*FDA Clinical Investigator Training Course*

# Real-World Evidence

**December 2022**


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# Disclaimer

- **Views and opinions expressed are those of the presenter and should not be attributed to the Food and Drug Administration**
- **No conflicts of interest exist related to this presentation**
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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- **Draft guidance for industry issued in Sep, Oct, Nov, Dec 2021**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 'Real-World' Definitions (2018)

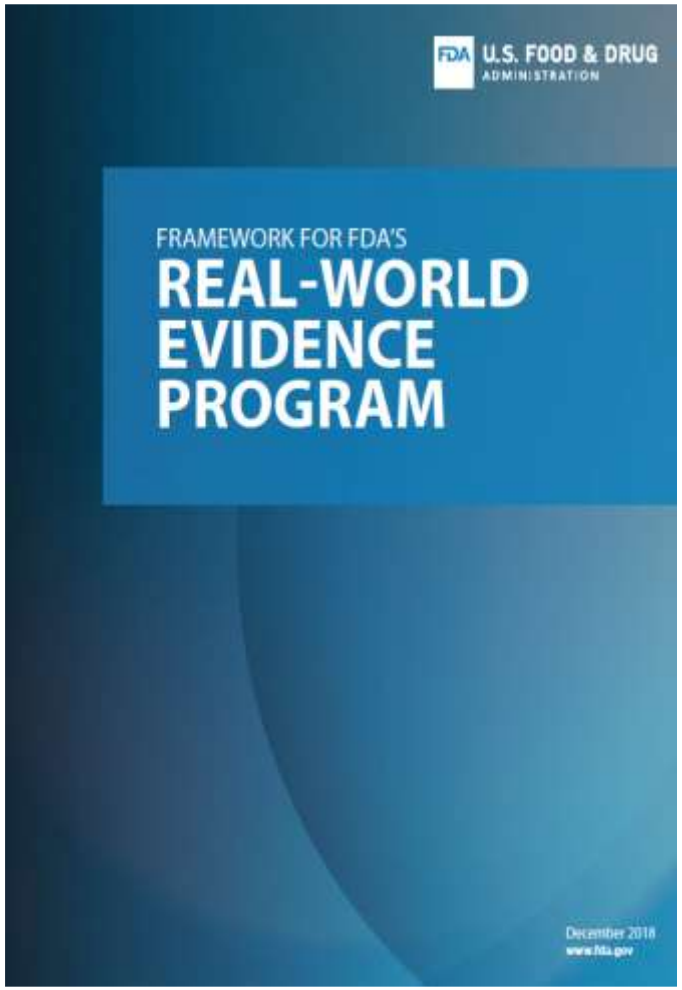
**Real-World Data (RWD)** are data relating to patient health status and/or delivery of health care **routinely collected from a variety of sources**

- **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

# 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 Draft RWE Guidance – Sep-Dec 2021

Guidance for Industry

*DRAFT GUIDANCE*

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

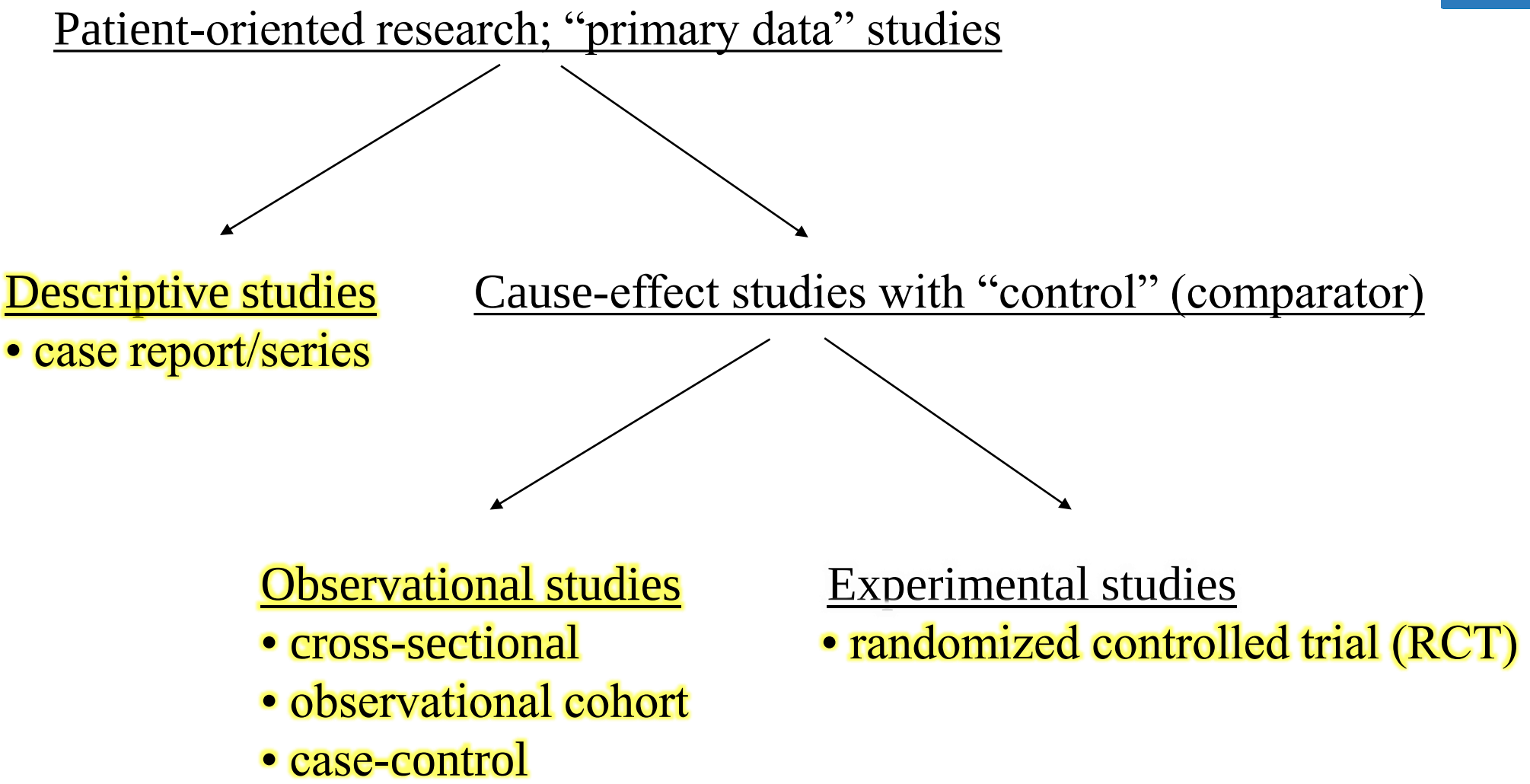
Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

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

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

# Traditional Terms for Study Design



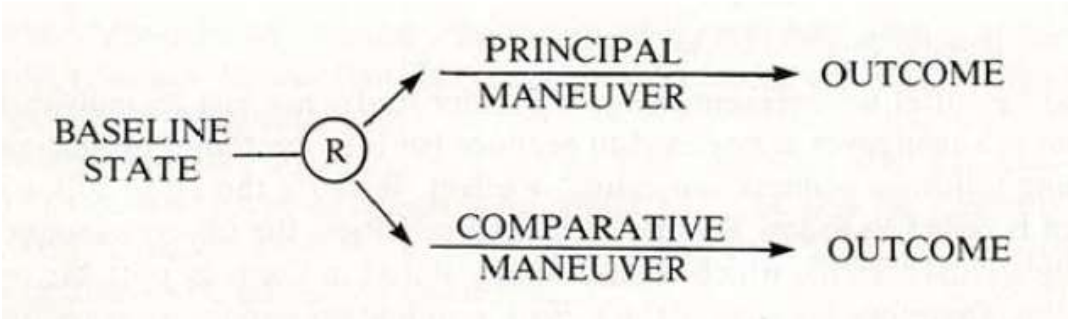

Concato *J Law and Policy* 2004;XII:489-507

# 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:**



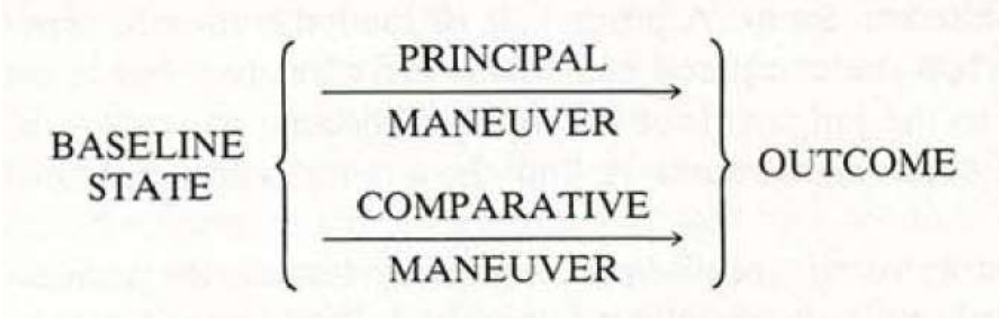

- **Is the validity of the comparison affected by source(s) of methodologic bias?**
  **- randomization promotes balance at baseline to help minimize bias—and for decades has been the preferred method for evaluating drug safety/efficacy**

# Attributes of Non-Randomized Studies

**Schematic of drug-outcome associations for safety & effectiveness:**

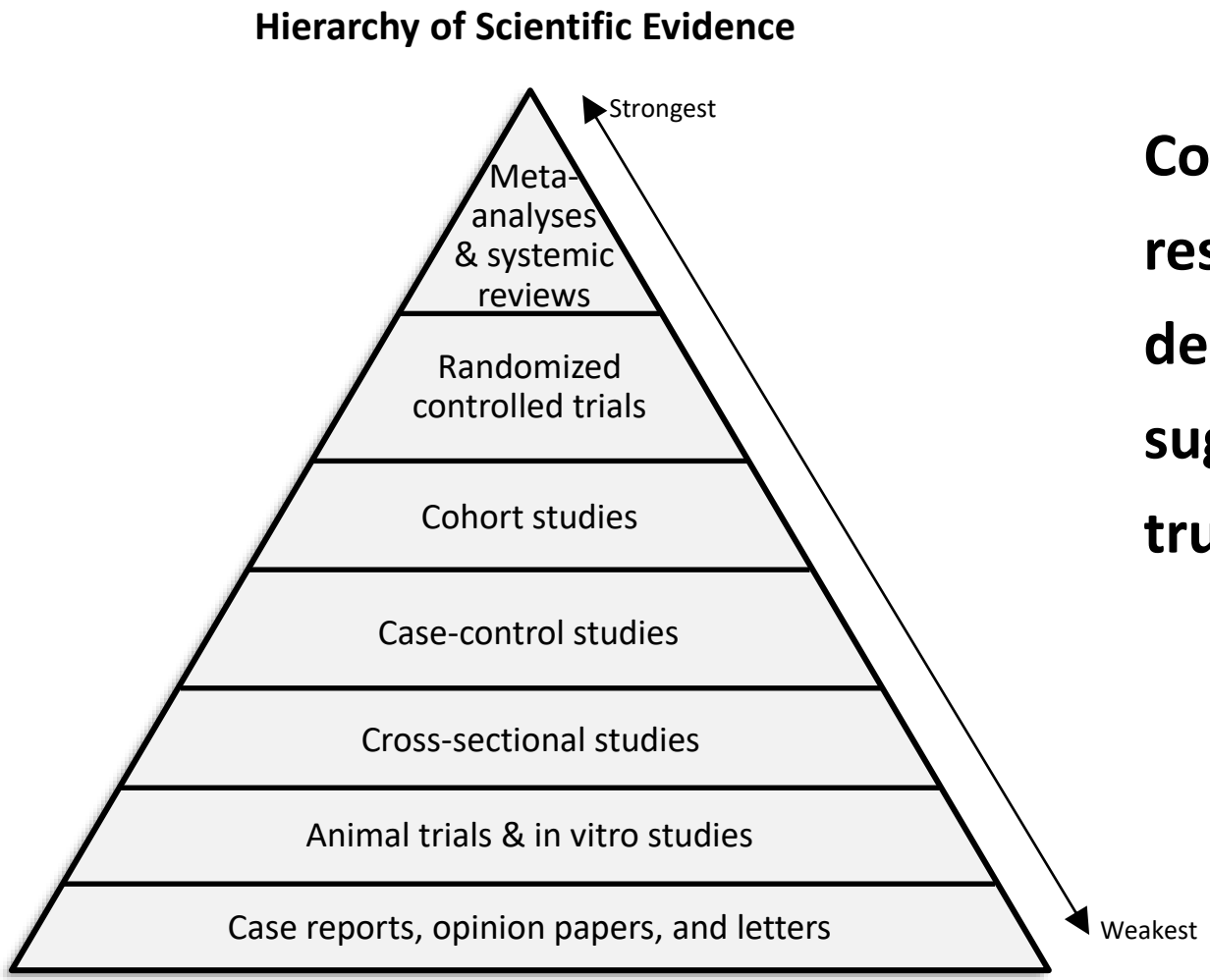
- **Patients at baseline → receipt of drug or comparator → evaluation of outcome**

**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

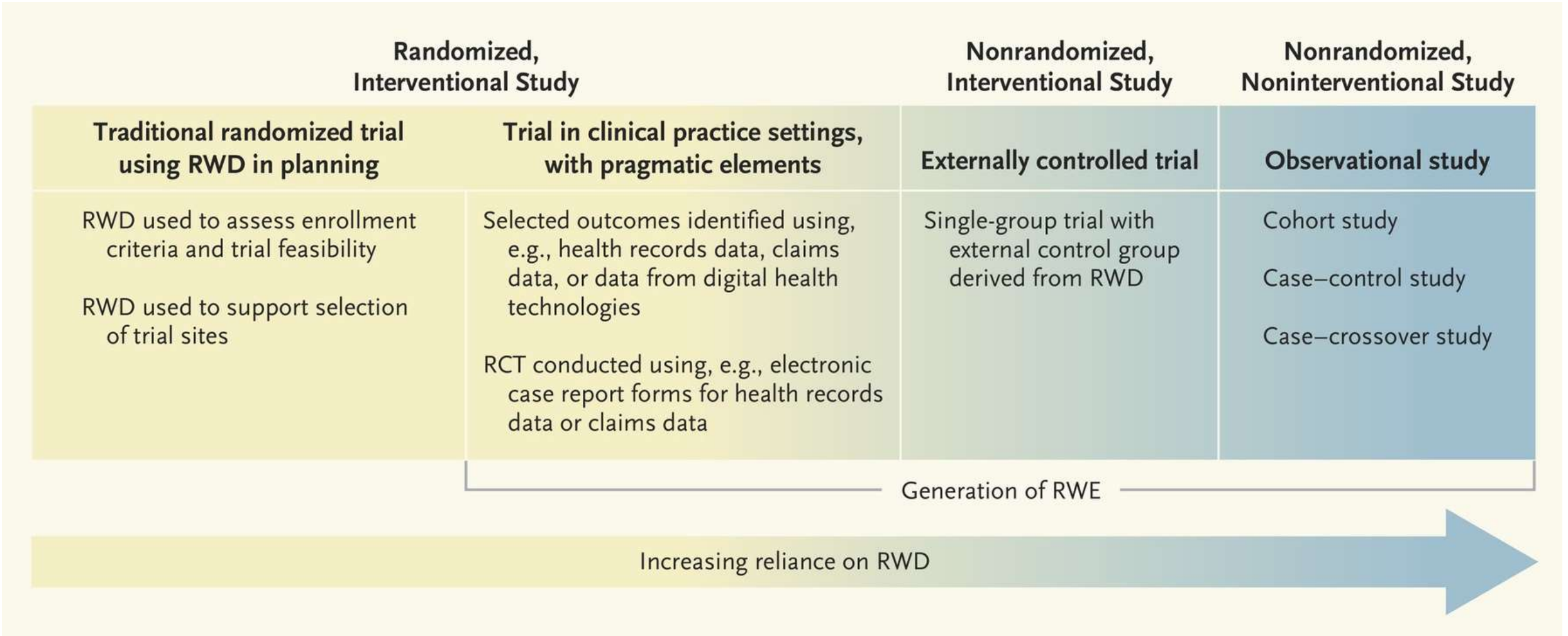
# Contemporary Terms for Study Design

- ***Interventional study*** **(*clinical trial*) – study in which patients are assigned to ≥1 treatment groups, according to a study protocol, to evaluate the effects of a treatment of interest on subsequent health-related outcomes**
  - **e.g., *randomized controlled trials*, *single-arm trials***
- ***Non-interventional*** **(*observational) study* – study in which patients are not assigned to a study arm according to a research protocol, but instead receive the drug of interest during routine medical practice**
  - **e.g., *observational cohort studies* (patients identified based on drugs received, with subsequent outcomes identified), or *case-control studies* (patients identified based on health outcomes, with antecedent drug use determined)**
- **Combination of interventional & non-interventional components**
  - **e.g., *externally controlled trials* (clinical trial arm & arm from other data source)**

# Real-World Evidence — Where Are We Now?

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

FDA

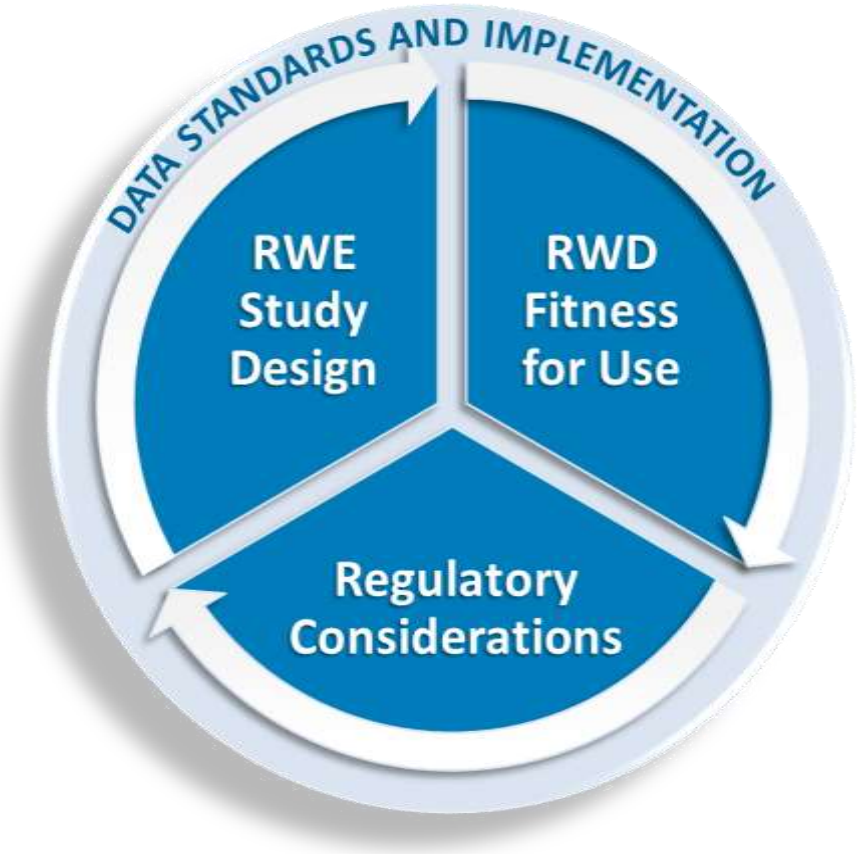



**Reliance on RWD in Representative Types of Study Design.**

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

# 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**

# RWE Informs Effectiveness When Fit-for-Purpose

| DRUG | INDICATION | APPROVED | DATA |
|---|---|---|---|
| **Carbaglu** *(carglumic acid)* | Treatment of NAGS deficiency | 2010 | ▪ Retrospective, unblinded **case series compared to historical control group** |
| **Voraxaze** *(glucarpidase)* | Treatment of MTX toxicity | 2012 | ▪ Approval based on open-label **NIH expanded access protocol** |
| **Blincyto** *(Blinatumomab)* | Treatment of Acute Lymphoblastic Leukemia | 2014 | ▪ Data from single-arm trial compared to patient-level **data from chart review of patients at EU and US sites** |
| **Vistogard** *(uridine triacetate)* | Overdose of chemotherapy drugs 5-fluorouracil (5-FU) | 2015 | ▪ Data from single-arm, open-label expanded access trials **compared to case-history control** |

List not exhaustive

**Bold** = RWD

# RWE Informs Effectiveness (cont'd)

| DRUG | INDICATION | APPROVED | DATA |
|---|---|---|---|
| **Defitelio** *(defibrotide sodium)* | Severe hepatic veno-occlusive disorder | 2016 | ▪ Two prospective clinical trials and an **expanded access study** |
| **Lutathera** *(lutetium 177 dotate)* | Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) | 2017 | ▪ Clinical trial and patients in open-label, single-arm, single institution study that started as an **expanded access program** |
| **Zostavax** *(Zoster vaccine Live)* | Prevention of herpes zoster (shingles) in persons 50 years of age and older | 2018 | ▪ Prospective, observational cohort study of persons >=50 years of age using **electronic health records in Kaiser Permanente Northern California** |
| **Zolgensma** *(onasemnogene abeparvovec-xioi)* | Patients <2 years of age w/ spinal muscular atrophy and a specific mutation | 2019 | ▪ Data from a single-arm trial compared to data in an external control group based on a **natural history study** |

List not exhaustive

**Bold** = RWD

# 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

# 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 applicable/existing regulations**

# 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**