

Overview of FDA's Real-World Evidence Program: Demonstration Projects & Guidances

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- No conflicts of interest to disclose
- Views expressed are those of the presenter and are not intended to convey official US Food and Drug Administration policy or guidance
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Outline of Presentation



- Background on FDA's Real-World Evidence Program for drugs and biological products (not devices, etc.)
- Overview of activities including RWE demonstration projects and RWE guidances
- Status of RWD/RWE at CDER/CBER
 - Conceptual overview of study design
 - Looking forward

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
- Series of draft guidance for industry issued starting September 2021
- PDUFA VII “Advancing RWE” initiatives launched October 2022
- FDA standard for substantial evidence remains unchanged

'Real-World' Definitions (FDA's 2018 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)

Healthcare claims data

Product and disease registries

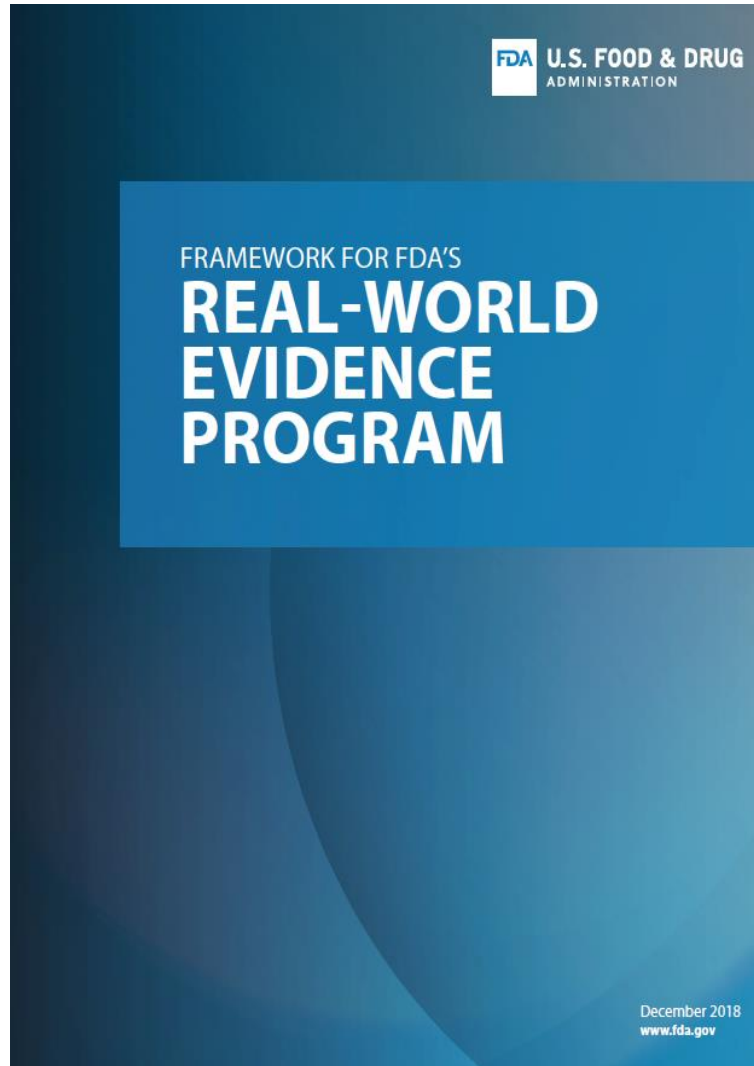
Patient-generated data, including from in-home settings

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 different study designs, including but not limited to randomized trials (e.g., large simple trials, pragmatic trials), externally controlled trials, or 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:
 - 1) Internal processes
 - 2) External stakeholder engagement
 - 3) Demonstration (research) projects
 - 4) Guidance development

1) Internal processes and 2) External Engagement



Real-World Evidence Subcommittee—FDA leadership and staff from multiple CDER and CBER offices

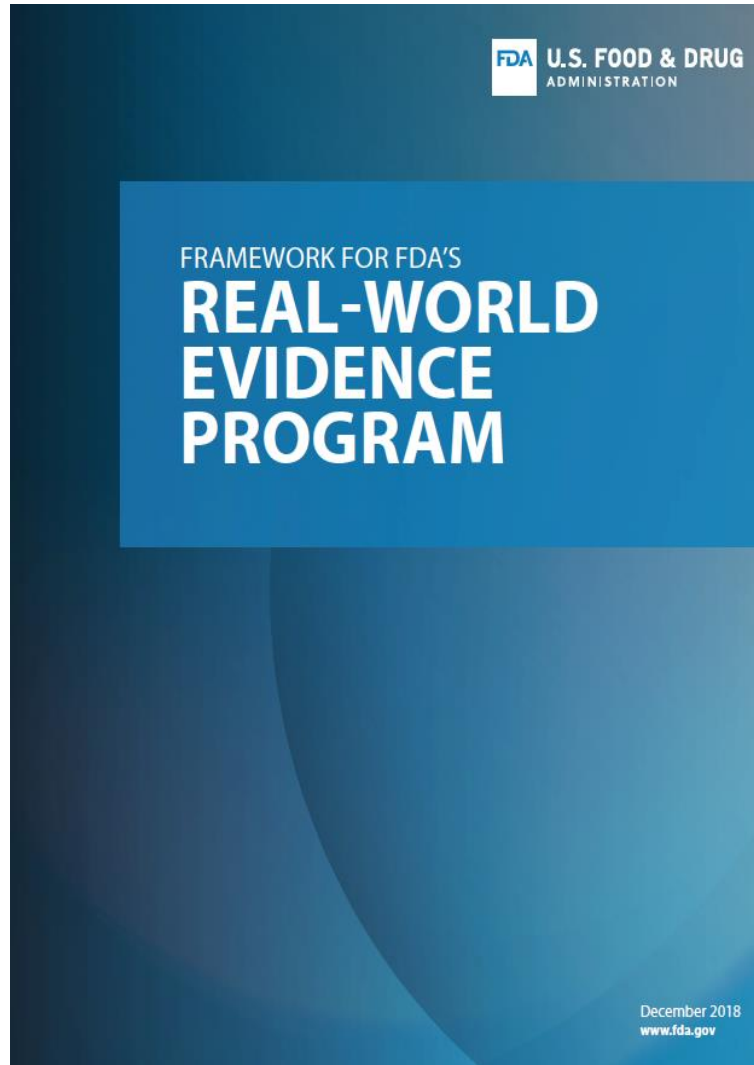
Internal activities:

- Oversight of policy development on RWE (e.g., guidances)
- Offering input, information, and resources (e.g., to review divisions)

External activities:

- Discussing RWE-related issues presented to Subcommittee
 - Providing feedback on RWE-related initiatives to sponsors, vendors
- **Additional activities, beyond Subcommittee:**
 - Holding FDA- or Center-level public meetings on RWE-related topics
 - Conducting FDA small business & industry webinars, speaking engagements

FDA RWE Framework (2018)



Applies to:

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 - 3) **Demonstration (research) projects**
 - 4) Guidance development

3) RWE Research Projects – Categories



Data



Study Design



Tools

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

3) RWE Research Projects – Examples: Data

BAA	Awardee
Leveraging EHRs for Clinical Research	<i>Duke Clinical Research Institute</i>
Integrating Clinical Trials and Real-World Endpoints Data (ICAREdata) <ul style="list-style-type: none"> • Data Capture and Standardization Study • Adverse event reporting 	<i>Alliance NCTN foundation</i>

U01	Awardee
Transforming real-world evidence with Unstructured and Structured EHR data (TRUST)	<i>Verantos, Inc</i>
Advancing standards and methodologies to generate RWE from RWD through a neonatal pilot project	<i>Critical Path Institute</i>

3) RWE Research Projects – Examples: Study Design



BAA and FDA-Catalyst	Awardee
RCT-DUPLICATE Trial emulation	<i>Brigham and Women's Hospital Harvard Medical School</i>
Alignment of MyStudies App with Pragmatic Trials and/or Registries – LIMIT JIA and SPARC IBD Registry	<i>Harvard Pilgrim Healthcare, Inc</i>
CMS linkage to the PCORI funded RELIANCE trial	<i>Harvard Pilgrim Healthcare, Inc</i>

U01	Awardee
Enhancing evidence generation by linking RCTs to RWD	<i>Brigham and Women's Hospital Harvard Medical School</i>

3) RWE Research Projects – Examples: Tools

BAAs and CERSIs	Awardee
Disease-Monitoring Solution Leveraging Wearable Sensors for Novel Patient-centered Outcome Measures among Patients with Heart Failure	<i>Yale University/Mayo Clinic CERSI</i>
Methodological Advances in the Assessment of Uncontrolled Confounding (DETECTe)	<i>University of North Carolina</i>

U01	Awardee
Novel statistical approaches to develop a decision framework for hybrid RCT designs combining internal control arms with data from real-world data sources	<i>Genentech/University of North Carolina</i>

Data: Verantos TRUST

Transforming RWE with Unstructured and Structured data to advance Tailored therapy



Knowledge gap: How does data quality impact results from real-world evidence?

Objective: To investigate data quality and to enable high-validity evidence through advanced data and technologies

Approach:

1: Implement an observational study that demonstrates an advanced EHR (deep) phenotype linked to exposure and outcome data

2: Set up a prospective registry automatically processed from EHR and other data across three health systems

3: Study clinical assertions and data validity based on the automated prospective registry against results using traditional structured data approaches

Data: Findings from related work by Verantos



Comparison of accuracy of two RWE approaches for identifying patients with heart failure (HF) and their phenotypic information

1. Traditional, i.e., structured query language applied to structured electronic health record (EHR) data
2. Advanced, i.e., artificial intelligence (AI) applied to unstructured EHR data

BMJ Open Retrospective comparison of traditional and artificial intelligence-based heart failure phenotyping in a US health system to enable real-world evidence

Arthur Reshad Garan ¹, Keri L Monda,² Ricardo E Dent-Acosta,² Daniel J Riskin,³ Ty J Gluckman⁴

Performance measured by the harmonic mean of precision and recall (F1 score) using manual annotation of medical records as a reference standard

Findings

- Advanced approach achieved superior F_1 scores for HF presence, phenotype, and associated comorbidities, but results varied dramatically based on extraction techniques.
- Traditional approach resulted in low data quality in patients with HF

Implications: Advanced approaches and accuracy measurement may be required to ensure data are fit-for-purpose in studies generating RWE

Study Design: RCT-DUPLICATE



Knowledge gap: When can RWE come to causal conclusions on treatment effects?

Objective: Emulate 30 completed RCTs using healthcare claims data and compare findings

Approach: Applied a pre-defined, transparent process to emulate RCTs with RWD and compare treatment effect estimates

Findings:

- 50% of the selected RCTs could be emulated closely regarding design, analysis
- Closely emulated RCTs found comparable treatment effects with RWD
- RCT and RWE findings were more likely to diverge when there were substantive emulation challenges; perhaps answering different target questions or due to bias

Implications: Rigorous epidemiologic methods combined with fit-for-purpose data and target trial approaches can produce valid inference from RWE studies

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.

Tools - Methodological Advances in the Assessment of Uncontrolled Confounding (DETECTe)

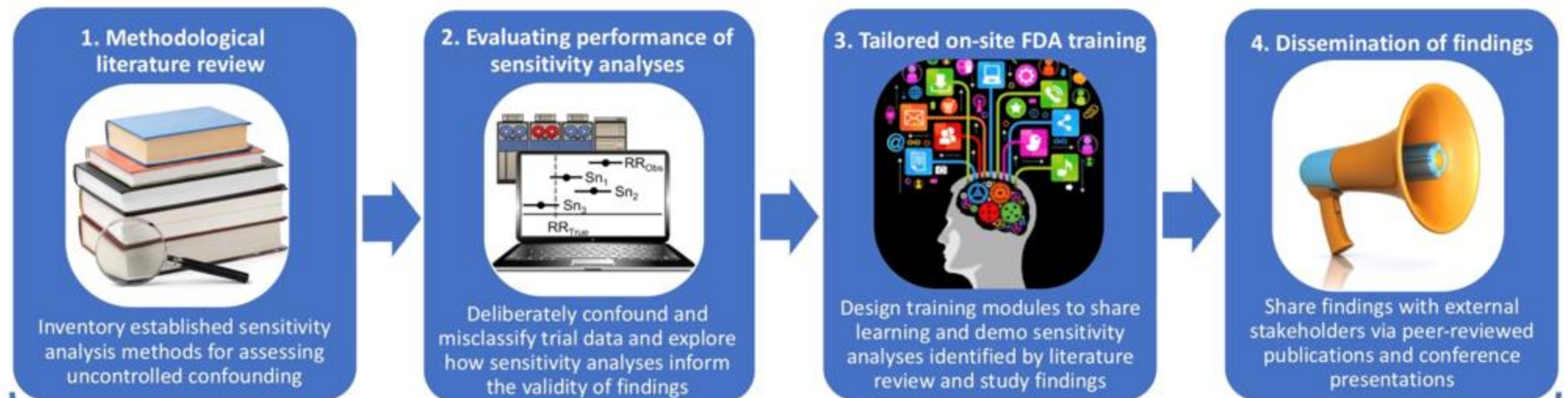


Knowledge Gap: Understanding magnitude and direction of uncontrolled confounding is critical to the interpretation of non-interventional RWE studies

Objectives:

- 1) Evaluate the performance of methods used to evaluate potential bias due to uncontrolled confounding in non-interventional RWE studies
- 2) Enhance FDA capacity to critically evaluate these methods and integrate findings into assessments of non-interventional studies

Approach:



Tools - Methodological Advances in the Assessment of Uncontrolled Confounding (DETECTe)



Findings:

Literature review

- 50% of studies employed approaches to examine uncontrolled confounding
- Use not yet widespread despite an increasing variety of approaches

Performance evaluation (9 methods in 106 scenarios across three therapeutic areas)

- Internal validation sample in which uncontrolled confounder assessed is best opportunity to evaluate its influence.
- Multiple imputation well suited, although quantitative bias analysis performed nearly as well

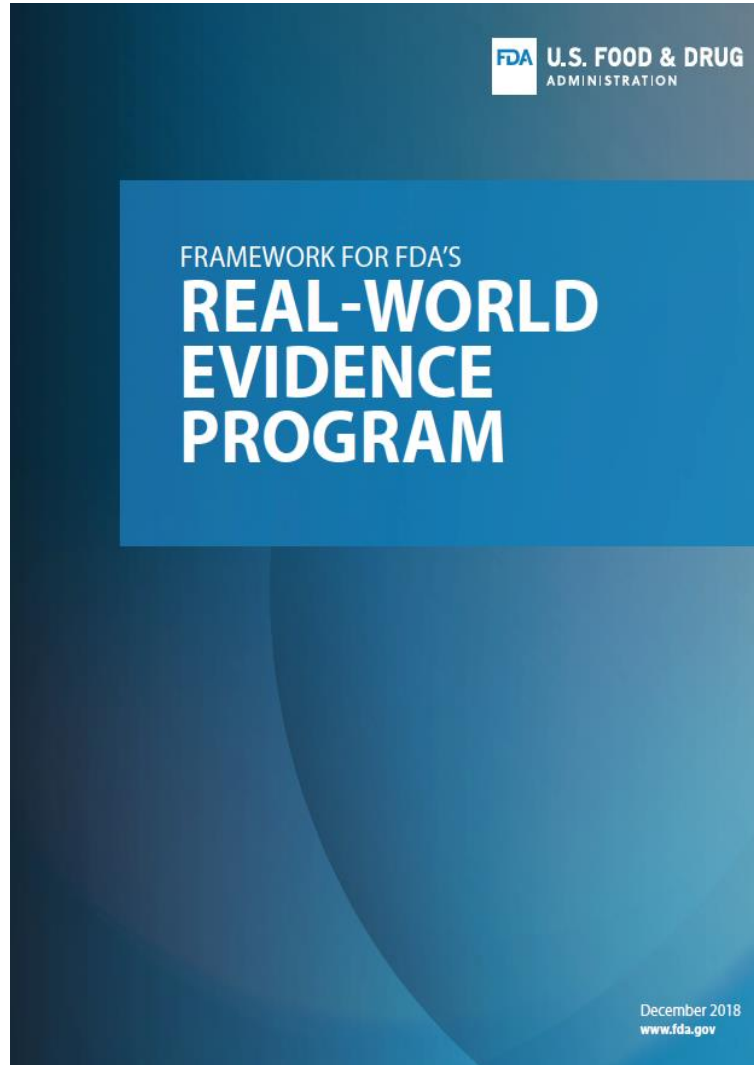
Training

- Materials covering assumptions, implementation, and interpretation of the methods examined were delivered to FDA staff

Implications:

- Enhanced understanding of methods for dealing with uncontrolled confounding and how to apply them appropriately in evaluating non-interventional studies
- FDA staff informed on choosing a robust approach to assess the threat of bias from uncontrolled confounding in non-interventional 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:
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4) FDA Draft 'RWE Guidance' – September to December 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>

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)

EHR/Claims Data Guidance – Overview



- **Data and data source(s)** e.g. selection of appropriate data source to adequately address the study question
- **Validation issues** e.g. development and validation of definitions for exposures, covariates, outcomes
- **Data provenance** during accrual, curation, transformation and analysis

Note: choice of study design or approach to statistical analysis are outside of guidance scope

Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance for Industry

DRAFT GUIDANCE

**February 2023
Real-World Data/Real-World Evidence (RWD/RWE)**

Externally controlled trials guidance- overview



- Considerations relating to
 - **Design:** study populations, attributes of treatment, designation of index date, assessment of outcomes
 - **Data:** data from clinical trials, data from RWD sources
 - **Analysis:** missing data, misclassification of available data
- Considerations to support regulatory review
 - Communication with FDA
 - Access to Data and Documents

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)

A. Applicability of 21 CFR Part 312

- Application to support drug safety/effectiveness must satisfy applicable legal standards, even if 21 CFR part 312 (Investigational New Drug Application) does not apply

B. Regulatory Considerations for Non-Interventional Studies

- 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)

- Not considered to be clinical investigations under 21 CFR part 312
- Nonetheless; sponsors must ensure applicable requirements met per FDA regulations 21 CFR parts 50 (Protection of Human Subjects) & 56 (Institutional Review Boards)

FDA RWE Guidance – Current Status



Topic	Category	Status	Date
EHRs and claims data	Data considerations	Draft published	September 2021
Data standards	Submission of data	Draft published	October 2021
Registry data	Data considerations	Draft published	November 2021
Regulatory considerations	Applicability of regulations	Final published	August 2023
Externally controlled trials	Design considerations	Draft published	February 2023
<i>RCTs in clinical practice settings</i>	<i>Design considerations</i>	<i>In development</i>	–
<i>Non Interventional Studies</i>	<i>Design considerations</i>	<i>In development</i>	–

Status of Real-World Evidence at CDER-CBER

Real-World Evidence — Where Are We Now?

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

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

Focus: Several years after passage of the 21st Century Cures Act, the terms RWD and RWE are being used inconsistently and interchangeably

Content:

- addressed two common misconceptions
- **provided conceptual overview of study design**
- described FDA demonstration projects and guidance
- 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. ³⁰ N ENGL J MED 386;18 NEJM.ORG MAY 5, 2022

Closing paragraph from 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.”***

- FDA RWE program established and has been active in several areas, per the 2018 RWE framework, including implementing RWE guidances and demonstration projects
- FDA's RWE guidance & related efforts, along with other stakeholders, are addressing current challenges in using RWD/RWE
- FDA will maintain evidentiary standards while considering RWD/RWE for regulatory decision-making

Acknowledgments



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- 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



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Overview of Laws, Regulations, and Guidances



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

Background on ‘Real-World Evidence’

History: “real-world data (RWD)” and “real-world evidence (RWE)” appeared in medical literature as of the 1970s or earlier, in various non-regulatory contexts

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