Real World Evidence

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Learning Objectives

- Become familiar with the legislative background for the FDA's RWE program as well as FDA's definitions for RWD and RWE

- Review FDA's Framework for evaluating RWE

21st Century Cures Act

- FDA shall establish a program *to evaluate the potential use* of real world evidence (RWE) to support:

    - Approval of new indication for an drug approved under section 505(c)

    - Satisfy post-approval study requirements

- Program is based on a framework that was issued in December 2018

    - Describes the priority areas, remaining challenges and potential pilot opportunities that the program will address

- Draft Guidance to be issued by 2021

CDRH RWE Guidance

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
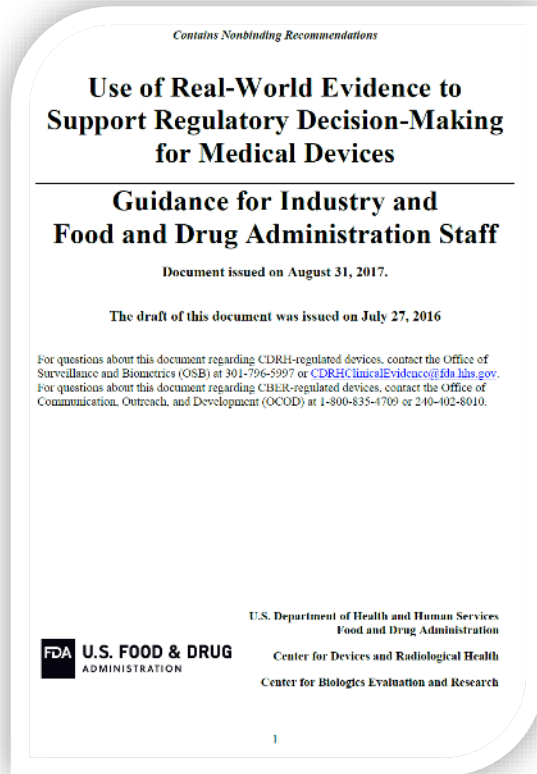
- Describes the potential use of Real World Evidence throughout the total product lifecycle for devices

  - Draft issued prior to 21st Century Cures Act

  - Definitions of Real World Data and Real World Evidence are harmonized with the FDA Framework

- CDRH, CBER, and CDER are coordinating as the 21st CC RWE program proceeds

https://www.fda.gov/ScienceResearch/SpecialTopics/RealWorldEvidence/default.htm

Definitions

- Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

- Real-World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.
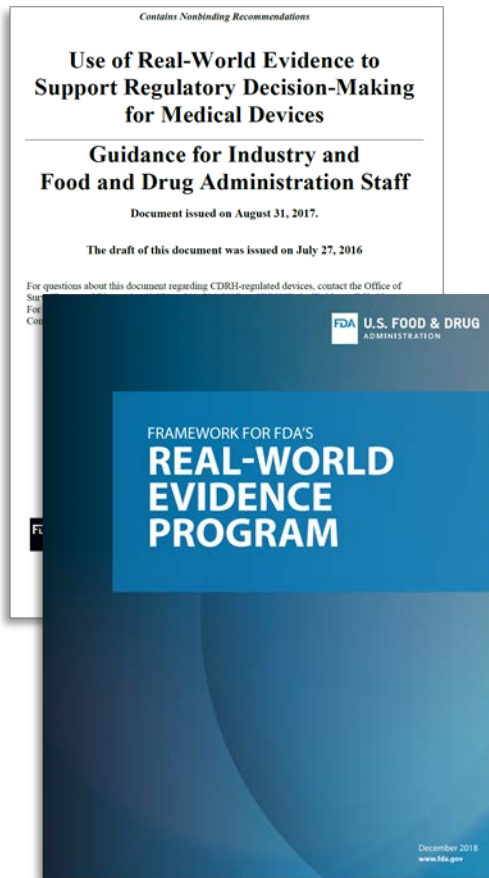
Potential Benefits of RWE

- Improve the efficiency of clinical research by capitalizing on data that is being captured every day

    - Digitization of health care as well as new analytics provide new opportunities to close the divide between research and clinical care

        - Additional settings, access to more diverse populations

- Big data – potential for detection of infrequent events or enrollment from relatively rare source populations

- Lower resource intensity – more questions answered

Benchmark

- Goal is to distinguish the effect of the drug from other influences such as spontaneous change in disease course, placebo effect, or bias

- Common practices:

  - Probabilistic control of confounding through randomization

  - Blinding

  - Controlled/standardized outcome assessment; Adjudication criteria; Audits

Framework for Evaluating RWE

- 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

RWD Fitness for Use

The Current State

- Data in pathology, radiology and lab reports as well as clinical notes are often unstructured (~80%)

- Linkage may be necessary to capture care in multiple health systems

- Structured data ≠ Standardized data

- Clinical outcome measures for drug approvals may not be used or consistently recorded in practice

Oncology Example
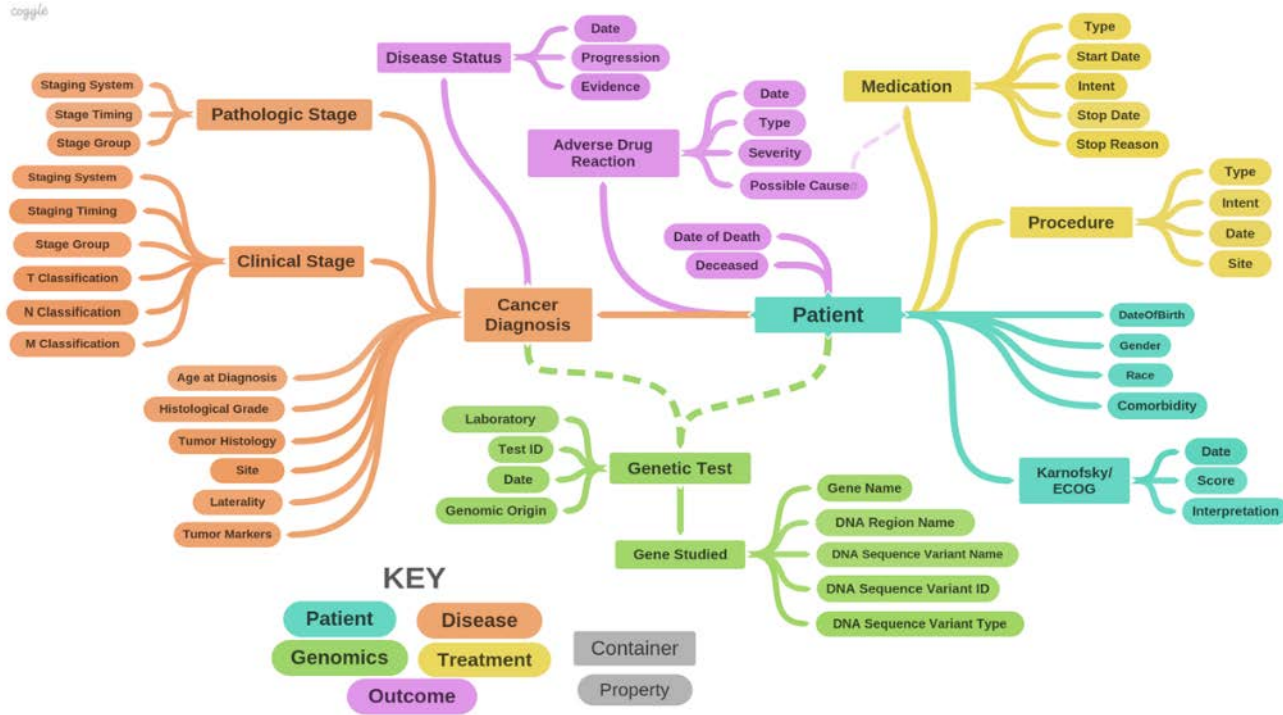
- mCODE: Minimal Clinical Oncology Data Elements - Data Model developed by ASCO, Alliance, and MITRE

FDA MyStudies

- Mobile App
  - Standard frameworks - ResearchKit (iOS), ResearchStack (Android)

- Web-based Configuration Portal (WCP)
  - Enables support of multiple types of medical product effectiveness and safety studies with minimal software development

- Secure Storage Environment
  - Generates secure tokens
  - Separates registration information and responses
  - Partitioned for multisite, decentralized, or distributed models

https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm625228.htm
https://www.fda.gov/Drugs/ScienceResearch/ucm624785.htm
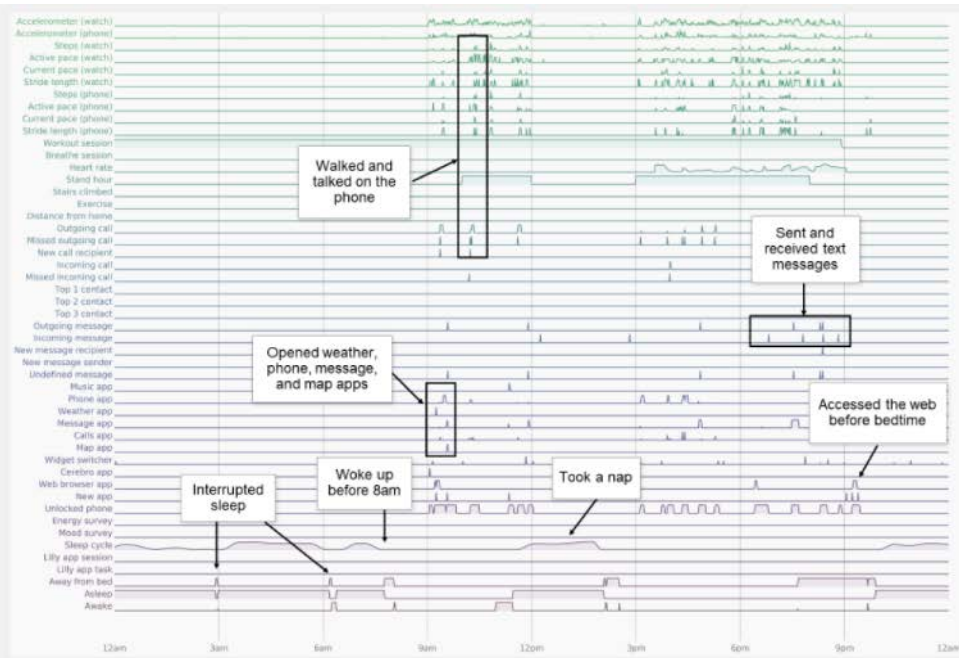https://github.com/PopMedNet-Team/FDA-My-Studies-Mobile-Application-System

Mobile + Wearables Example

The behaviorgram offers a rich representation of an individual's behavior.

It also serves as tool for data exploration, hypothesis generation, and most importantly, a way inspect the quality of the data.

- Presented by Ernesto Ramirez, Ph.D., Evidation, at the Duke-Margolis Developing RWD and Evidence Meeting, October 3, 2019

RWE Study Design

RWE incorporating Randomization

- Some factors to consider

    – What types of interventions might be well-suited to routine clinical care settings?

    – Capture of Existing Endpoints vs. Novel Endpoints

    – RWD lags, if applicable

    – Masking/Blinding

    – Monitoring

    – Source data

RELIANCE trial

- **RofLumilast or Azithromycin to prevent COPD Exacerbations**
  - Randomized "real world" trial; 1,600 adults in each arm
  - **Azithromycin** - macrolide with anti-inflammatory properties
  - **Roflumilast** - noncorticosteroid anti-inflammatory; phosphodiesterase type 4 inhibitor
  - Both guideline recommended but Roflumilast is FDA approved for this indication
- **Primary outcomes**
  - All cause hospitalization
  - All cause mortality
- **Follow-up**
  - 6-36 months, no visits, call center, Patient Portal, Site EMR
 - CMS linkage through FDA-Catalyst for outcomes and exposures

RCT Duplication Demonstration Projects

- Substantial assessment of the comparability of randomized and non-randomized designs necessary to gain confidence that non-interventional designs could provide credible evidence of drug effect

  - Comparable results with similar clinical questions?

  - Reasons for differences?

- Retrospective replication: 40 trials -> approximately 30

- Prospective replication: 10 trials -> approximately 7 in advance of trial findings

Regulatory Considerations

Regulatory Considerations
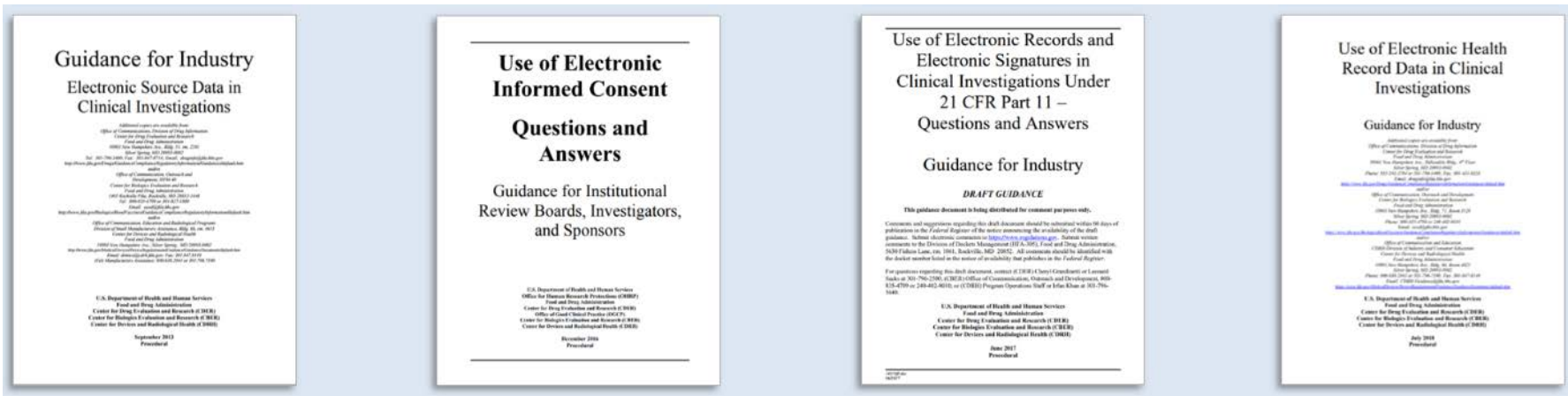
- Develop guidance as needed regarding the applicability of regulatory requirements to use of RWD in RCTs and observational studies, including informed consent, oversight, transparency
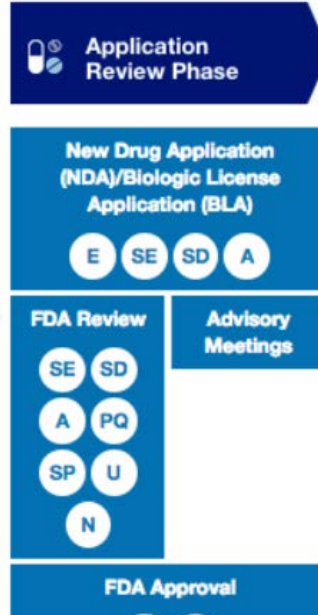
Data Standards
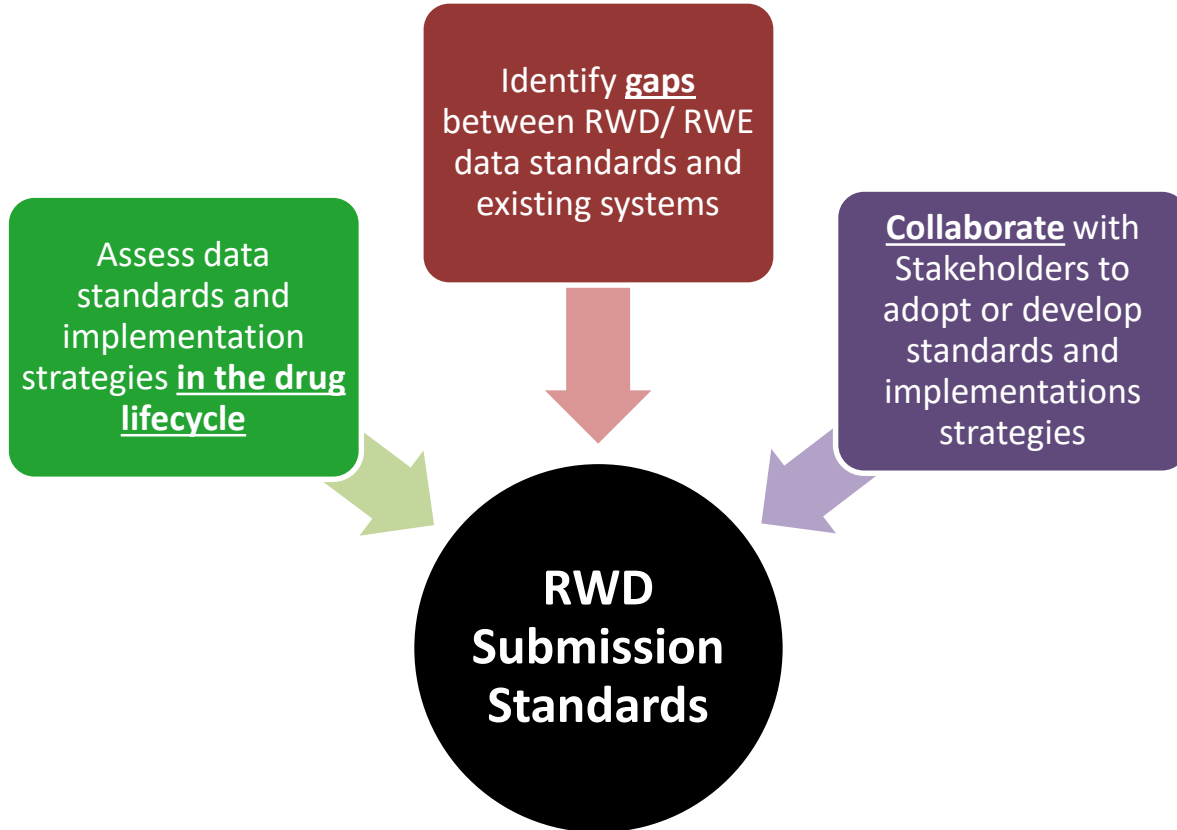
Data Standards in the Drug Lifecycle

Data Standards and Implementation

Identify **gaps** between RWD/ RWE data standards and existing systems

Assess data standards and implementation strategies **in the drug lifecycle**

Collaborate with Stakeholders to adopt or develop standards and implementations strategies

RWD Submission Standards

RWE Inbox

- CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

Challenge Questions

FDA

- True/False. Real-world data sources include only electronic health records (EHRs) and medical claims and billing data.

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Challenge Questions

Which topics are within the scope of the FDA RWE Program?

- A. Fitness for Use (EHR, claims, registries, digital health technologies)

- B. Regulatory Considerations

- C. Study Design (clinical trials in the real world setting, observational studies)

- D. Data Standards

- E. All of the Above

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