



NIH Pragmatic Trials Collaboratory Grand Rounds

FDA Draft Guidance on Real-World Evidence

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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

1

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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2

2

Objectives



- Recognize historical context leading to current focus on “real-world evidence” as new terminology
- Understand main components of FDA’s Real-World Evidence Program, focusing on guidance development
- Identify challenges and potential contributions of using real-world data and real-world evidence

3

3

Outline of Presentation



- Background on aspects of data & study design in clinical research
- Overview of FDA’s Real-World Evidence Program for drugs and biological products (not devices, etc.), including guidance
- Real-world data/evidence now & going forward; summary

4

4

Outline of Presentation

FDA

- Background on aspects of data & study design in clinical research

5

5

Background on ‘Big Data’

FDA

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

6

6

Background on ‘Real-World Evidence’

FDA

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 (*terms to be defined in subsequent slide*)

Contemporary usage: RWD and RWE have specific regulatory implications

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” is not synonymous with “observational study”; additional details are needed to classify study design

7

7

‘20th Century’ Overview of Data and Design

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Columns = interventional (clinical trial) vs. non-interventional (observational) design

Rows = primary data collection vs. secondary use of existing clinical data


	Interventional	Non-Interventional
Primary data collection for research	<ul style="list-style-type: none">• traditional RCTs	
Secondary use of clinical data		<ul style="list-style-type: none">• health records- or claims-based analyses*

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

8

8

Update on Data and Design



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


	Interventional	Non-Interventional
Primary data collection for research	<ul style="list-style-type: none">• traditional RCTs• decentralized RCTs	<ul style="list-style-type: none">• registry-based analyses*
Secondary use of clinical data	<ul style="list-style-type: none">• pragmatic RCTs• cluster RCTs	<ul style="list-style-type: none">• health records- or claims-based analyses*

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

Pharmacoepidemiol Drug Saf. 2020;1–4. DOI: 10.1002/pds.5123

9


Outline of Presentation




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- Overview of FDA’s Real-World Evidence Program for drugs and biological products (not devices, etc.), including guidance

10

21st Century Cures Act (2016) – RWE






- 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


11

11

Background: ‘Real-World’ Definitions (FDA 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
- patient-generated data, including from in-home settings
- other sources that can inform on health status, such as “wearable” devices

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



12

12

Overview of Laws, Regulations, and Guidances

FDA

Law

- Food, Drug, and Cosmetic Act ‘Drug Amendments’ of 1962: requires *substantial evidence of effectiveness* from *adequate and well-controlled investigations*
- Food and Drug Administration Modernization Act of 1997: allows for evidence from *one adequate and well-controlled investigation* and *confirmatory evidence*

Regulation

- 21 Code of Federal Regulations 314.126 for **adequate and well-controlled studies** provides criteria for distinguishing effect of a drug from other influences, such as spontaneous change in course of disease, placebo effect, or biased observation

Guidance

- ‘Demonstrating Substantial Evidence of Effectiveness [...]’ of 2019 offers details

13

13

FDA RWE Framework (2018)

FDA



- Applies to Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), & Oncology Center of Excellence (OCE); not to Center for Devices and Radiological Health (CDRH)
- Multifaceted program to implement RWE:
 - 1) internal processes
 - 2) external stakeholder engagement
 - 3) demonstration projects
 - 4) **guidance development**

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

14

14

1) Internal and 2) External Engagement



- Real-World Evidence Subcommittee *internal* activities, w/ membership comprised of FDA staff from multiple CDER and CBER Offices:
 - providing oversight of policy development on RWE (e.g., guidances)
 - offering resources and leadership (e.g., to review divisions)
 - other activities
- RWE Subcommittee *external* activities include:
 - providing feedback on early-stage proposals from sponsors, vendors, etc.
 - discussing initiatives presented to Subcommittee for consideration
- *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

15

15

3) FDA-Supported RWE Research Projects – Examples



- ‘OneSource’ project
- ‘ICAREdata’ project
- Unstructured EHR data



- RCT-DUPLICATE trial emulations
- Statistical tests for RCT designs w/ hybrid control arms



- Evaluating confounded treatment effects
- Targeted learning framework for causal effect estimation

16

16

'OneSource' Demonstration Project



- **Conceptual approach of OneSource: improve the quality of real-world data; “enter the right clinical data once, use the data many times” (including for research)**
- **Focus on integration of standards-based tools within the EHR, to bring together health care and research (e.g., populate electronic case report forms directly from EHR)**
- **Collaboration between FDA and the University of California, San Francisco**
- **Ongoing demonstration in breast cancer clinical trials**



Courtesy of Dr. Laura Esserman
and Susan Dubman

17

17

'U01' Awards for RWD/RWE



Funding Opportunity Title

Exploring the use of Real-World Data to Generate Real-World Evidence in Regulatory Decision-Making (U01) Clinical Trials Optional RFA-FD-20-030


N=31 applications received; n=4 applications funded

Number	Applicant	Project Title
1 U01FD007213-01	Brigham and Women's Hospital	Enhancing evidence generation by linking RCTs to RWD
1 U01FD007206-01	Genentech-UNC	Applying novel statistical approaches to develop a decision framework for hybrid RCT designs, combining internal control arms with data from RWD sources
1 U01FD007172-01	Verantos, Inc.	Transforming RWE with <i>Un</i> structured and Structured data to advance Tailored therapy (TRUST)
1 U01FD007220-01	Critical Path Institute	Advancing standards and methodologies to generate RWE from RWD through a neonatal pilot project

18

18

4) 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>

19

RWE Draft Guidance – EHR/Claims Data



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

Guidance for Industry

DRAFT GUIDANCE

September 2021

Real World Data/Real World Evidence (RWD/RWE)

20

EHR/Claims Data Guidance – Overview

FDA

Focus of draft guidance:

- Selection of data source(s) to appropriately address the study question
- Development and validation of definitions for exposures, covariates, outcomes
- Data provenance during accrual, curation, analysis

Note: choice of study design and method of statistical analysis are outside of guidance scope

21

21

EHR/Claims Guidance – ‘Life Cycle of EHR Data’

FDA

Excerpts from *Real-World Data: Assessing Electronic Health Records and Medical Claims [...]* (Sep 2021)

- “[...] the process for examining the quality of the data [...] is not a one-time assessment”
- “[...] rather, it is an ongoing process [...] in multiple phases of the [life cycle of HER data]”

The diagram illustrates the 'Life Cycle of EHR Data' as a vertical flow from Source Data to Analytic Dataset, with a horizontal flow from Source Data to Clinical Data Repository. On the left, a vertical stack shows the stages: SOURCE DATA, CURATED DATA, TRANSFORMED DATA, and ANALYTIC DATASET. On the right, the horizontal flow starts with SOURCE DATA (represented by a table of EHR data types) feeding into the CLINICAL DATA REPOSITORY. From there, data moves to the DATA WAREHOUSE, then to the STUDY-SPECIFIC DATASET, and finally to the ANALYTIC DATASET. Key processes include: 'Linkage to External Sources of Data' and 'Manual Curation' between Source and Clinical Data; 'Unstructured Data Processing' and 'Structured Data Processing' between Clinical Data and Data Warehouse; 'Clean and Standardize' between Data Warehouse and Study-Specific Dataset; 'Linkage to Fill Gaps' and 'De-identification' between Study-Specific Dataset and Data Warehouse; 'Subset Sample and Build Cohort' and 'Derived and Subset Variables' between Data Warehouse and Study-Specific Dataset; and 'Extract, Transform, Load (ETL) for Common Data Models (CDMs)' between Study-Specific Dataset and Data Warehouse.


EHR				
Medical Claims	Discharge Notes	Healthcare Provider Notes	Demographics	Visits
Birth or Death Certificates	Radiology Reports	Pathology Reports	Vital Signs	Orders/medications, labs, etc.
Registries	Procedural Notes		Diagnosis	Lab Results

See <https://www.fda.gov/media/152503/download>

22

22

Comment on EHR/Claims Guidance



How Real-World Evidence is Shaping the Future of Healthcare

Riskin D, *Forbes* Technology Council Post, 18 Nov 2021

“In September, the Food and Drug Administration published draft guidance on the use of real-world evidence (RWE) to support regulatory decision-making. While draft guidance might seem underwhelming, it’s a critical step toward a larger, nationwide plan that will ultimately transform healthcare.”

[...]

“The FDA draft guidance may be viewed in a limited way as one more regulatory document. But I prefer to think the government, industry, and providers are coming together in an emerging golden age of healthcare to apply newly available data, technology and processing power to create a better healthcare system.”

23

23

RWE Draft Guidance – Registry Data



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

DRAFT GUIDANCE

November 2021

Real World Data/Real World Evidence (RWD/RWE)

24

24

Registry Data Guidance – Overview

FDA

TABLE OF CONTENTS

I. INTRODUCTION.....

II. BACKGROUND

III. DISCUSSION

A. Using Registry Data to Support Regulatory Decisions.....

B. Relevance of Registry Data

C. Reliability of Registry Data.....

D. Considerations When Linking a Registry to Another Registry or Another Data System

E. Considerations for Regulatory Review

GLOSSARY.....

1

2

4

4

5

7

10


11

13

25

- Registry Data Guidance – Representative Topics

FDA
- Registry fitness-for-use in regulatory decision-making, focusing on attributes that support collection of relevant and reliable data
 - Linking a registry to other data source(s) for supplemental information, such as data from medical claims, electronic health records (EHRs), digital health technologies, or other registries
 - FDA review of submissions that include registry data
- Note: The guidance does not provide recommendations on choice of study design or approach to statistical analysis
- 26

RWE Draft Guidance – Data Standards

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


Guidance for Industry

DRAFT GUIDANCE

October 2021
Real-World Data/Real-World Evidence (RWD/RWE)

27

27

Data Standards Guidance – Overview

Focus of draft guidance:


- Processes for managing RWD
- Conforming RWD to FDA data standards
- Mapping RWD to FDA submission standards
- Considerations for data transformations

Note: this guidance applies regardless of the type of RWD

28

28

Data Standards Guidance – Take-Home Points




Preparing RWD for submission using current study data standards:

- FDA recognizes no “one size fits all” approach exists for using current data standards for study data derived from RWD sources
- Sponsors should discuss possible approaches with FDA as early as possible
- All data transformations, mappings, etc., should be documented
- Examples provided in the guidance Appendix are illustrative

29

29

RWE Draft Guidance – Regulatory Considerations



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

DRAFT GUIDANCE

December 2021
Real World Data/Real World Evidence (RWD/RWE)

30

30

Regulatory Considerations Guidance – Overview




TABLE OF CONTENTS

I. INTRODUCTION..... 1

II. BACKGROUND 2

III. REGULATORY CONSIDERATIONS ADDRESSED 3

A. Applicability of 21 CFR Part 312 3

B. Regulatory Considerations for Non-Interventional (Observational) Studies..... 4

1. Overview 4

2. Transparency Regarding Data Collection and Analysis 4

3. RWD Data Access 5

4. Study Monitoring 6


5. Safety Reporting..... 7

6. Other Sponsor Responsibilities..... 7

GLOSSARY..... 9

31

Regulatory Considerations Guidance – Comments



- Marketing application to support safety/effectiveness of a drug must satisfy applicable legal standards to be approved or licensed, even if 21 CFR part 312 (Investigational New Drug Application) does not apply
- Two classifications of non-interventional studies:
 - 1) *involve only* analysis of data on use of marketed drug in routine practice
 - 2) *include* ancillary protocol-specified activities or procedures (e.g., lab tests, imaging studies, questionnaires)
 - FDA does not consider these types of studies to be clinical investigations under 21 CFR part 312
 - Nonetheless, protection of human subjects is critical; sponsors must ensure applicable requirements met per FDA regulations 21 CFR parts 50 (Protection of Human Subjects) & 56 (Institutional Review Boards)

32

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16

Status of RWE Draft Guidance – as of June 2022			
			FDA
Topic	Category	Status	Date
EHRs and claims data	Data considerations	published	Sep 2021
Data standards	Submission of data	published	Oct 2021
Registry data	Data considerations	published	Nov 2021
Regulatory considerations	Applicability of regulations	published	Dec 2021
Externally controlled trials	Design considerations	in development	–
RCTs in clinical practice settings	Design considerations	in development	–

Draft Guidance – Digital Health Technologies

FDA

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

DRAFT GUIDANCE

December 2021
Clinical/Medical

DHT Guidance – Overview



Focus of draft guidance:

- Selection of suitable DHTs for clinical research
- Verification and validation of DHT to be used
- Use of DHT to collect trial endpoints
- Risks (and management of risk) associated with DHT use

Note: Whether a DHT meets the definition of a device under section 201(h) of the FD&C Act is beyond the scope of the guidance

35

35

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36

36

Current Status of Real-World Evidence



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 21st 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 demonstration projects and guidance
- highlighted regulatory approvals
- offered path forward

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

37

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”

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38

Real-World Evidence — Where Are We Now?

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

FDA

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.

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39

RWE Informs Effectiveness When Fit-for-Purpose

FDA

DRUG	INDICATION	APPROVED	DATA
Carbaglu (carglumic acid)	Treatment of NAGS deficiency	2010	▪ Retrospective, non-random, unblinded case series of 23 patients compared to historical control group
Voraxaze (glucarpidase)	Treatment of MTX toxicity	2012	▪ Approval based on open-label, NIH expanded access protocol
Blinicyto (Blinatumomab)	Treatment of Acute Lymphoblastic Leukemia	2014	▪ Single-arm trial ▪ Reference group weighted analysis of patient level data on chart review of 694 patients at EU and US study sites
Vistogard (uridine triacetate)	Overdose of chemotherapy drugs 5-fluorouracil (5-FU)	2015	▪ Two single-arm, open-label expanded access trial of 137 patients compared to case history control

List not exhaustive

Bold = RWD

40

RWE Informs Effectiveness (cont'd)			
DRUG	INDICATION	APPROVED	DATA
Defitelio (defibrotide sodium)	Severe hepatic veno-occlusive disorder	2016	▪ Two prospective clinical trials enrolling 179 patients and an expanded access study with 351 patients
Lutathera (lutetium 177 dotate)	Gastroenteropancreatic neuroendocrine tumours (GEP-NETs)	2017	▪ Open-label clinical trial ▪ Analysis of a subset of 360 patients who participated in an investigator sponsored, open-label, single-arm, single institution study of 1214 patients 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 using electronic health records in Kaiser Permanente Northern California to characterize the duration of protection in persons 50 years of age and older
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	

41

RWE – Representative (Overlapping) Problems
<p><u>Real-world data sources:</u></p> <ul style="list-style-type: none">- issues related to data reliability and clinical relevance- need for linkage to other data sources- missing or “mistimed” data- suitable capture of endpoints <p><u>Non-randomized study designs:</u></p> <ul style="list-style-type: none">- threat of residual confounding- problems with index date (“zero time”)- use of inappropriate comparator <p><u>Conduct of non-randomized studies:</u></p> <ul style="list-style-type: none">- insufficient confirmation of <i>pre-specified</i> protocol and analysis plan- issues related to FDA inspection

42

RWE – Specific Opportunity Regarding Diversity

FDA


- Decentralized and point-of-care clinical trials have the potential to reduce costs & increase study diversity; digital health tech can reach populations that have less access to research studies
- Real-world data sources tend to be more likely (vs. traditional trials) to contain data on diverse study populations, providing potential opportunities for addressing health disparities
 - Note: When real-world data are analyzed using machine learning or other artificial intelligence tools, algorithms used should avoid perpetuating historical or societal inequities

43

43

RWE for Effectiveness: Overview of FDA Approach

FDA



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**

44

44

New Indication for Prograf® Based on RWE

FDA

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

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- 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

45

New Indication for Prograf® Based on RWE (cont’d)

FDA

Data: US Scientific Registry of Transplant Recipients (SRTR) data on all lung transplants in US during 1999–2017

Design and conduct: non-interventional (observational) treatment arm, compared to historical controls; analysis plan & 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.

46

Looking Forward

FDA

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.”

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47

47

Summary

FDA

- “Big data” has contributed to changes in how evidence generation is approached & described; research methods are also evolving
- FDA’s RWE guidance & related efforts, along with other stakeholders, are addressing current challenges in using real-world data & evidence
- FDA will maintain evidentiary standards while considering RWD/RWE for regulatory decision-making

48

48

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 - Center for Biologics Evaluation & Research; Oncology Center of Excellence; Center for Devices & Radiological Health
 - Office of the Commissioner

49

49



CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

50