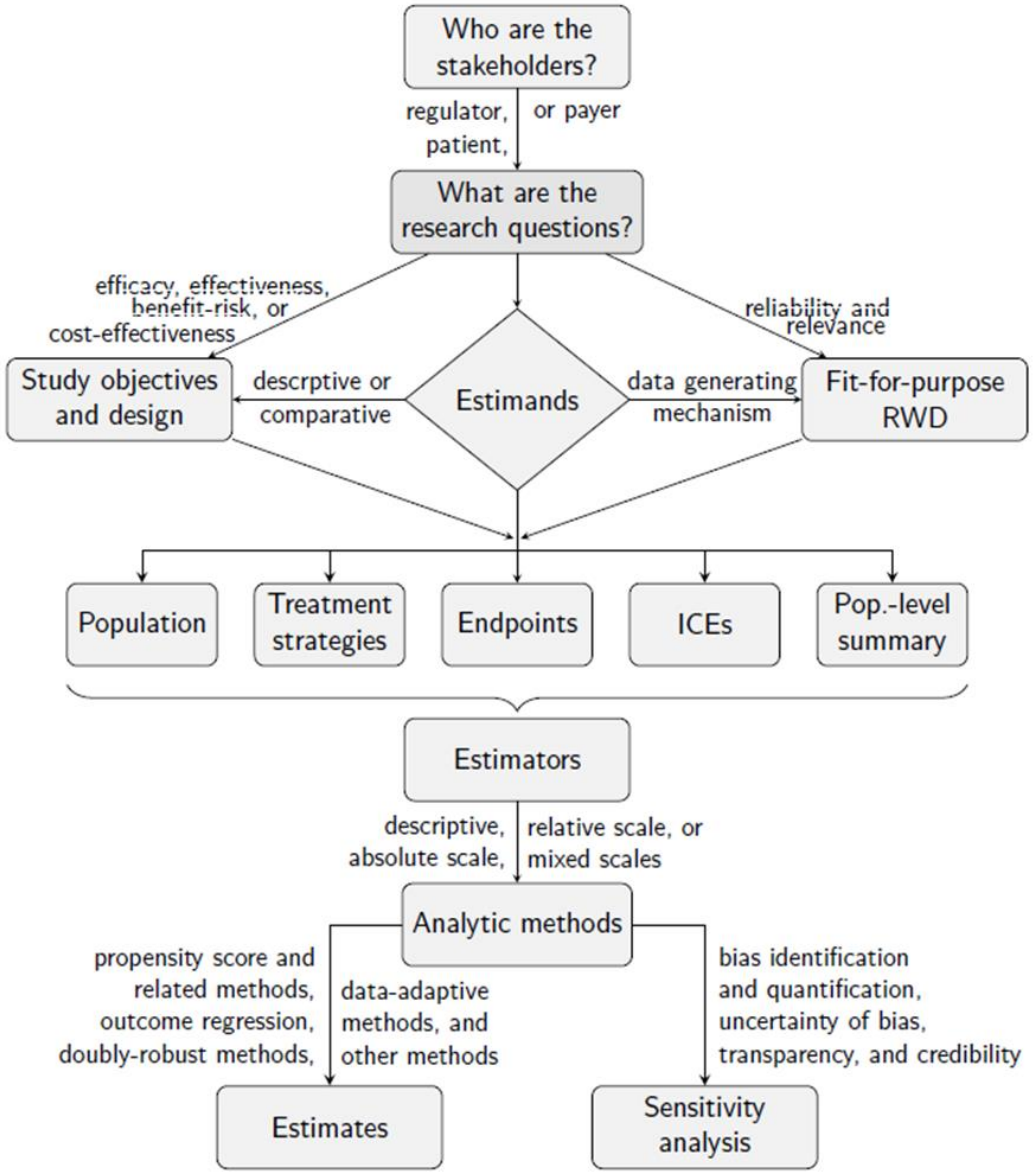
- Commonly used population-level measurements
  - Incidence rate and response rate
  - Comparative, e.g., absolute or relative difference
  - Multiple endpoints to quantify different aspects
- Summaries in RCT are usually obtained through simple statistical techniques (e.g., Least-squared means) or models (e.g., Cox model)
- RW studies commonly employ ***causal inference framework*** to account for measured and unmeasured confounding
  - Validity of some causal assumptions may not be validated but their impact can be explored via sensitivity analysis

Attribute of Summary – Similarities & Differences

Similarities/ differences	TCTs	RWE studies
Similarities	*Population-level summary* • Summary measures are pre-defined in study protocol • The summary measures can be descriptive or comparative, followed by sensitivity analyses	
Differences	• Simple statistical methods are often used to estimate the estimands • Results bear statistical interpretation	• Causal methods are often used to account for issues with non-randomization • Results can be interpreted causally if causal assumptions hold

Roadmap to Choose Appropriate Estimand:

– Who are stakeholders
  - Regulatory: efficacy, safety, benefit-risk
  - Payers: effectiveness, cost effectiveness
  - Patients: precision medicine
– What are research questions
– What are study objectives and designs
– What are fit-for-purpose RWD
– What are treatment regimes of interest
– What are possible ICEs
– How to address ICEs



Outline

- Introduction
- General considerations in defining estimand for RW studies (RWSs)
  - Similarities and differences between RCT and RWS
  - Roadmap for defining estimand
- **Critical assessment of case studies under estimand framework**
- **Conclusions**

Example I: Tafasitamab in Diffuse Large B-Cell Lymphoma

- Diffuse large B-cell lymphoma (DLBCL) is the most common high-grade non-Hodgkin lymphomas (NHLs). The first-line standard of care regardless of stage is the combination therapy R-CHOP
- Majority of relapsed or refractory (R/R) DLBCL patients are not eligible to receive intensive immunochemotherapy or autologous stem cell transplantation (ASCT) and have survival times ranging from 6-12 months
- Tafasitamab is an Fc-modified antibody that binds to CD19 antigen. It received the designations of fast-track review, orphan drug and breakthrough therapy.
- Its **combination** with lenalidomide received accelerated approval from FDA for the treatment of adult R/R DLBCL ineligible for ASCT in 2019

He et al (2023). Applications using real-world evidence to accelerate medical product development. *Springer*, book chapter in “Real-World Evidence in Medical Product Development”.

Tafasitamab Studies in Submission Package

- The approval is based on the open-label, single-arm, Phase 2 L-MIND study for the drug combination using overall response rate (ORR) and duration of response (DOR)
  - 71 patients out of 81 enrolled had confirmed DLBCL, received at least one dose of both drugs and formed the primary efficacy analysis population
- Contribution in efficacy effect from tafasitamab was confirmed by Phase 2a study MOR208C201
  - 35 patients received the single agent of tafasitamab
- A retrospective observational cohort study MOR208C206 (RE-MIND) included patients on single agent lenalidomide in comparable patient population
  - RE-MIND data was retrospectively collected from health records in academic hospitals, public hospitals and private practice in North America, Europe and Asia Pacific region with eligibility criteria mimics that of L-MIND
  - Primary endpoint follows similar definition which was best ORR as assessed by the investigator

FDA Feedback for Tafasitamab Real-World Study RE-MIND

- Population comparability
  - Only patients from comparable geographic regions and relevant initial dose of lenalidomide at index date should be included
- Endpoint quality
  - Differences in type of data being collected, covariates (measured or unmeasured)
  - Validity of outcome assessment
  - Amount of missing and duration of follow-up
  - Clinically important covariates should be included comprehensively
  - Imputation of missing data could not be accepted for the purpose of estimating propensity score.
- Analytic method to account for confounding and handling of ICE
- Evidence to support RWD collection being adequate, accurate, and non-differential need to be demonstrated

Revisions to Incorporate FDA Feedback

- Population comparability:140 out of 524 patients fulfilled the criteria
  - Only study sites from EU and US were selected to be consistent with L-MIND
  - Only patients initiating a lenalidomide dose of 25 mg/day were included.
  - Only patients with complete data on nine prespecified baseline covariates of clinical importance were included
- Endpoint validity
  - Outcome of ORR was validated for a subset of patients by an independent committee
  - To enable accurate assessment of response rate, all patients were required to have a minimal 6-month follow-up
- Intercurrent event (ICE) handling
  - To address the treatment change ICE, the ORR status has to be assessed between lenalidomide initiation and starting a new anti-DLBCL medication or death – while on treatment strategy
- Multiple sensitivity analyses were included to assess the robustness of results, e.g., adoption of doubly robust method and address residual imbalance in addition to the propensity score matching
- All 76 patients from L-MIND were successfully matched with 1:1 ratio (Zinzani et al 2021)
  - Best ORR was 67.1% (95% CI: 55.4%-77.5%) for the combination therapy versus 34.2% (95% CI: 23.7%-46.0%) in the lenalidomide monotherapy
  - Among patients who responded, DOR was 20.5 versus 6.6 months in the combination and monotherapy cohorts, respectively. Sensitivity analyses confirmed the findings from primary analyses.

Example II: Predicting CAROLINA Trial with RW Study

CAROLINE Trial: Non-inferiority of DPP-4 linagliptin vs glimepiride on CV outcome (Rosenstock 2019)

- Population
  - Adult patients with type 2 diabetes and elevated cardiovascular risk (N=6033)
- Treatment
  - 5 mg of linagliptin once daily (n = 3023)
  - 1 to 4 mg of glimepiride once daily (n = 3010), in addition to usual care
- Endpoints
  - Primary: time to first occurrence of non-fatal MI, stroke or CV death
  - Secondary: HbA1c reduction, occurrence of hypoglycemia
- Summary: hazard ratio for time-to-event
- ICEs: prematurely discontinuing study drug and intensifying glycemic treatments
  - ***Treatment policy*** strategy was used to address ICEs (median follow-up of ***6.3 years***)

Predicting CAROLINA Trial using RW Studies (Cont'd)

Data Source: US claims database of Medicare, MarketScan, Optum (Patorno 2019)

- Population
  - Mimicking CAROLINA criteria (***adapted as necessary*** with available data elements)
  - 1:1 propensity score matched patients initiating linagliptin or glimepiride (***N= 48,262***)
  - Excellent balance for ≥ 120 confounders
- Endpoints
  - Non-fatal MI or stroke, CV death ***as recorded*** in health insurance claims databases
  - Secondary: HbA1c, hypoglycemia as available in claims databases
- ICEs: prematurely discontinuing study drug and intensifying glycemic treatments
  - ***On-treatment strategy*** was used, i.e., patients were followed until treatment discontinuation or switch to a comparator
  - Leading to a median follow-up time of ***~7 months***

Predicting CAROLINA Trial using RW Studies (Cont'd)

CAROLINA Trial

- CV Endpoints: HR=0.98 (0.84, 1.14)
- Hypoglycemia: HR=0.23 (0.21, 0.26)

RW Study

- CV Endpoints: HR=0.91 (0.79, 1.05)
- Hypoglycemia: HR=0.42 (0.32, 0.56)

This RW Study vs. CAROLINA Trial

- Includes US patients only
- Older patients (mean of 70 vs 64 years)
- Shorter follow-up time (median of ~7 months vs 6.3 years)
- Different definitions for hypoglycemia and CV events
- HbA1c is available for a small subset of population

Conclusions

- RW studies play a critical role in clinical development and life-cycle management to fulfil evidence requirements for regulatory, HTA bodies and other stakeholders
- Estimand provides a framework for both RCTs and RW studies
  - Five attributes in RW studies are much more complicated which demand thoughtful design and sophisticated analytic approaches
  - Provide general considerations and roadmap for choosing appropriate estimand in RW studies
- RW studies address wide range of research questions and employ diverse designs, many are not well served by the current estimand framework
- In addition, fit-for-purpose RW data source selection, causal inference accounting for confounders, computational infrastructure and transparent process are critical for robust RWE generation

PANEL DISCUSSION

Estimands in Real-World Evidence Studies

Note: 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

Birol Emir Presentation

Why is estimand framework not still used widely?

1. Conceptual Shift: The estimand framework requires a shift in thinking: from focusing primarily on treatment effect estimation to precisely defining the treatment effect of interest in a structured way (population, variable, intercurrent events, summary measure). This level of abstraction is not traditionally part of clinical training.

2. Complexity of Intercurrent Events: Concepts like handling intercurrent events (e.g., treatment discontinuation, rescue medication) involve nuanced choices (e.g., treatment policy vs. hypothetical strategies) that are often unfamiliar to clinicians.

3. Terminology Barrier: Words like estimand, intercurrent events, strategy (in this context), and summary measure sound statistical and abstract, creating psychological distance.

4. Limited Practical Examples: Many trial protocols have not fully operationalized estimands in ways that resonate with clinical practice, limiting clinicians' exposure to tangible examples.

Statisticians' Role in the Gap

• Over-technical communication: Statisticians often present the estimand framework using statistical jargon, without enough contextual translation for clinicians.

• Under-engagement: In many settings, statisticians have not adequately involved clinicians during the protocol development stage where estimands should be jointly defined.

• Inward focus: There has been a tendency to implement estimands as a compliance or regulatory checkbox rather than a clinical conversation tool.

Solutions

CLINICIAN-FRIENDLY TRAINING

FRAME ESTIMANDS USING CLINICAL CASE STUDIES AND PATIENT SCENARIOS, FOCUSING ON THE WHY BEHIND EACH STRATEGY CHOICE.

EARLY ENGAGEMENT

STATISTICIANS SHOULD BRING CLINICIANS INTO THE ESTIMAND DISCUSSION EARLY — NOT AS REVIEWERS, BUT AS CO-CREATORS.

VISUAL AND INTUITIVE COMMUNICATION

USE DIAGRAMS, TIMELINES, AND PATIENT JOURNEYS TO EXPLAIN HOW DIFFERENT ESTIMAND STRATEGIES AFFECT INTERPRETATION.

REGULATORY AND HTA INCENTIVES

HIGHLIGHT HOW A WELL-DEFINED ESTIMAND SUPPORTS CLAIMS, LABELING, AND PAYER COMMUNICATION TO MAKE IT MORE RELEVANT FOR CLINICAL LEADERS.

- The estimand framework is not widely understood by clinicians because of conceptual, educational, and communication gaps. Statisticians bear some responsibility for these challenges — especially in how the framework has been introduced and implemented. However, solving the problem requires a cultural shift across disciplines. Bridging this gap offers an opportunity to enhance trial relevance, regulatory clarity, and ultimately, patient-centered research.