FDA Clinical Investigator Training Course

Real-World Evidence

December 2023

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Objectives (& Outline) of Presentation

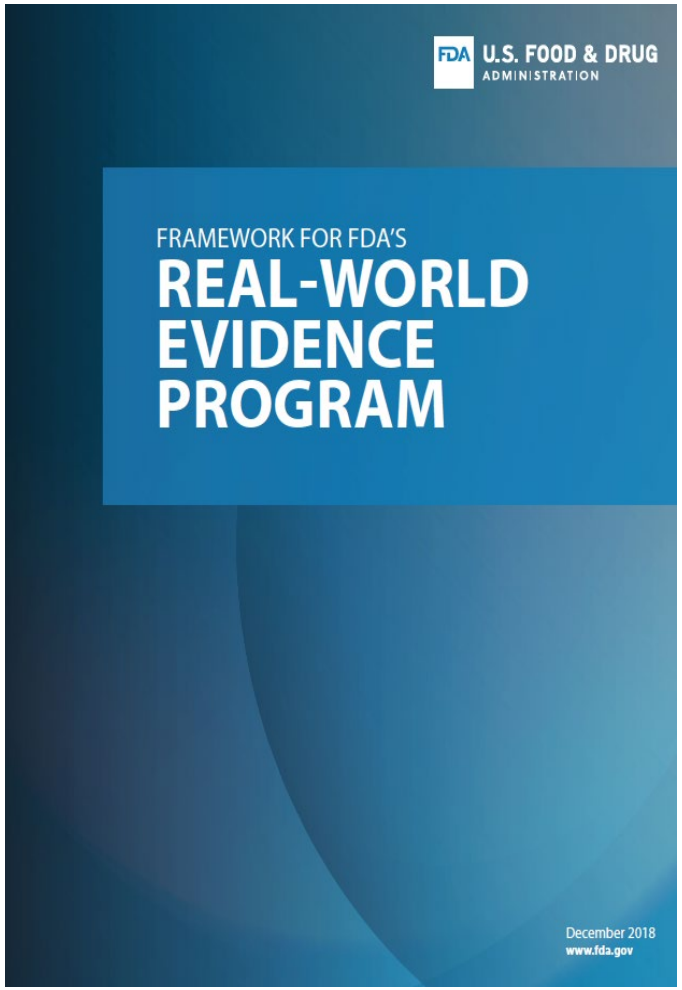
Attendees will be able to:

- **Describe the scope of FDA's Real-World Evidence (RWE) Program**
- **Recognize the intersection of scientific and legal/regulatory issues related to study design in the RWE era**
- **Interpret terms commonly used for study design in drug development**
- **Identify examples of "RWE" in drug approvals**

21st Century Cures Act of 2016

- **FDA established a program to evaluate the potential use of real-world evidence (RWE) to:**
  - **Support a new indication for a drug approved under section 505(c)**
  - **Satisfy post-approval study requirements**
- **Draft framework issued in December 2018:**
  - **Describe sources of RWE, challenges, pilot opportunities, etc.**
- **Draft guidance for industry issued in Sep, Oct, Nov, Dec 2021**
- **Standard for substantial evidence remains unchanged; commitments met for Prescription Drug User Fee Act (PDUFA) VI; new Advancing RWE initiatives in PDUFA VII**

FDA RWE Framework (2018)



- **Applies to Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), & Oncology Center of Excellence (OCE)**

- **Multifaceted program to implement RWE:**
  - **internal processes**
  - **external stakeholder engagement**
  - **demonstration projects**
  - **guidance development**

https://www.fda.gov/media/120060/download

FDA 'Real-World' Definitions (2018)

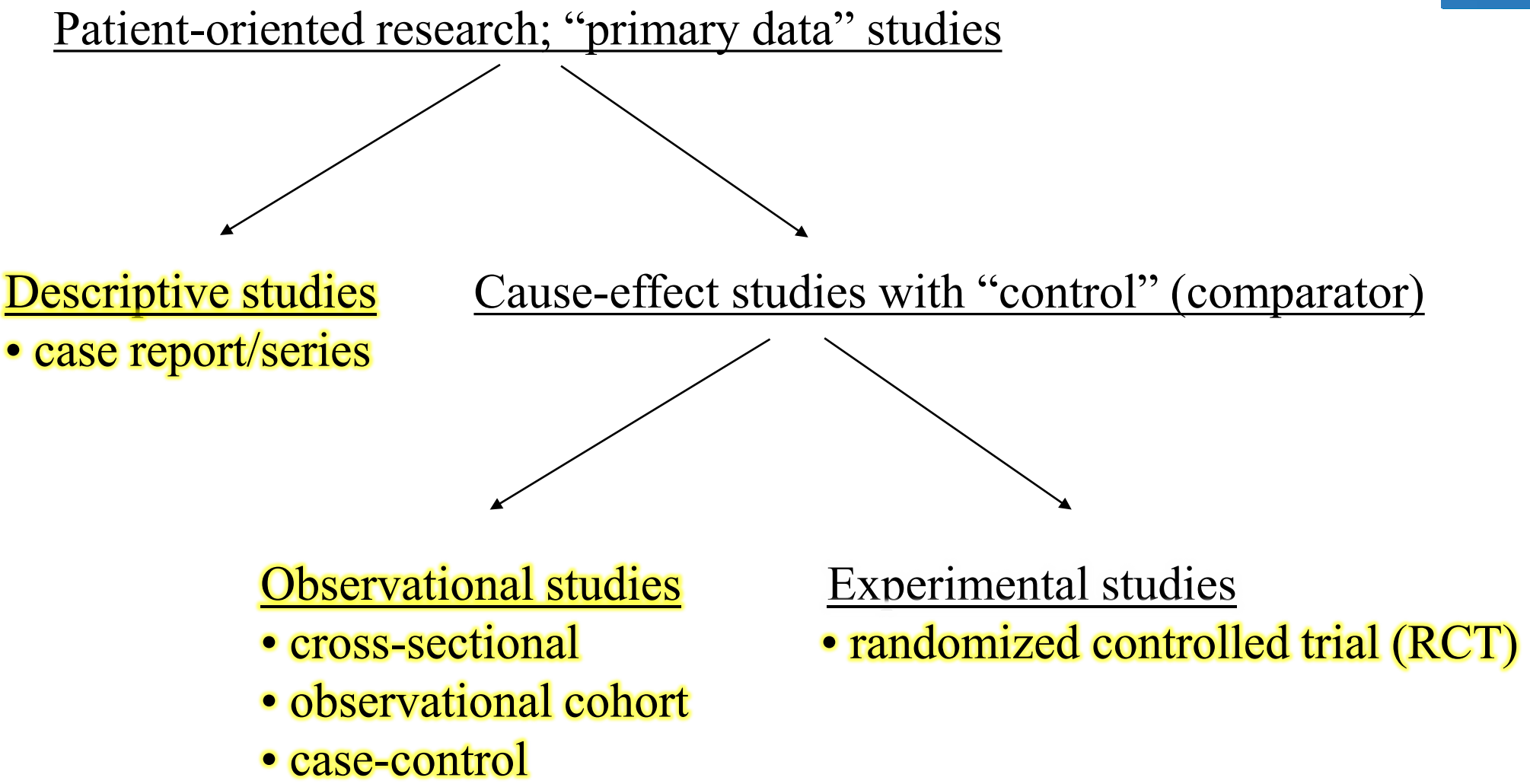
Real-World Data (RWD) are data relating to patient health status and/or delivery of health care **routinely collected from a variety of sources**

- **electronic health records (EHRs)**
- **medical claims data**
- **product and disease registries**
- **data from digital health technologies in non-research setting**
- **other data sources that can inform on health status, such as questionnaires**

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

Generated using various study designs—including but not limited to **randomized trials (e.g., pragmatic clinical trials)**, externally controlled trials, and observational studies

Traditional Terms for Study Design



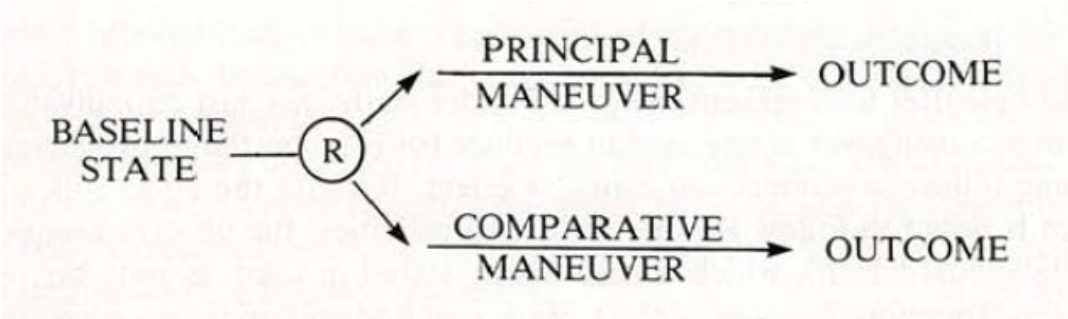
Concato *J Law and Policy* 2004;XII:489-507

Attributes of Randomized Studies

Schematic of drug-outcome associations for safety & effectiveness:

- **Patients at baseline → receipt of drug or comparator → evaluation of outcome**

Example of randomized trial:



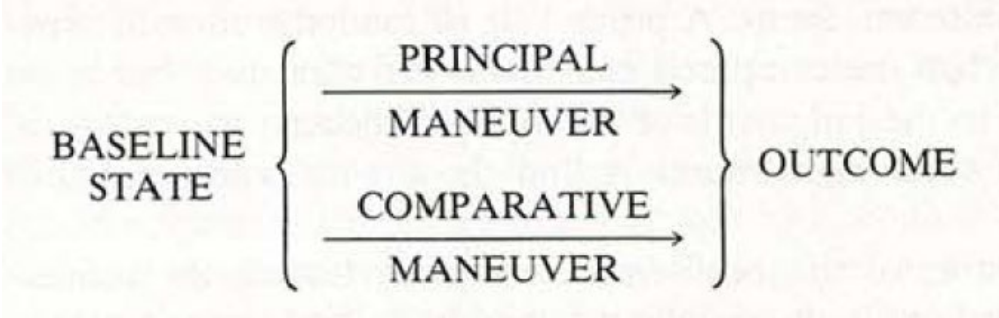
- **Is the validity of the comparison affected by source(s) of methodologic bias?**
  - randomization promotes balance at baseline to help minimize bias—and for decades has been the preferred method for evaluating drug safety/efficacy

Attributes of Non-Randomized Studies

Schematic of drug-outcome associations for safety & effectiveness:

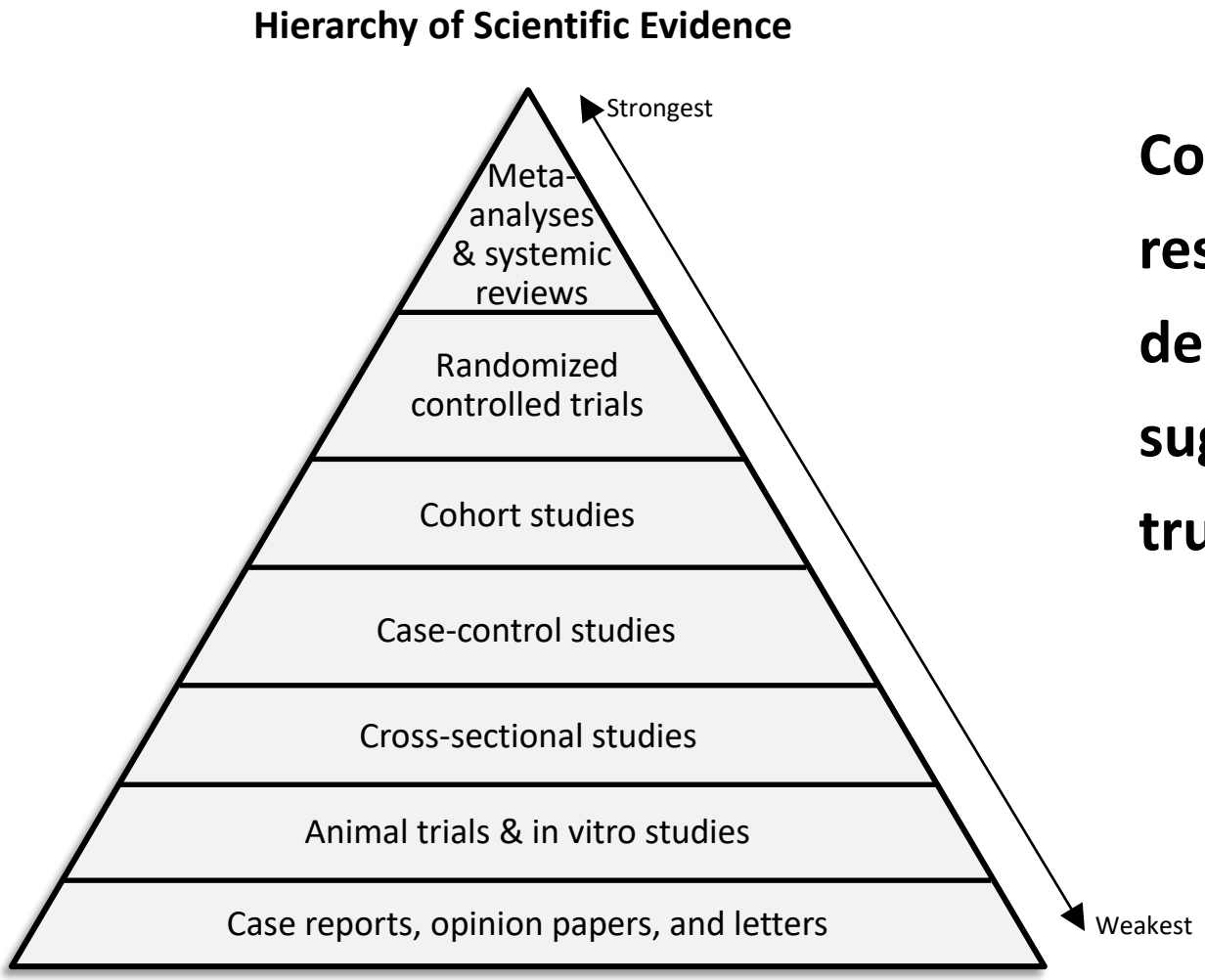
- **Patients at baseline → receipt of drug or comparator → evaluation of outcome**

Example without randomization:



- **Is the validity of the comparison affected by source(s) of methodologic bias?**
  - **"observational" studies need to address baseline imbalances to minimize bias (e.g., account for drug of interest given preferentially to patients more likely to have better or worse outcomes)**

Hierarchies of Study Design



Adapted from Sackett Evidence-Based Medicine, BMJ 1996

Comment: Simplistic hierarchies of research design evolved in the 1990s, designating RCTs as "gold standard" and suggesting other study designs are not trustworthy

Contemporary Opinions Regarding Study Design

'The Magic of Randomization versus the Myth of Real-World Evidence'

"[…] because of the potential biases in observational studies, such studies cannot generally be trusted […] the replacement of randomized trials with nonrandomized observational analyses is a false solution to the serious problem of ensuring that patients receive treatments that are both safe and effective." (Collins, *New Engl J Med* 2020;382:674)

'Misunderstanding randomized controlled trials'

"We argue that any special status for RCTs is unwarranted. Which method is likely to yield a good causal inference depends on what we are trying to discover as well as on what is already known." (Deaton & Cartwright, *Soc Sci Med*, 2018;210:2)

Study Design in the Era of Real-World Evidence

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

John Concato[1] | Peter Stein[2] | Gerald J. Dal Pan[3] | Robert Ball[3] | Jacqueline Corrigan-Curay[1]

In the current era of RWE, the FDA is evaluating whether and how observational studies intended to evaluate efficacy can contribute persuasive results from scientific and regulatory perspectives. In this context, a "randomized trial versus observational study" dichotomy is overly simplistic as short hand for strength of study design to support causal inference. Clarity is needed regarding interventional or noninterventional design, primary collection or secondary use of data, and characteristics of comparison group(s), as well as an assessment of prognostic determinism for the corresponding cause-effect association.

Pharmacoepidemiol Drug Saf. 2020;29:1514–1517

Comments on ‘Big Data’

Origin: term appeared in computer science literature during 1990s, often referring to data too large to be stored in then-conventional storage systems

Contemporary usage: “It’s unclear when ‘big data’ became the buzzword of the day. Or, really, what it means.” (Fallik *Health Aff (Millwood)* 2014;33:1111)

Perspective: integration and analysis of large-scale data has always been integral to epidemiology, but modern technology has increased quantity and forms of available data as well as the speed to merge and manipulate data

Comments on 'Real-World Evidence'

Origin: "real world" is a non-specific modifier; "real-world data" (RWD) and "real-world evidence" (RWE) appeared in medical literature as of the 1970s or earlier, in various contexts

Contemporary usage: RWD and RWE have formal regulatory definitions

Perspective: older epidemiologic terms were sufficient, but emergence of big data and enactment of 21st Century Cures has led to (sometimes confusing) use of different taxonomies for study design

Example: RWE study ≠ observational study; specific details are needed to classify study design

Contemporary Terms for Study Design

Interventional study (clinical trial) patients assigned to treatment by study protocol

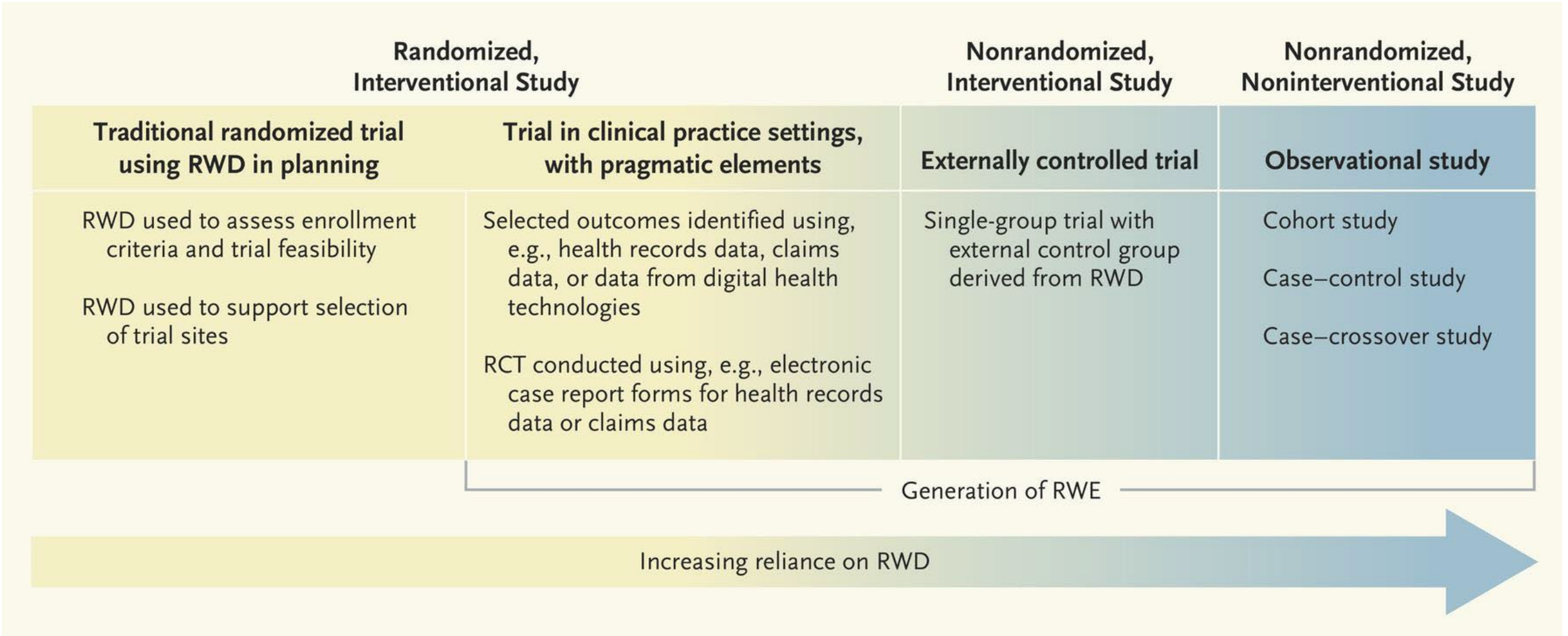
Non-interventional (observational) study patients receive treatment during routine medical care

A study can have components of both, for example, an externally controlled trial with interventional treatment arm & non-interventional control arm

Real-World Evidence — Where Are We Now?

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

FDA



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

Recent FDA Publication on Real-World Evidence

COMMENTARY

WILEY

When can real-world data generate real-world evidence?

Motiur Rahman[1] | Gerald Dal Pan[2] | Peter Stein[3] | Mark Levenson[4] | Stefanie Kraus[5] | Aloka Chakravarty[6] | Donna R. Rivera[7] | Richard Forshee[8] | John Concato[1,9]

Pharmacoepidemiol Drug Saf. 2023 Oct 19. doi: 10.1002/pds.5715. Online ahead of print.

Recent FDA Publication on Real-World Evidence (cont'd)

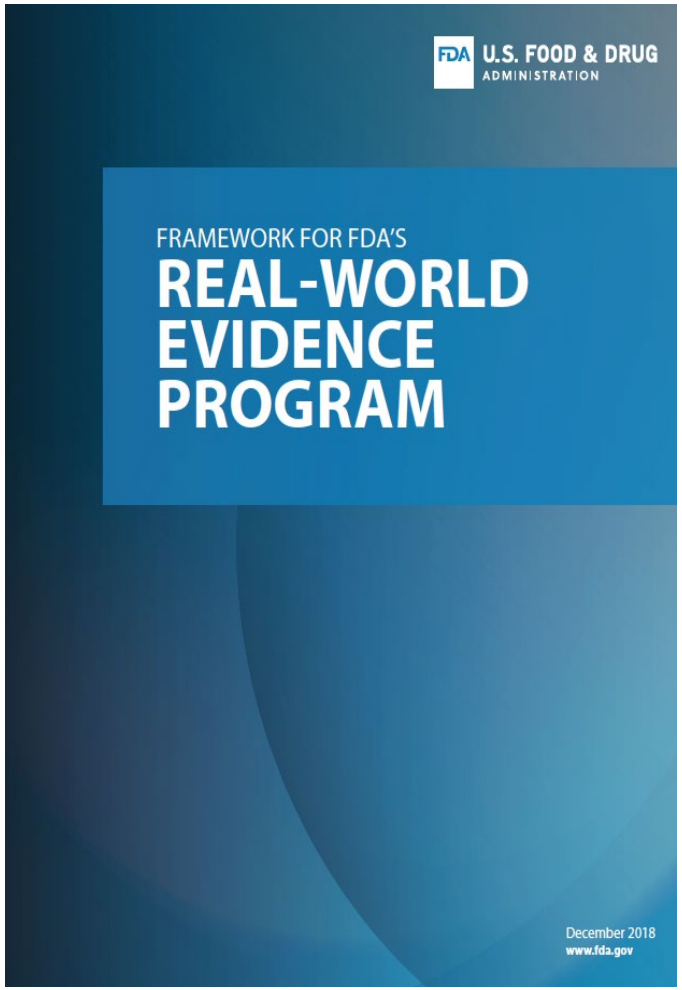
Pharmacoepidemiol Drug Saf. 2023 Oct 19. doi: 10.1002/pds.5715. Online ahead of print.

Study design	Is RWE generated? No	Yes
Interventional studies		
Randomized, controlled trials		
Real-world data (RWD) used to develop a study (e.g., to identify potential participants, select trial sites)	✓	
RWD used to assess impact of various enrollment criteria	✓	
Data from trial-provided digital health technology	✓	
Open-label extension studies not using RWD	✓	
RWD used for trial endpoint		✓
Data from digital health technology used in non-research settings		✓
Open-label extension studies including RWD		✓

Study design	Is RWE generated? No	Yes
Interventional studies		
Externally controlled trials		
Single-arm trial with summary level estimate as comparator	✓	
External control arm data* from a clinical trial	✓	
External control arm data* from a RWD source		✓
Non-interventional studies		
Observational cohort study		✓
Case–control study		✓
Case-crossover study		✓
Self-controlled case series		✓

*Data on a specific group of patients as a comparator

FDA RWE Framework (2018)



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- **Multifaceted program to implement RWE:**
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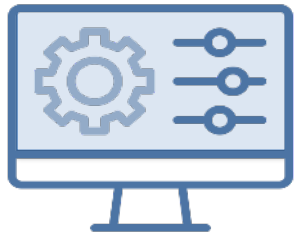
RWD/RWE Demonstration Projects – Categories & Examples

Data

- ‘OneSource’ project to improve quality of EHR data
- Unstructured EHR data project to increase scope of RWD

Study Design

- RCT-DUPLICATE trial emulations
- Statistical approach for trial designs w/ ‘hybrid’ control arms



Tools

- Evaluation of confounded treatment effects
- Targeted learning framework for causal effect estimation

Demonstration Projects

RCT-DUPLICATE – Publication

JAMA | Original Investigation

Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses
Results of 32 Clinical Trials

Shirley V. Wang, PhD, ScM; Sebastian Schneeweiss, MD, ScD; and the RCT-DUPLICATE Initiative

CONCLUSIONS AND RELEVANCE Real-world evidence studies can reach similar conclusions as RCTs when design and measurements can be closely emulated, but this may be difficult to achieve. Concordance in results varied depending on the agreement metric. Emulation differences, chance, and residual confounding can contribute to divergence in results and are difficult to disentangle.

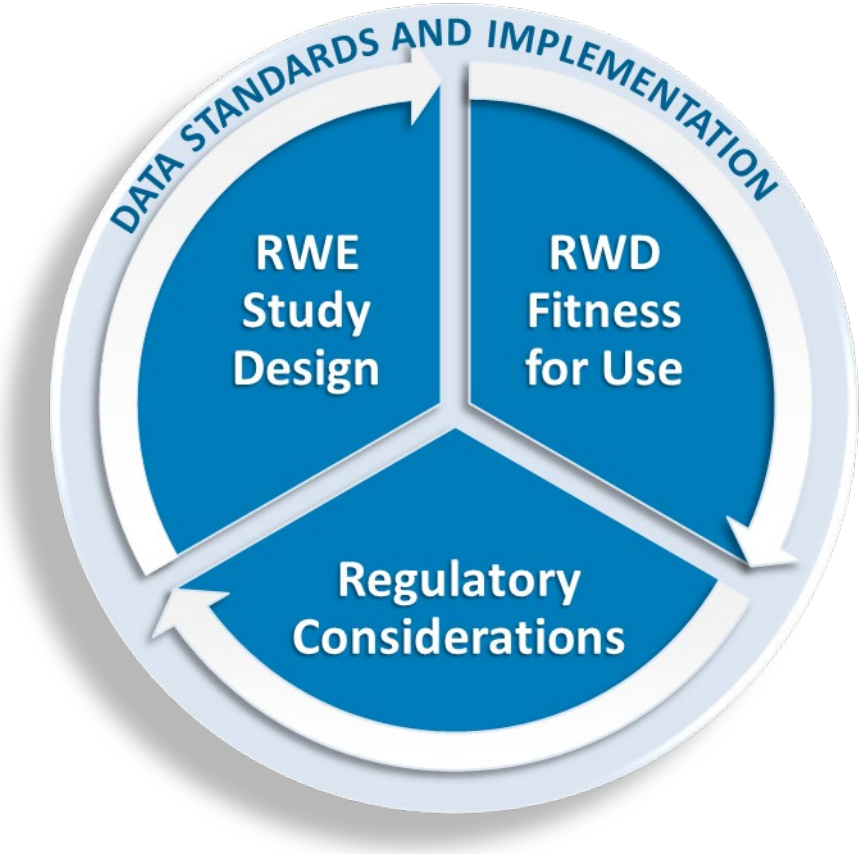
JAMA April 25, 2023 Volume 329, Number 16

FDA RWD/RWE Guidance (2021-2023)

Topic	Category	Status
EHRs and claims data	**Data considerations**	**draft issued**
Registry data	**Data considerations**	**draft issued**
Data standards	**Submission of data**	**draft issued**
Regulatory considerations	**Applicability of regulations**	**final issued**
Externally controlled trials	**Design considerations**	**draft issued**
Non-interventional studies	***Design considerations***	***in development***
RCTs in clinical practice settings	***Design considerations***	***in development***
Submitting RWE	**Procedural**	**final issued**

https://www.fda.gov/science-research/real-world-evidence/center-biologics-evaluation-and-research-center-drug-evaluation-and-research-real-world-evidence

FDA Approach to Evaluating RWE



Key considerations:

- **Whether the RWD are fit for use**
- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question**
- **Whether the study conduct meets FDA regulatory requirements**

New Indication for Prograf Based on RWE

- **Prograf® (tacrolimus) approved for prophylaxis of organ rejection in patients receiving liver transplants in 1994 (later for kidney & heart) based on RCT evidence, and the drug is used widely in clinical care**
- **RCTs not done for lung transplant, but sponsor (Astellas Pharma US) submitted supplemental New Drug Application to FDA with non-interventional 'RWE' study**
- **Study data and design were evaluated according to FDA standards**
- **Approval for preventing rejection/death in lung transplant granted 16 Jul 2021**

New Indication for Prograf Based on RWE (cont'd)

Data: US Scientific Registry of Transplant Recipients (SRTR) data on all lung transplants in US during 1999–2017; data collected w/ standard analysis files

Design: non-interventional (observational) treatment arm, compared to historical controls; analysis plan and patient-level data provided to FDA

Review: FDA determined this non-interventional study w/ historical controls to be adequate and well-controlled. Of note, outcomes of organ rejection and death are virtually certain without therapy, and the dramatic effect of treatment helps to preclude bias as explanation of results.

https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence

Representative Challenges with Use of RWE

Real-world data sources:

- data reliability and clinical relevance
- missing or “mistimed” data
- suitable capture of endpoint data
- need for linkage with other data sources

Design and interpretation of non-randomized studies:

- residual confounding
- problems with index date (“zero time”)
- use of inappropriate comparator

Conduct of non-randomized studies:

- protocol and analysis plan not *pre-specified*
- access to patient-level data and ability to inspect RWD sources

Summary

- **FDA Real-World Evidence Program is advancing as outlined in the agency's 2018 Framework for Real-World Evidence**
- **New terminology linked to emergence of "big data" and passage of 21st Century Cures Act is often used inconsistently; *randomized trials vs. observational studies* is an oversimplified dichotomy**
- **Older terms for study design in drug development are now joined by newer terms describing the same designs**
- **FDA approves drugs and biological products using "real-world evidence" based on existing regulations and evidentiary standards**

Knowledge Check

True or false?

- **Randomized trials are not within the scope of real-world data/real-world evidence**
- **Real-world evidence studies for effectiveness are held to a different (i.e., lower) evidentiary standard than randomized trials**