

Computational Science Symposium 2022

Real-World Evidence: Where Are We Now?

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- **Views and opinions expressed are those of the presenter and should not be attributed to the Food and Drug Administration**
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Outline of Presentation

- **Background and definitions**
- **Overview of FDA's Real-World Evidence Program**
- **Current perspectives and example of FDA “RWE” approval**
- **Summary**



- In response to the 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- Draft guidance for industry issued in Sep, Oct, Nov, Dec 2021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

FDA 'Real-World' Definitions (from 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)

medical claims data

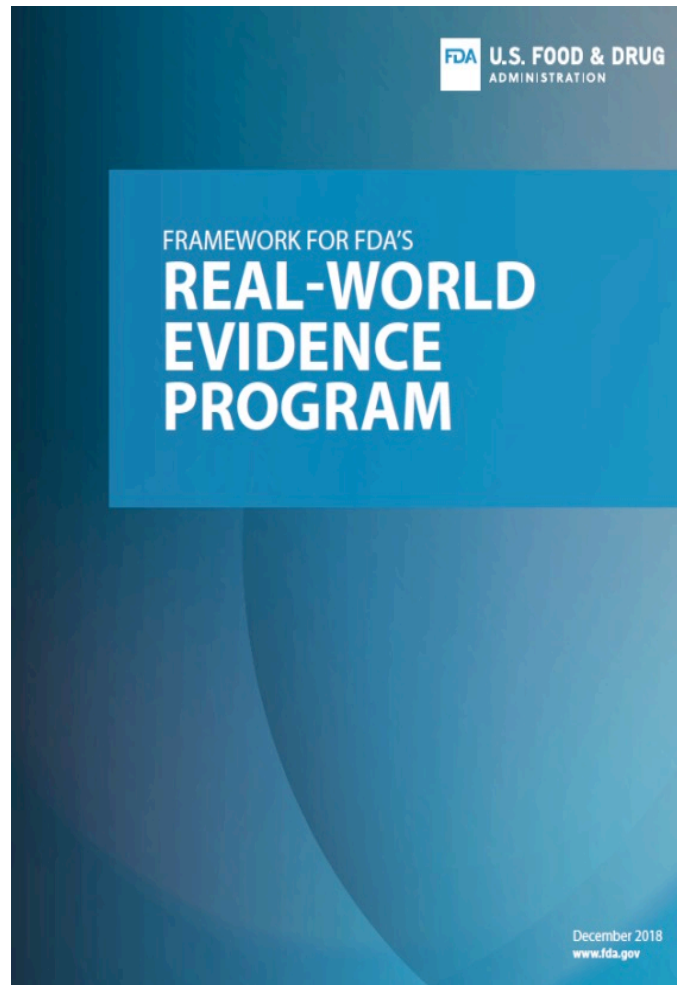
product and disease registries

data from digital health technologies in non-research setting

other 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



- **Applies to Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Oncology Center of Excellence (OCE); Center for Devices and Radiological Health (CDRH) has separate program**
- **Multifaceted program to implement RWE:**
 - 1) internal processes**
 - 2) external stakeholder engagement**
 - 3) guidance development**
 - 4) demonstration projects**

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

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

3) 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>

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

DRAFT GUIDANCE

December 2021
Clinical/Medical

<https://www.fda.gov/media/155022/download>

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products

Guidance for Industry

**September 2022
Procedural**

<https://www.fda.gov/media/124795/download>

4) FDA-Supported RWE Research Projects – Examples



- **'OneSource' project to improve quality of EHR data**
- **project to enable access to unstructured EHR data**

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

- **Evaluate confounded treatment effects**
- **Targeted learning framework for causal effect estimation**

FDA '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 Unstructured 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

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

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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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.

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**

Example of New Indication Based on RWE

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



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- Lung transplant patients are rare disease population: $\approx 2,500$ new transplants performed each year and $\approx 14,000$ patients are alive (2017 data) in U.S.
- Prograf® (tacrolimus) approved for prophylaxis of organ rejection in patients receiving liver transplants in 1994 (later for kidney & heart) based on RCT evidence, and drug is used widely in clinical care for lung transplants
- RCTs not submitted to FDA for lung, but sponsor (Astellas Pharma US) submitted supplemental New Drug Application with non-interventional “RWE” study

Prograf® Application: Aspects of Data and Design



- **U.S. Scientific Registry of Transplant Recipients (SRTR) operates under federal contract; data provided for all lung transplants in US during 1999–2017, including standard analysis files from Organ Procurement & Transplantation Network**
- **Data include baseline characteristics, treatments, and outcomes (e.g., graft failure, re-transplant, death) for all US transplant recipients; linked information obtained from Social Security Administration Death Master File**
- **Randomized controlled trial of Prograf not feasible at this time; study design = non-interventional treatment arm vs. historical control data, with cumulative incidence of graft failure or death at one year as primary endpoint**
- **In the absence of immunosuppressive treatment, outcome of graft failure or death at one year would be 100% based on historical control data**

Prograf®: Study Results

Graft failure or death within one year (vs. 100% in comparator):

Population	Group	# of Patients at Risk	# of Events	Cumulative Incidence % (95% CI)
Adult	TAC IR + MMF	15,478	1,398	9.1 (8.6, 9.5)
	TAC IR + AZA	4,263	390	9.2 (8.3, 10.0)
Pediatric	TAC IR + MMF	450	37	8.3 (5.7, 10.8)
	TAC IR + AZA	72	11	15.3 (6.5, 23.2)

TAC IR=tacrolimus immediate release; MMF=mycophenolate mofetil; AZA=azathioprine

Data source: Scientific Registry of Transplant Recipients; data reliability & relevance similar to what would have been collected if an interventional study had been done

Study design & conduct: non-interventional (observational) treatment arm compared to historical controls; analysis plan & patient-level data submitted 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

See <https://www.accessdata.fda.gov/scripts/cder/daf/>

Assessment of tacrolimus for lung transplantation:

- Are the RWD fit-for-use? **Yes; the registry data are relevant and reliable for the scientific question involved**
- Does the trial or study design used to generate RWE provide adequate scientific evidence to answer or help answer the regulatory question? **Yes; although non-interventional (observational), the single-arm data compared to historical controls provide strong evidence of effectiveness in this setting**
- Did the study conduct meet FDA regulatory requirements? **Yes; *info not shown***

RWE in General – Representative Problems



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 (“zero time”)
- use of inappropriate comparator

Conduct of non-randomized studies:

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

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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