FDA Real-World Evidence Program

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Disclaimer

- **The 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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21st Century Cures Act (2016)

- FDA shall establish a program *to evaluate the potential use* of real-world evidence (RWE) to:
  - Support new indication for a drug approved under section 505(c)
  - Satisfy post-approval study requirements
- Draft framework to be issued by December 2018:
  - Describe sources of RWE, challenges, pilot opportunities, etc.
- Draft guidance for industry to be issued by December 2021
- Standard for *substantial evidence* remains unchanged; commitments are aligned with Prescription Drug User Fee Act (PDUFA)

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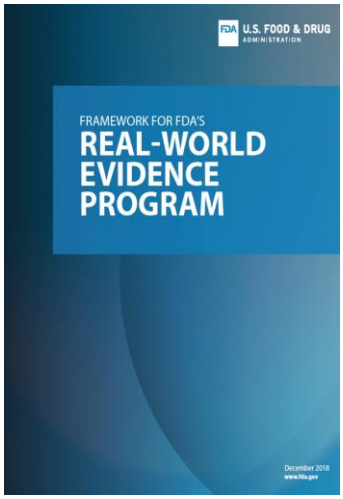
FDA RWE Framework (2018)



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

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‘Real-World’ Definitions (from 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)
- 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 different study designs, including but not limited to randomized trials (e.g., large simple trials, pragmatic trials), externally controlled trials, or observational studies

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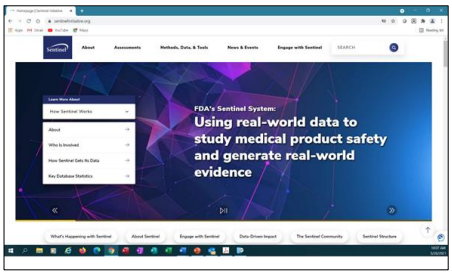
RWE for Safety: FDA Sentinel Initiative

Individual Drug Queries

***FDA queries and studies conducted in the Sentinel System from the start of Mini-Sentinel in 2009 to present**



Title	Medical Product	Outcomes	Date
Incidence Rate of Severe Uterine Bleeding Among New Users of Oral Anticoagulants: A Descriptive Analysis Exploratory Analyses	apixaban, dabigatran, oral anticoagulant, rivaroxaban, warfarin	severe uterine bleed	05/18/2021
Angioedema following Sacubitril/Valsartan Use in Patients with Heart Failure: A Propensity Score Analysis Safety Analyses	sacubitril/valsartan	angioedema	04/21/2021
Utilization of Sacubitril/Valsartan: A Descriptive Analysis Exploratory Analyses	sacubitril/valsartan		04/19/2021

* https://www.sentinelinitiative.org/assessments/drugs/individual-drug-queries#fda-sentinel-queries-from-aria-and-other-sentinel-data-sources

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Study Design in the Era of Real-World Evidence

FDA

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

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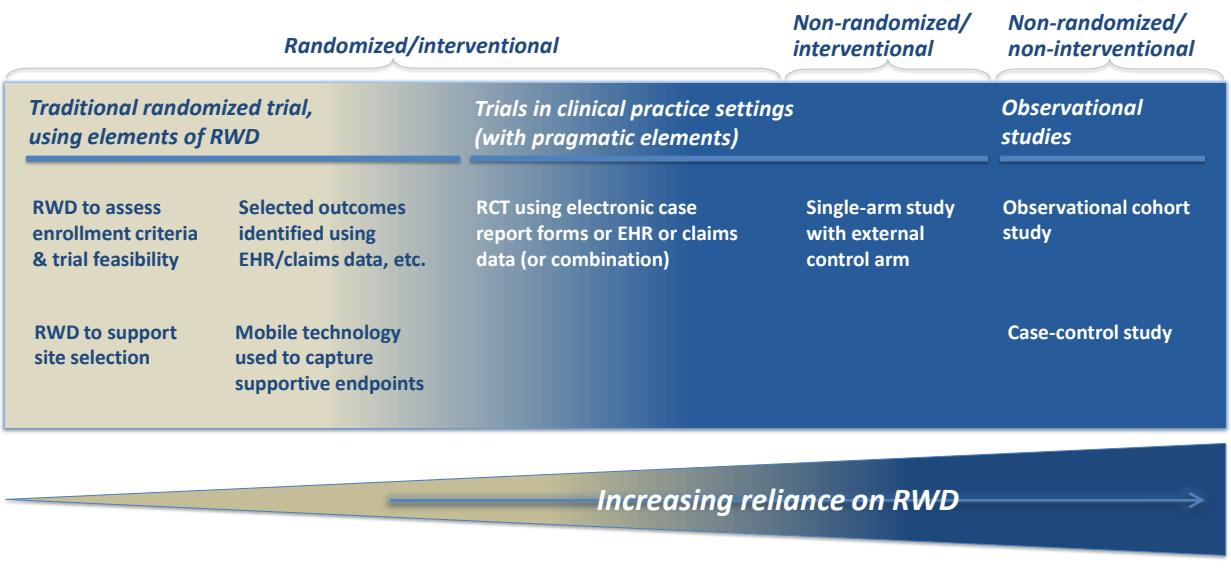
Overview of Real-World Data and Study Design

FDA



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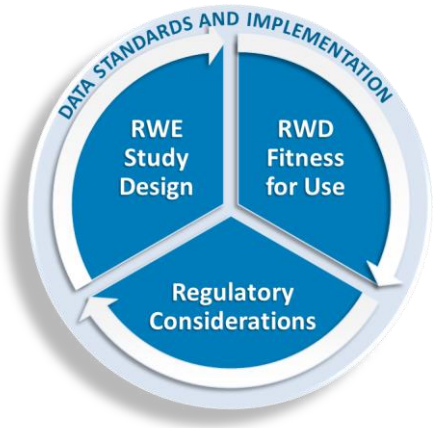
FDA Approach to Evaluating RWE



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**

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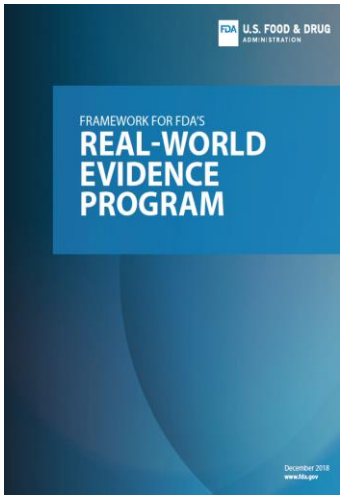
FDA RWE Framework (2018)



- **Applies to Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)**
- **Multifaceted program to implement RWE:**
  - **internal processes**
  - **external stakeholder engagement**

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RWE: FDA Internal and External Engagement

- Real-World Evidence Subcommittee internal activities (membership comprised of FDA staff from multiple CDER and CBER Offices):
  - provide oversight of policy development on RWE (e.g., guidances)
  - offer resources and leadership (e.g., to review divisions)
  - other activities

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- RWE Subcommittee external activities:
  - provide feedback on early-stage proposals from sponsors, vendors, etc.
  - discuss initiatives presented to Subcommittee for consideration

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- **Additional activities beyond the Subcommittee:**
  - **hold FDA- or Center-level public workshops on RWE-related topics**
  - **conduct webinars and other speaking engagements**

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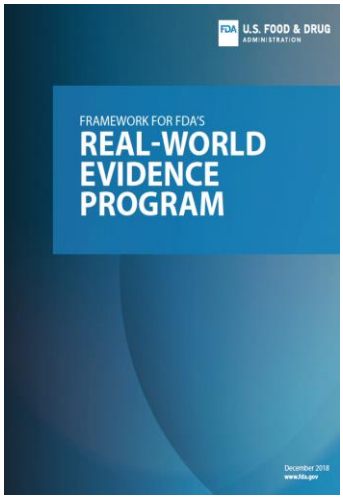
FDA RWE Framework (2018)



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FDA Guidance Development

- **Real-world evidence topics (from 2018 RWE Framework):**

- **"Submitting Documents Using RWD and RWE to FDA […]" Guidance, May 2019**
- **Ongoing work on other draft guidance documents (Dec 2021 target date)**

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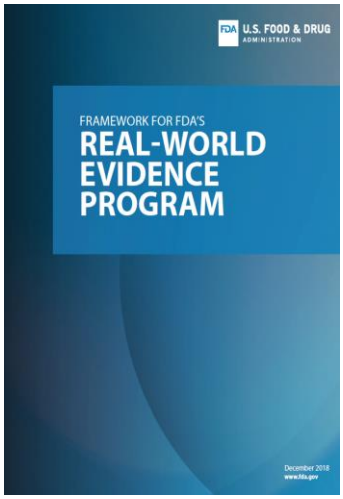
FDA RWE Framework (2018)



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Demonstration Projects – Examples

- Duke-Harmony EHR project
- VESALIUS EHR project
- ICAREdata project

- IMPACT AFib trial
- RCT-Duplicate project
- Genentech 'hybrid' RCT design project

- FDA MyStudies app
- 'DETECTe' project
- 'TMLE' project

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Example of Demonstration Project to Improve RWD

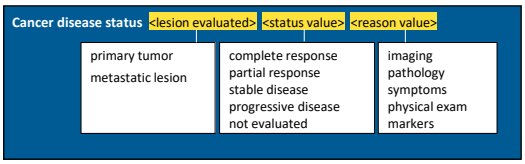
'ICAREdata': Develop and validate EHR-based measures in oncology

Cancer disease status

Clinical Assessment

Based on the data available today (at the time of evaluation), categorize the patient's disease extent.

ICAREdata Question Format



Example of Resulting Structured Phrase

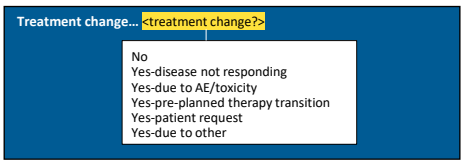
#Cancer disease status observed for #primary tumor was #progressive disease based on #imaging and #symptoms*

Treatment change

Clinical Assessment

Based on your evaluation today, are you making a change in treatment?

ICAREdata Question Format



Example of Resulting Structured Phrase

#Treatment change and #yes-disease not responding*

*** Blue font denotes controlled vocabularies**

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New RWE Development Projects

Funding Opportunity Title: Exploring the use of Real-World Data to Generate Real-World Evidenc
RFA-FD-20-030
(N=31 applications r

Number		
1 U01FD007213-01	B V H	Applying novel statistical approaches to develop a decision framework for hybrid RCT designs, combining internal control arms with data from RWD sources
1 U01FD007206-01	G	Transforming RWE with *U*nstructured and *S*tructured data to advance *T*ailored therapy (TRUST)
1 U01FD007172-01	V	Advancing standards and methodologies to generate RWE from RWD through a neonatal pilot project
1 U01FD007220-01	C Institute	RWD through a neonatal pilot project

Enhancing evidence generation by linking RCTs to RWD

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RWE Informs Effectiveness When Fit-for-Purpose

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**
Blincyto *(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 = RWE

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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 (KPNC)** to characterize the duration of protection in persons 50 years of age and older
Ibrance *(palbociclib)*	Men with certain types of advanced or metastatic breast cancer	2019	▪ Data from electronic health records and postmarketing reports of the **real-world use of IBRANCE in male patients**

List not exhaustive

Bold = RWE

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New Indication for Prograf Based on RWE

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**

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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 historical 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.

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Regulatory Standard for Adequate Evidence

- **Code of Federal Regulations at § 314.126 for adequate and well-controlled studies; goal is to distinguish the effect of the drug from other influences, such as spontaneous change in disease course, placebo effect, or biased observation**
- **Reports of adequate and well-controlled studies provide the primary basis for determining whether "substantial evidence" exists to support claims of effectiveness for new drugs**
- **Established practices, using traditional randomized controlled trials, include probabilistic control of confounding through randomization, blinding, standardized outcome assessment, adjudication criteria, and audits of study data**
- **"Observational" methods are being evaluated in this context**

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