

# **Real-World Evidence: Another Tool in the Toolbox**

## **EBHC Conference The Ecosystem of Evidence 26 October 2023**

**John Concato, MD, MS, MPH**

**Associate Director for Real-World Evidence Analytics, Office of Medical Policy,  
Center for Drug Evaluation and Research, U.S. Food and Drug Administration**

**Adjunct Professor of Medicine, Yale University School of Medicine**

- **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**
- **Mention of a commercial product should not be construed as actual or implied endorsement**

- **Recognize historical context leading to current use of “real-world evidence” and related terminology**
- **Understand main components of FDA’s Real-World Evidence Program**
- **Identify challenges and potential contributions of using real-world data (RWD) and real-world evidence (RWE) in drug development**
- **Describe the impact of the COVID-19 pandemic on evidence generation**

# Outline of Presentation

- **Introduction**
- **Everything old is new again**
- **Where are we now?**
- **RWE and COVID-19**
- **Summary**

# Outline of Presentation

- **Introduction**

# 21st Century Cures Act (2016) – Real-World Evidence



- FDA established a program to evaluate the potential use of real-world evidence to:
  - support a new indication for an already approved drug
  - satisfy post-approval study requirements
- FDA issued a draft framework in December 2018:
  - describes sources of RWE, challenges, opportunities, etc.
- Guidance for industry on RWD/RWE topics published as of 2021, and additional guidance in development
- U.S. FDA standard for effectiveness remains unchanged

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

# 'Real-World' Definitions (from 2018 FDA Framework)

**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

# Emergence of Real-World Evidence

## Interest in real-world evidence (RWE) can be attributed to:

- Improved access to, and rapid analysis of, information in the era of big data
- Research showing observational studies can generate results similar to those of randomized controlled trials (RCTs)
- 21<sup>st</sup> Century Cures Act mandating U.S. Food and Drug Administration (FDA) evaluate the potential use of RWE for medical product approvals
- Popularity of “real-world” as a term; other factors, including COVID-19

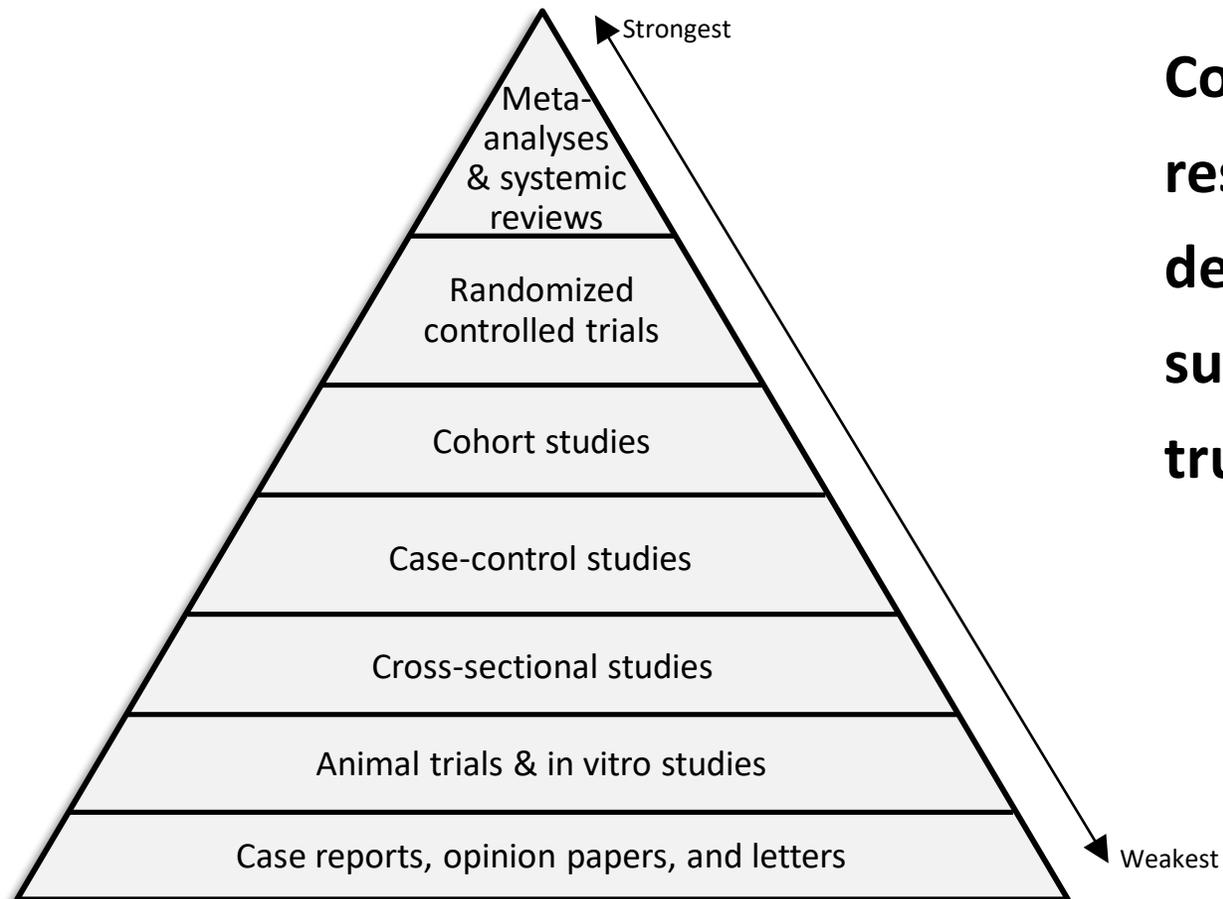
*Note: Confusion exists when using the terms “RWD” and “RWE,” but most of the underlying methodology isn’t new*

# Outline of Presentation

- Introduction
- **Everything old is new again**

# Background – Hierarchy of Study Design

Hierarchy of Scientific Evidence



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

# Observational Studies – As of 2000

## A COMPARISON OF OBSERVATIONAL STUDIES AND RANDOMIZED, CONTROLLED TRIALS

KJELL BENSON, B.A., AND ARTHUR J. HARTZ, M.D., PH.D.

*Conclusions* We found little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtained in randomized, controlled trials. (N Engl J Med 2000;342:1878-86.)

---

## RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES, AND THE HIERARCHY OF RESEARCH DESIGNS

JOHN CONCATO, M.D., M.P.H., NIRAV SHAH, M.D., M.P.H., AND RALPH I. HORWITZ, M.D.

*Conclusions* The results of well-designed observational studies (with either a cohort or a case-control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic. (N Engl J Med 2000;342:1887-92.)

# Observational Studies – ‘Old’

A COMPARISON OF OBSERVATIONAL STUDIES AND RANDOMIZED,  
CONTROLLED TRIALS

KJELL BENSON, B.A., AND ARTHUR J. HARTZ, M.D., PH.D.

RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES,  
AND THE HIERARCHY OF RESEARCH DESIGNS

JOHN CONCATO, M.D., M.P.H., NIRAV SHAH, M.D., M.P.H., AND RALPH I. HORWITZ, M.D.

**Accompanied by editorial: *Randomized trials or observational tribulations?***

**“Only randomized treatment assignment can provide a reliably unbiased estimate of treatment effects” [...] perhaps we have not tried hard enough to convert the skeptics.” (Pocock, *New Engl J Med* 2000;342:1907)**

# What's Changed? – Availability of '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:** *Big Data* represents “[...] shorthand for advancing trends in technology that open the door to a new approach to understanding the world and making decisions” (Lohr S, *New York Times*, 11 Feb 2012)

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

# What's Changed? – Views on Observational Studies

## Cochrane Collaboration – 2014:

- “[...] on average, there is little evidence for significant effect estimate differences between observational studies and RCTs [...]”
- “Factors other than study design *per se* need to be considered when exploring reasons for a lack of agreement between results of RCTs and observational studies”

**Citation:** Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: MR000034. DOI: 10.1002/14651858.MR000034.pub2.

# What's Changed? – New Terminology

**Origin:** “Real world” is a non-specific term; “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 specific regulatory implications

**Perspective:** Older epidemiologic terms were sufficient, but emergence of big data and enactment of 21<sup>st</sup> Century Cures in 2016 has led to sometimes confusing use of different taxonomies for study design

**Example:** “RWE study” is not synonymous with “observational study”; additional details are needed to classify 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 [...] 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’

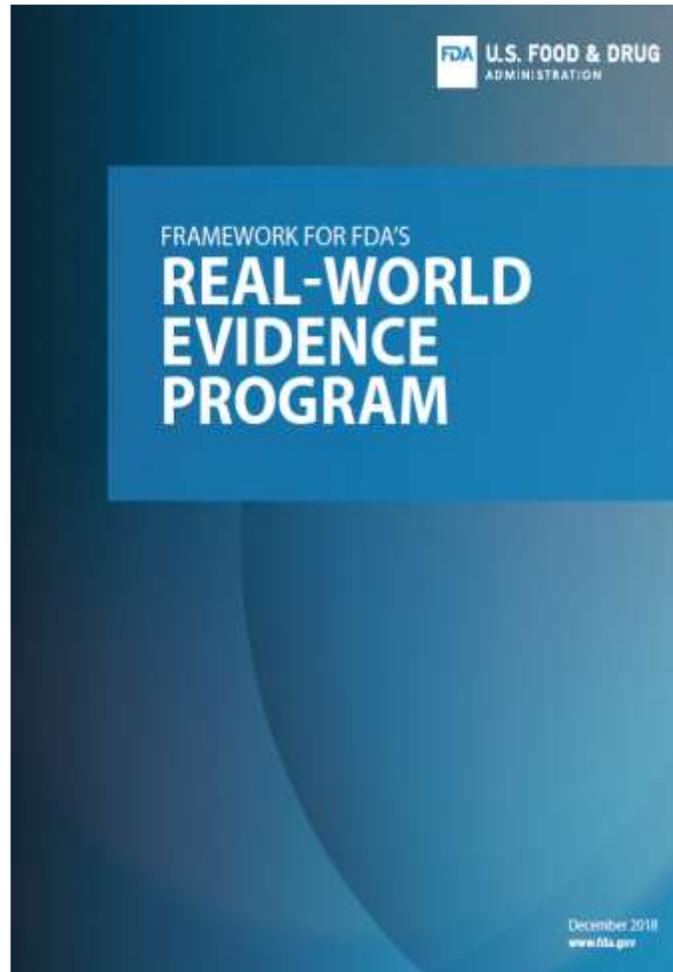
**“We argue that any special status for RCTs is unwarranted. Which method is likely to yield a good causal inference depends on what we are trying to discover as well as on what is already known.” (Deaton & Cartwright,**

***Soc Sci Med*, 2018;210:2)**

# Outline of Presentation

- Introduction
- Everything old is new again
- **Where are we now?**

# FDA RWE Framework (2018)



- **Applies to Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Oncology Center of Excellence (OCE)**
- **Multifaceted program to implement RWE:**
  - **internal agency processes**
  - **external stakeholder engagement**
  - **guidance development**
  - **demonstration projects**

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

## Real-World Evidence — Where Are We Now?

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

**Issue being addressed: More than five years after passage of the 21<sup>st</sup> Century Cures Act, the terms RWD and RWE are being used inconsistently and interchangeably**

### **Content of article:**

- addressed two common misconceptions
- provided conceptual overview of study design
- described FDA guidance and demonstration projects
- highlighted regulatory approvals
- offered path forward

# Real-World Evidence — Where Are We Now?

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

## Randomized, Interventional Study

## Nonrandomized, Interventional Study

## Nonrandomized, Noninterventional Study

### Traditional randomized trial using RWD in planning

### Trial in clinical practice settings, with pragmatic elements

### Externally controlled trial

### Observational study

RWD used to assess enrollment criteria and trial feasibility

RWD used to support selection of trial sites

Selected outcomes identified using, e.g., health records data, claims data, or data from digital health technologies

RCT conducted using, e.g., electronic case report forms for health records data or claims data

Single-group trial with external control group derived from RWD

Cohort study

Case-control study

Case-crossover study

Generation of RWE

Increasing reliance on RWD

Reliance on RWD in Representative Types of Study Design.

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

# Misconceptions Regarding RWD & RWE

## Frequent instances of:

- ***Misconception #1 – RWD & RWE are new concepts: “In reality, sources of data and types of study design haven’t fundamentally changed, but electronic access to more detailed clinical data is evolving & the data are becoming more relevant and reliable”***
- ***Misconception #2 – A simple dichotomy of randomized trials vs. observational studies exists: “In reality, clinical trials are defined by assignment of treatment according to an investigational protocol, and single-arm trials face challenges similar to those in observational studies in determining whether difference in clinical outcomes (compared to an external control group) represent actual treatment effects”***

# FDA Internal and External Engagements

- **Real-World Evidence Subcommittee *internal* activities, w/ membership comprised of FDA staff from multiple centers and offices:**
  - providing oversight of policy development on RWE (e.g., guidances)
  - offering resources and leadership (e.g., to review divisions)
- **Real-World Evidence Subcommittee *external* activities include:**
  - “listening sessions” on initiatives from sponsors, vendors, etc.
- ***Additional* activities, beyond the Subcommittee, include:**
  - holding FDA- or Center-level public meetings on RWE-related topics
  - conducting FDA small business & industry webinars, speaking engagements

# 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
<i>Non-interventional studies</i>	<i>Design considerations</i>	<i>in development</i>
<i>RCTs in clinical practice settings</i>	<i>Design considerations</i>	<i>in development</i>
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>

# RWD/RWE Demonstration Projects – Categories & Examples



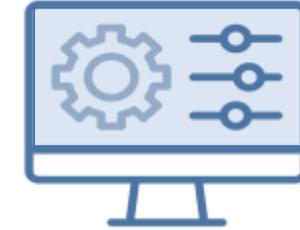
## Data

- ‘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

- Methods for assessing confounding in non-interventional studies
- Targeted learning framework for causal effect estimation

<https://www.fda.gov/science-research/real-world-evidence/rwd-and-rwe-focused-demonstration-projects>

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.

# RWE for Effectiveness – Overview of FDA Approach



## Key considerations (from 2018 Framework):

- 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**

## FDA Approves New Use of Transplant Drug Based on Real-World Evidence



- 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
- No indication for lung transplant; sponsor (Astellas Pharma US) submitted supplemental New Drug Application to FDA with non-interventional study
- Study data and design were evaluated according to FDA standards
- Approval for preventing rejection/death in lung transplant granted July 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

**Design:** non-interventional (observational) treatment arm compared to hx controls

**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>

## Real-world data sources:

- issues related to data reliability and clinical relevance
- need for linkage to other data sources
- missing or “mistimed” data
- suitable capture of endpoints

## Non-randomized study designs:

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

## Conduct of non-randomized studies:

- insufficient confirmation of *pre-specified* protocol and analysis plan
- issues related to FDA inspection of RWD sources

# Outline of Presentation

- Introduction
- Everything old is new again
- Where are we now?
- **RWE and COVID-19**

# Real-World Data on COVID-19 – Example #1

## Analyses conducted by FDA Office of Surveillance and Epidemiology:



- **Concern regarding safety of systemic corticosteroids in non-hospitalized COVID-19 patients**
- **RWD from multiple US data sources analyzed to examine utilization of corticosteroids**
- **Despite recommendations to the contrary, steroid Rx in such patients was found (up to 21%)**
- **U.S. CDC issued health advisory on potentially inappropriate use of corticosteroids in COVID-19**
- **RWD had role in informing public health and advancing pandemic preparedness and response**

## Analyses conducted by U.S. Department of Veterans Affairs:

Annals of Internal Medicine

ORIGINAL RESEARCH

### Effectiveness of COVID-19 Treatment With Nirmatrelvir-Ritonavir or Molnupiravir Among U.S. Veterans: Target Trial Emulation Studies With One-Month and Six-Month Outcomes

Kristina L. Bajema, MD, MSc; Kristin Berry, PhD; Elani Streja, PhD; Nallakkandi Rajeevan, PhD; Yuli Li, MS; Pradeep Mutalik, MD; Lei Yan, PhD; Francesca Cunningham, PharmD; Denise M. Hynes, MPH, PhD, RN; Mazhgan Rowneki, MPH; Amy Bohnert, PhD, MHS; Edward J. Boyko, MD, MPH; Theodore J. Iwashyna, MD, PhD; Matthew L. Maciejewski, PhD; Thomas F. Osborne, MD; Elizabeth M. Viglianti, MD, MPH, MSc; Mihaela Aslan, PhD; Grant D. Huang, MPH, PhD; and George N. Ioannou, BMBCh, MS

**Objective:** To measure the effectiveness of nirmatrelvir-ritonavir and molnupiravir for outpatient treatment of COVID-19.

**Design:** Three retrospective target trial emulation studies comparing matched cohorts of nirmatrelvir-ritonavir versus no treatment, molnupiravir versus no treatment, and nirmatrelvir-ritonavir versus molnupiravir.

**Conclusion:** Nirmatrelvir-ritonavir was effective in reducing 30-day hospitalization and death. Molnupiravir was associated with a benefit for 30-day mortality but not hospitalization. Further reductions in mortality from 31 to 180 days were observed with both antivirals.

*Ann Intern Med.* 2023;176:807-816. doi:10.7326/M22-3565

- **Real-world data continued to accumulate as the pandemic unfolded; valid real-world evidence to inform pandemic response was beneficial; progress was made from “lessons learned”**
- **More data aren’t always better; challenges in diagnosing, treating, and reporting on a new disease created methodological problems; our understanding of COVID-19 evolved over time**
- **COVID-19 pandemic presented an opportunity to leverage real-world data to inform clinical and regulatory decisions; scientific rigor must be maintained**

# Outline of Presentation

- Introduction
- Everything old is new again
- Where are we now?
- RWE and COVID-19
- **Summary**

## Closing paragraph from recent NEJM article:

- **“The FDA remains committed to robust policy development aligned with the 21st Century Cures Act while maintaining evidentiary standards in honoring our obligation to protect and promote public health. Focusing on the distinction between interventional studies and noninterventional studies can help researchers, sponsors, and regulators better understand and describe relevant methodologic issues. Gaining more experience, including conduct of rigorous noninterventional studies, will help to advance drug development.”**

- The terms *RWD* & *RWE* can be confusing when failing to describe specific sources of data and types of research architecture
- FDA's guidance & related efforts, along with other stakeholders, are addressing current challenges in generating real-world evidence
- The COVID-19 pandemic focused more attention on RWE
- FDA will maintain evidentiary standards while considering RWD/RWE as “another tool in the toolbox” for regulatory decision-making

# Acknowledgments

- **Jacqueline Corrigan-Curay, M. Khair ElZarrad; Marie Bradley, Phil Budashewitz, Tala Fakhouri, Kayla Garvin, Scott Gordon, Stefanie Kraus, Beth Kunkoski, Jie (Jenni) Li, Juanita Marner, Kristen Miller, Dianne Paraoan, Ken Quinto, Motiur Rahman, Leonard Sacks, Kim Smith**
- **Other colleagues in:**
  - **CDER Offices of Medical Policy, New Drugs, Surveillance & Epidemiology, Biostatistics, Regulatory Policy, Scientific Investigations, Strategic Programs, Translational Sciences**
  - **Center for Biologics Evaluation & Research; Oncology Center of Excellence; Center for Devices & Radiological Health**
  - **Office of the Commissioner**

# Thank you



[CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov](mailto:CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov)