U.S. FOOD & DRUG ADMINISTRATION

Framework for FDA's Real-World Evidence Program

Jacqueline Corrigan-Curay, J.D., M.D.

Director, Office of Medical Policy

Center for Drug Evaluation and Research

Food and Drug Administration

March 15, 2019

Objectives

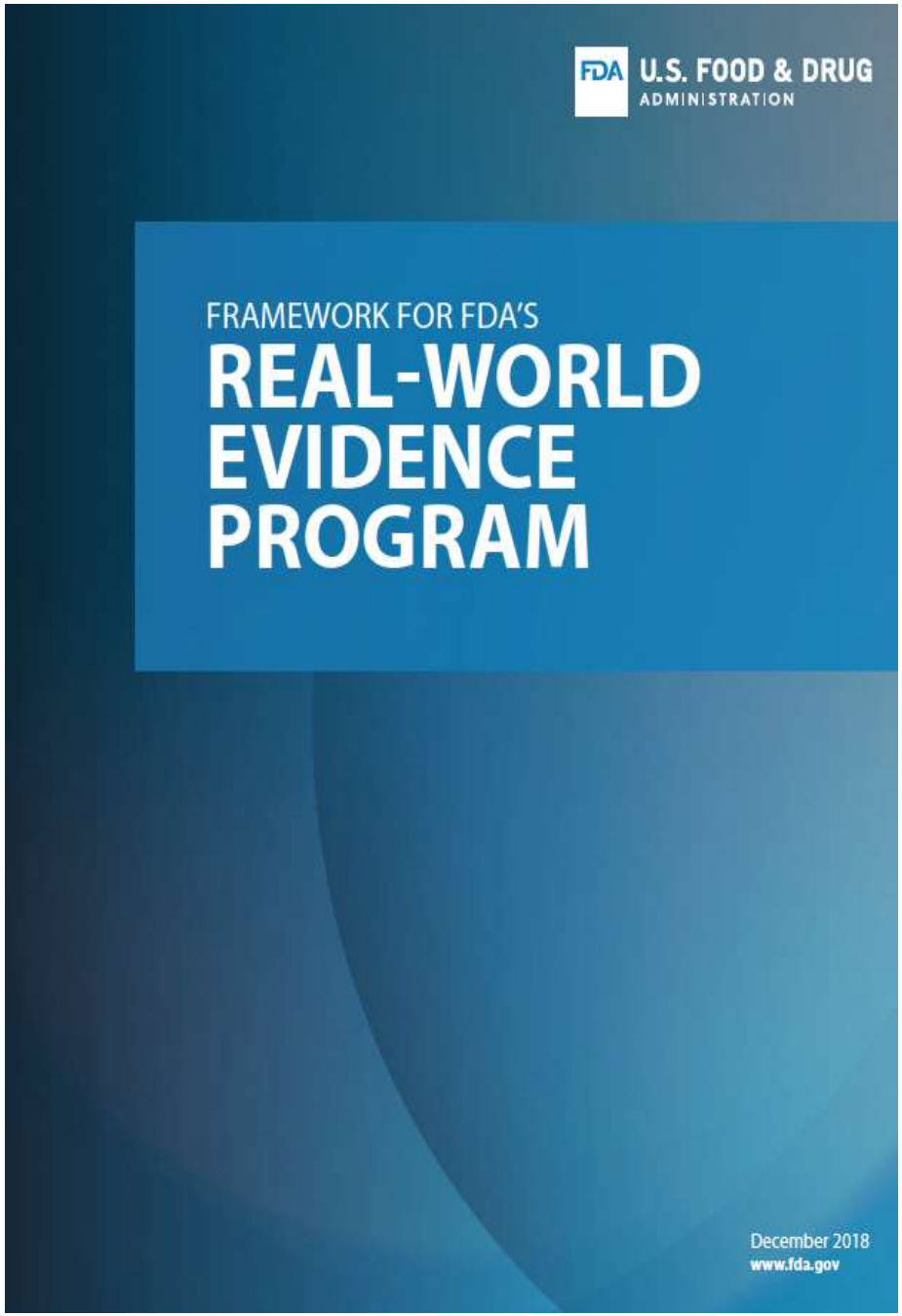
At the end of this presentation, participants will:

1. Describe the main elements of FDA's real-world evidence (RWE) Program.
2. List FDA considerations for evaluating the use of real-world data to generate RWE for regulatory decisions.
3. Explain program items the Agency plans to address in the RWE Program.
4. Describe at least one demonstration project that will help inform the use of RWD and RWE.

21st Century Cures Deliverables

- **FDA shall establish a program to evaluate the potential use of real world evidence (RWE) to:**
  - **Help support approval of a new indication for a drug approved under section 505(c)**
  - **Help satisfy post-approval study requirements**
- **Program will be based on a framework that was to be issued by 2018**

Real world evidence means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than *traditional clinical trials*



- **Intended for drug and biological products**
- **Outlines FDA's plan to implement the RWE program**
- **Multifaceted program**
  - **Internal processes**
  - **Guidance development**
  - **Stakeholder engagement**
  - **Demonstration projects**
- **Comment period closes April 16, 2019**

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

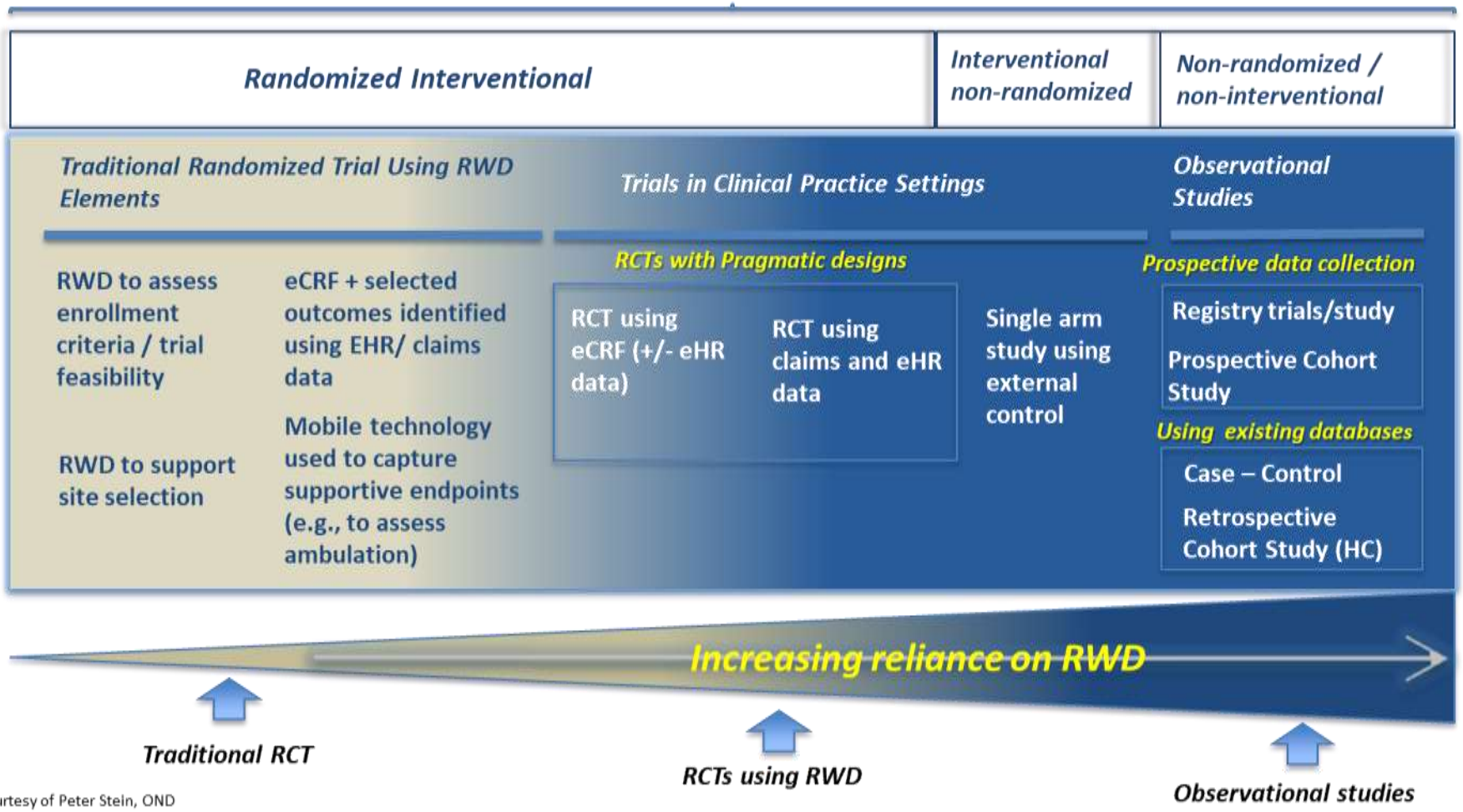
Scope of the RWE Program

Evaluates the potential use of RWE to support changes to labeling about drug product effectiveness, including:

- Adding or modifying an indication, such as a change in dose, dose regimen, or route of administration
- Adding a new population
- Adding comparative effectiveness or safety information

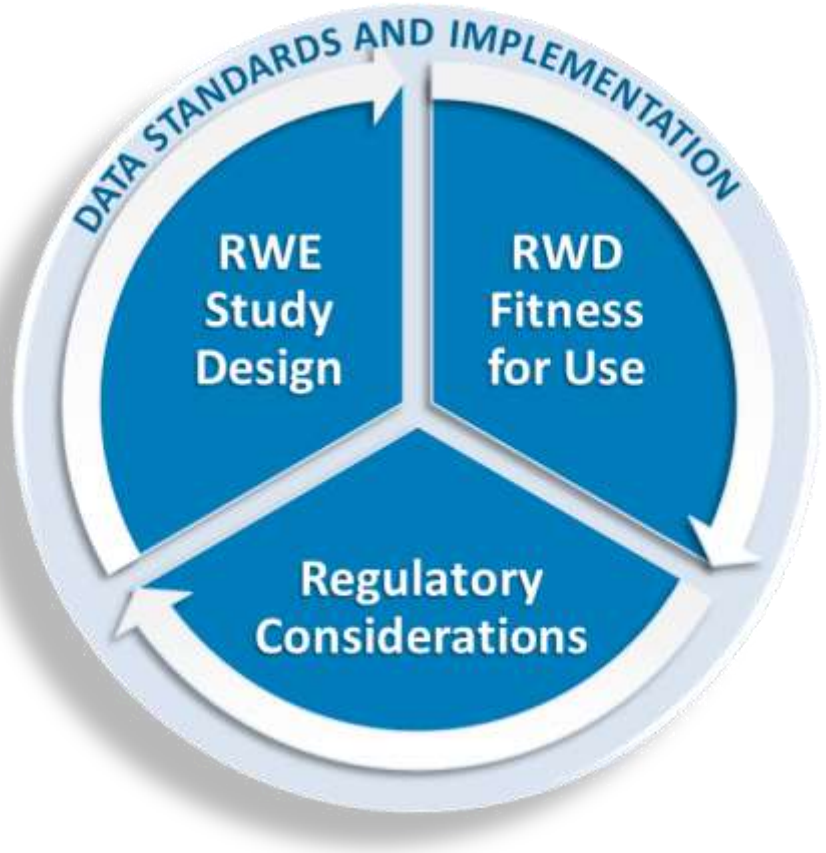
Wide Spectrum of Potential Uses of RWD / RWE in Clinical Studies

Different challenges and opportunities for each approach



Courtesy of Peter Stein, OND

Framework for Evaluating RWD/RWE for Use in Regulatory Decisions



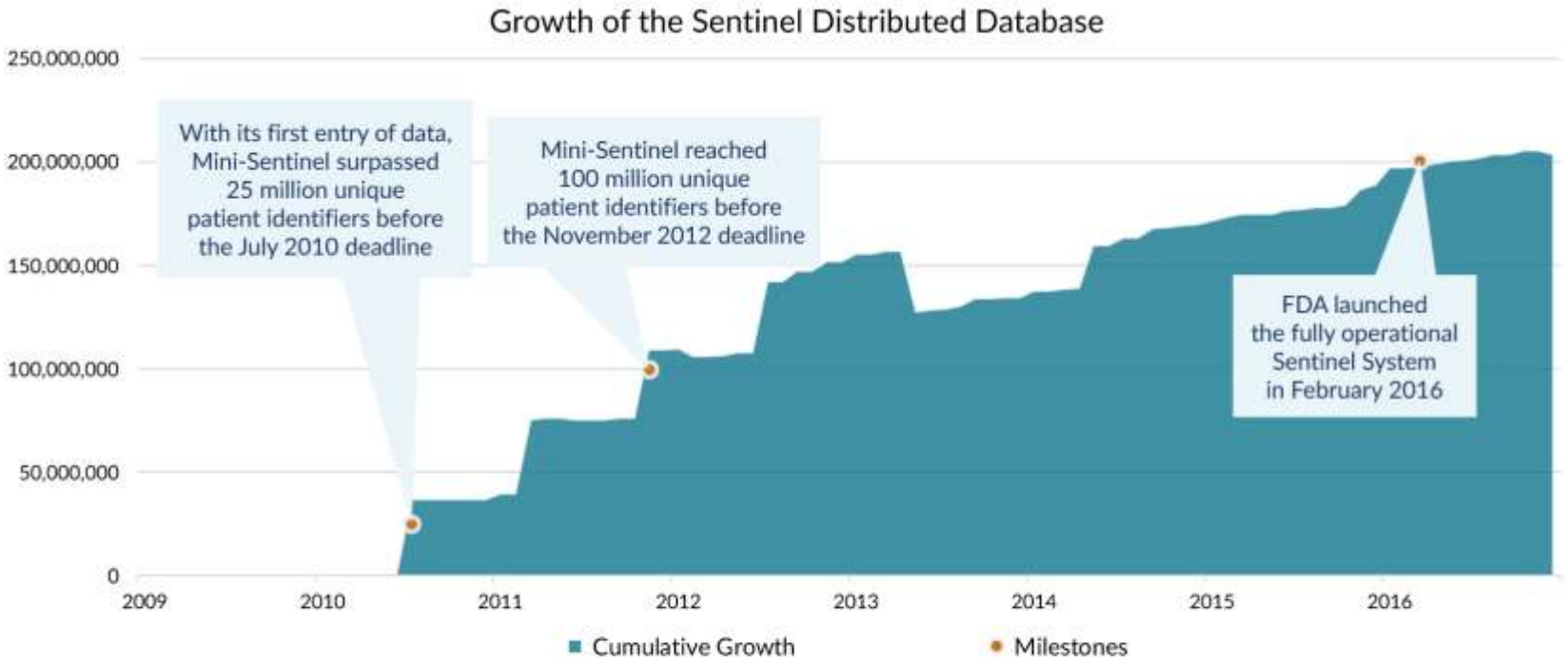
Considerations

- **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

- **Data reliability (data accrual and data quality control) and relevance**
  - Data must be collected and maintained in a way that provides an appropriate level of reliability
  - Data must be suitable to address specific regulatory question of interest
    - Challenges of capturing clinical effectiveness outcomes
- **FDA does not endorse any one type of RWD**
- **<u>Challenge</u>: A single source of RWD may not capture all data elements, and multiple data sources may be needed**
  - How to integrate data sources and address duplication

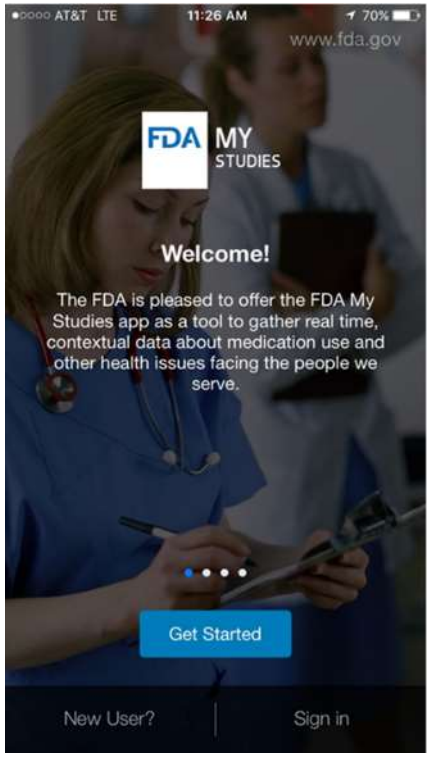
Gained Experience



The area above depicts the cumulative number of unique patient identifiers in the Sentinel Distributed Database from 2010 to present. If patients move health plans, they may have more than one patient identifier.

- 18 data partners
- Sentinel 5-year Strategic Plan 2019-2023
  - One strategic aim is to leverage the Sentinel System to accelerate access to and broader use of RWD for RWE generation
  - FDA-Catalyst

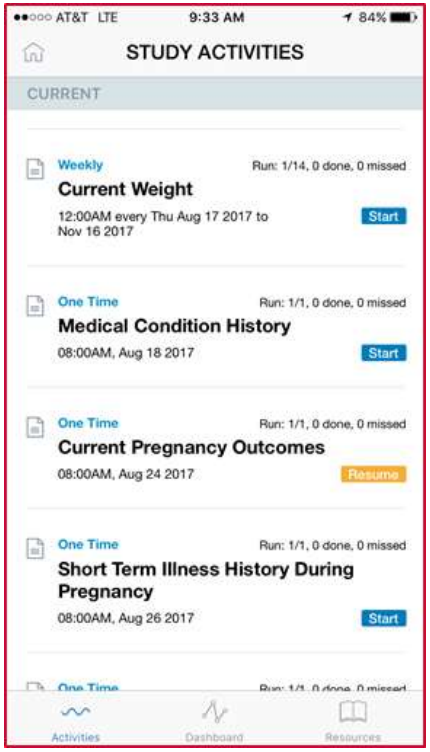
Sources of Patient-Centric RWD Beyond Health Care Records



JAMA Cardiology | Original Investigation

Passive Detection of Atrial Fibrillation Using a Commercially Available Smartwatch

Geoffrey H. Tison, MD, MPH; José M. Sanchez, MD; Brandon Ballinger, BS; Avesh Singh, MS; Jeffrey E. Olgin, MD; Mark J. Pletcher, MD, MPH; Eric Vittinghoff, PhD; Emily S. Lee, BA; Shannon M. Fan, BA; Rachel A. Gladstone, BA; Carlos Mikell, BS; Nimit Sohoni, BS; Johnson Hsieh, MS; Gregory M. Marcus, MD, MAS



RWD Fitness for Use

FDA

PROGRAM ITEMS:

- **Guidance on how to assess whether RWD from medical claims, EHRs and/or registries are fit for use to generate RWE in support of drug product effectiveness**
- **Explore the use of digital technology tools, electronic PROs, and wearables to potentially fill gaps**

Potential for Study Designs Using RWD to Support Effectiveness

FDA

Factors when considering embedding a randomized trial in clinical settings in order to access RWD

- What types of interventions and therapeutic areas might be well-suited to routine clinical care settings?
- What is the quality of data that can be captured in these settings?
- Bridging between regulatory endpoints and clinical practice

PROGRAM ITEM:

Guidance on considerations for using RWD in randomized clinical trials for regulatory purposes, including use of pragmatic design elements

Potential for Study Designs Using RWD to Support Effectiveness

FDA

Non-randomized, single arm trials with external RWD control

- RWD as a basis for external controls is not without challenges given potential differences between trial participants and non-trial participants
- However, robust RWD on patients currently receiving other treatments together with statistical methods could improve quality of external control data

PROGRAM ITEM:

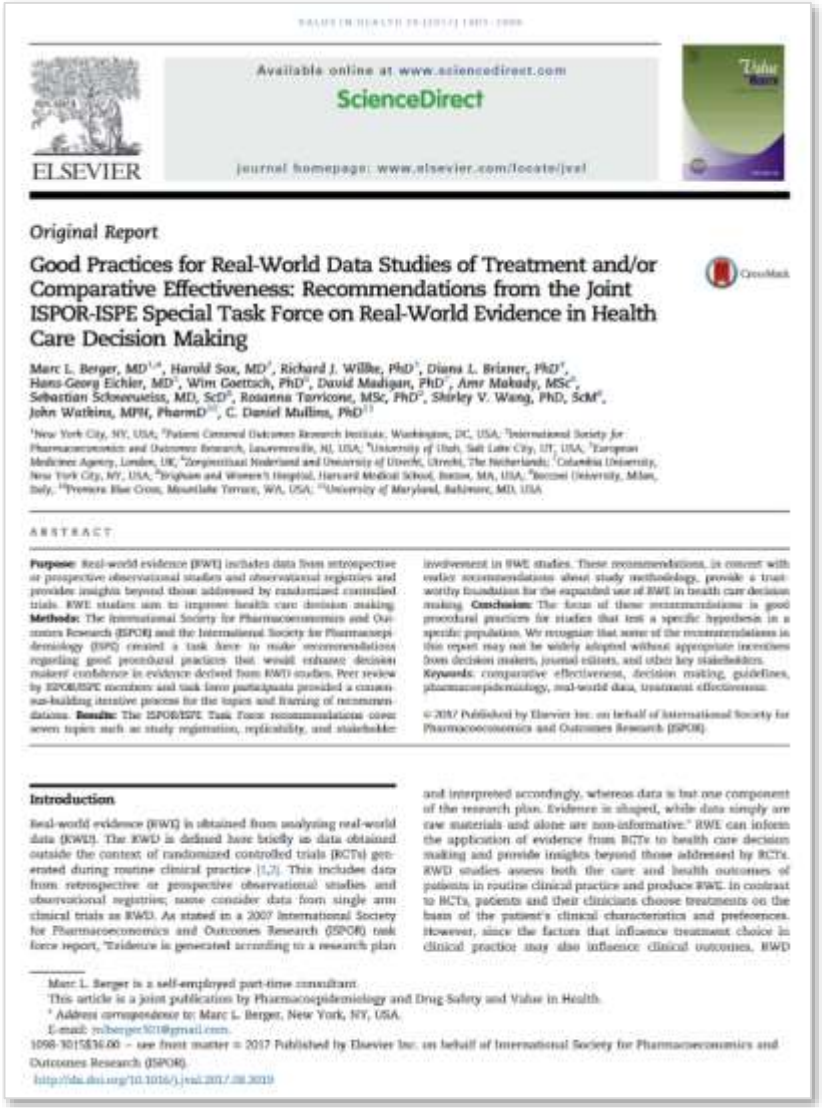
Guidance on the use of RWD to generate external control arms is also being considered

Potential for Study Designs Using RWD to Support Effectiveness

FDA

Observational studies

- Transparency about study design and analysis before execution is critical for ensuring confidence in the result
- What should transparency for observational studies look like?



ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Original Report

Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making

Marc L. Berger, MD[1,*], Harold Sox, MD[2], Richard J. Willke, PhD[3], Diana L. Brixner, PhD[4], Hans-Georg Eichler, MD[5], Wim Goettsch, PhD[6], David Madigan, PhD[7], Amr Makady, MSc[6], Sebastian Schneeweiss, MD, ScD[8], Rosanna Tarricone, MSc, PhD[9], Shirley V. Wang, PhD, ScM[8], John Watkins, MPH, PharmD[10], C. Daniel Mullins, PhD[11]

ABSTRACT

Purpose: Real-world evidence (RWE) includes data from retrospective or prospective observational studies and observational registries and provides insights beyond those addressed by randomized controlled trials. RWE studies aim to improve health care decision making. **Methods:** The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) created a task force to make recommendations regarding good procedural practices that would enhance decision makers' confidence in evidence derived from RWD studies. Peer review by ISPOR/ISPE members and task force participants provided a consensus-building iterative process for the topics and framing of recommendations. **Results:** The ISPOR/ISPE Task Force recommendations cover seven topics such as study registration, replicability, and stakeholder involvement in RWE studies. These recommendations, in concert with earlier recommendations about study methodology, provide a trustworthy foundation for the expanded use of RWE in health care decision making. **Conclusion:** The focus of these recommendations is good procedural practices for studies that test a specific hypothesis in a specific population. We recognize that some of the recommendations in this report may not be widely adopted without appropriate incentives from decision makers, journal editors, and other key stakeholders.

Keywords: comparative effectiveness, decision making, guidelines, pharmacoepidemiology, real-world data, treatment effectiveness.

Introduction

Real-world evidence (RWE) is obtained from analyzing real-world data (RWD). The RWD is defined here briefly as data obtained outside the context of randomized controlled trials (RCTs) generated during routine clinical practice [1,2]. This includes data from retrospective or prospective observational studies and observational registries; some consider data from single arm clinical trials as RWD. As stated in a 2007 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force report, "Evidence is generated according to a research plan and interpreted accordingly, whereas data is but one component of the research plan. Evidence is shaped, while data simply are raw materials and alone are non-informative." RWE can inform the application of evidence from RCTs to health care decision making and provide insights beyond those addressed by RCTs. RWD studies assess both the care and health outcomes of patients in routine clinical practice and produce RWE. In contrast to RCTs, patients and their clinicians choose treatments on the basis of the patient's clinical characteristics and preferences. However, since the factors that influence treatment choice in clinical practice may also influence clinical outcomes, RWD

Marc L. Berger is a self-employed part-time consultant.
This article is a joint publication by Pharmacoepidemiology and Drug Safety and Value in Health.
* Address correspondence to: Marc L. Berger, New York, NY, USA.
E-mail: mlberger301@gmail.com.

1098-3015/$36.00 – see front matter © 2017 Published by Elsevier Inc. on behalf of International Society for Pharmacoeconomics and Outcomes Research (ISPOR).
http://dx.doi.org/10.1016/j.jval.2017.08.3019

Observational Studies: Initial Questions[1]

- **What are the characteristics of the data?**
  - ✓ Diagnostic precision, consistency in data on exposure, relevant endpoint outcome captured across populations, lack of missing data, robust data on covariates
- **What are the characteristics of the study design and analysis that improve the chance of a valid result?**
  - ✓ Can use of an active comparator improve the chance of a valid result?
  - ✓ Are there prespecified sensitivity analyses and statistical diagnostics that can provide confidence that the effect of unmeasured cofounders would not change the causal inference?

1- not all-inclusive

Potential for Study Designs Using RWD to Support Effectiveness

FDA

PROGRAM ITEM:

Guidance about observational study designs using RWD, including whether and how these studies might provide RWE to support product effectiveness in regulatory decision making

Regulatory Considerations

- **Identify potential questions regarding the applicability of regulatory requirements to use of RWD for regulatory decisions in RCTs and observational studies, including informed consent and oversight**

- **Assess whether current guidance documents on the use of electronic source data are sufficient**

Foundation for Use of Electronic Source Data

FDA

Guidance for Industry

Electronic Source Data in Clinical Investigations

U.S. Department of Health and Human Service
Food and Drug Administration
Center for Drug Evaluation and Research (CDE
Center for Biologics Evaluation and Research (CB
Center for Devices and Radiological Health (CD

September 2013
Procedural

Use of Electronic Informed Consent

Questions and Answers

Guidance for Institutional Review Boards, Investigator and Sponsors

U.S. Department of Health and Human Services
Office for Human Research Protections (OHRP)
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Good Clinical Practice (OGCP)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2016
Procedural

Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers

Guidance for Indu

DRAFT GUIDANCE

This guidance document is being distributed for comment p

Comments and suggestions regarding this draft document should be su
publication in the *Federal Register* of the notice announcing the availa
guidance. Submit electronic comments to https://www.regulations.gov
comments to the Division of Dockets Management (HFA-305), Food a
5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments sh
the docket number listed in the notice of availability that publishes in t

For questions regarding this draft document, contact (CDER) Cheryl G
Sacks at 301-796-2500; (CBER) Office of Communication, Outreach a
835-4709 or 240-402-8010; or (CDRH) Program Operations Staff or In
5640.

U.S. Department of Health and Human Servi
Food and Drug Administration
Center for Drug Evaluation and Research (CD
Center for Biologics Evaluation and Research (C
Center for Devices and Radiological Health (CI

June 2017
Procedural

Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

July 2018
Procedural

Regulatory Considerations

FDA

PROGRAM ITEMS:

- **Guidance as needed on regulatory considerations raised by different study designs to generate RWE that is submitted to support drug product effectiveness**

- **Consider whether additional guidance on use of electronic source data is needed**

Data Standards and Implementation

Activities include:

- Identifying and assessing data standards and implementation strategies required to use RWD/ RWE
- Identifying gaps between RWD/ RWE data standards and existing FDA systems
- Collaborating with stakeholders to adapt or develop standards and implementation strategies

Continued Active Stakeholder Engagement

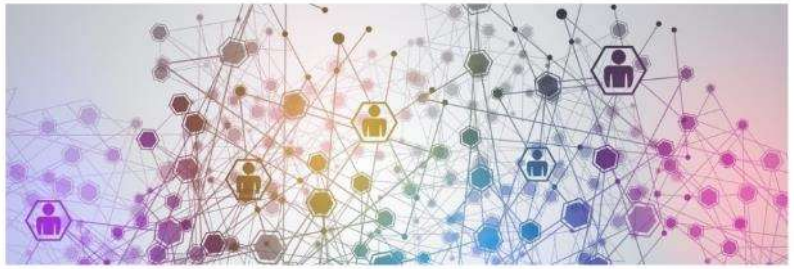
A Framework for Regulatory Use of Real-World Evidence
September 13, 2017

The National Academies of SCIENCES ENGINEERING MEDICINE

National Academies RWE Workshop Series |

FRIENDS of CANCER RESEARCH

Real world evidence scoping roundtable



DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

The Academy of Medical Sciences

Stakeholder Engagement

Internal Engagement

- **Launched internal website and outreach to engage FDA staff**
- **Established the RWE Subcommittee of the Medical Policy Program and Review Committee, which…**
  - Includes leadership from CDER Offices, CBER, and CDRH.
  - Serves as a cross-cutting forum for RWD/RWE issues; focuses on CDER's evaluation of RWE and guides policy development.
  - Provides advisory recommendations on whether the underlying data, methods, and study design elements are appropriate for regulatory decisions.
  - Provides a platform to engage with stakeholders as the community at large continues to explore the utility of RWD.

Demonstration Projects

- Relevancy
- Quality
- Linkage

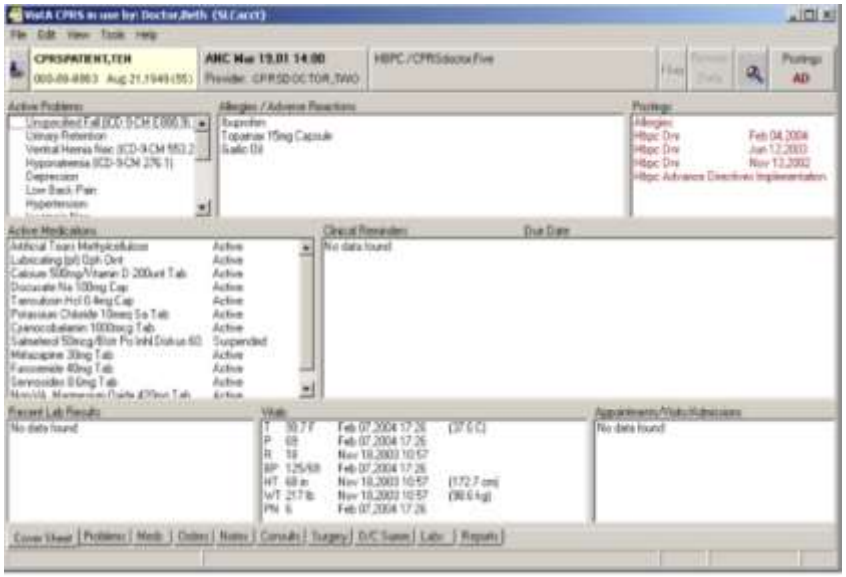
- Common data models
- Digital technology tools

- Randomized trials
- Assessment of observational studies

EHRs: Greatest Potential and Challenge

EHR data have advantages of:

- Presenting a more complete and granular clinical picture
- Including labs/imaging/ pathology reports



Challenges include:

- Data in pathology/ radiology and clinical notes are often unstructured (80%)
- Typing ≠ consistency/complete documentation
- Clinical outcome measures for drug approvals may not be used or consistently recorded in practice

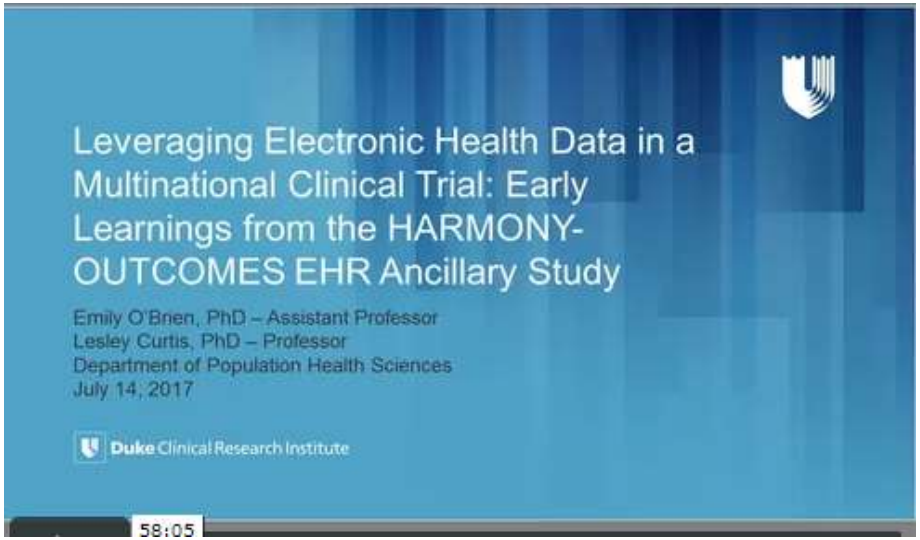
Creating Quality Clinical/Research Records – Design for Multiuse

- **OneSource: "enter the right clinical data once, use many times"**
- **FDA collaboration with Dr. Laura Esserman (UCSF)**
- **Integration of standards based tools into the EHR to bring together health care and research**
- **Demonstration in breast cancer clinical trials**

Courtesy of Dr. Laura Esserman and Susan Dubman

HARMONY-Outcomes Ancillary Study

- **Collaboration with Duke Clinical Research Institute and Glaxo SmithKline**
- **Supported by FDA**
- **Assess EHR ability to:**
  - Facilitate recruitment
  - Populate baseline characteristics
  - Identify clinical endpoints



July 14, 2017: Leveraging Electronic Health Data in a Multinational Clinical Trial: Early Learnings from the HARMONY-Outcomes EHR Ancillary Study

http://www.rethinkingclinicaltrials.org/grand-rounds-7-14-17/

Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus – NCT02465515

Demonstration Project

LimitJIA

pcori

FDA

Table 1: Primary Inclusion and Exclusion Criteria	
Inclusion Criteria: • Clinical diagnosis JIA by a pediatric rheumatologist within the past 6 months • Arthritis affecting ≤4 joints between disease onset and enrollment • Clinically active arthritis of at least 1 joint at the time of enrollment • Age ≥ 2 years old and < 17 years old • Prior or concurrent enrollment in the CARRA Registry	**Exclusion Criteria:** • Systemic JIA as defined by 2004 ILAR criteria[1] • Sacroiliitis (clinical or radiographic) • Inflammatory bowel disease • Psoriasis • History of uveitis or currently active uveitis • Prior treatment with systemic DMARD(s) or biologics • Current treatment with systemic glucocorticoids (past 30 days)

- **FDA-Catalyst is planning to align with the trial by providing support from the My Studies App**
  - Collection of primary outcome (uveitis) from ophthalmology appointments (also reminders for appointments)
  - Potential support for the Childhood Arthritis & Rheumatology Research Alliance (CARRA) Registry

Table of Scheduled Visits for Uveitis Screening[85]

ILAR Category	ANA	Age at JIA Onset	Screen	M 3	M 6	M 9	M 12	M 15	M 18
Oligoarthritis, Psoriatic arthritis,Undifferentiated	+	≤ 6	X	X	X	X	X	X	X
Oligoarthritis, Psoriatic arthritis,Undifferentiated	+	> 6	X	X		X		X	
Oligoarthritis, Psoriatic arthritis,Undifferentiated	-	≤ 6	X	X		X		X	
Oligoarthritis, Psoriatic arthritis,Undifferentiated	-	> 6	X	X				X	
Enthesitis-related arthritis	Any	Any	X	X				X	

CARRA
Childhood Arthritis and Rheumatology Research Alliance

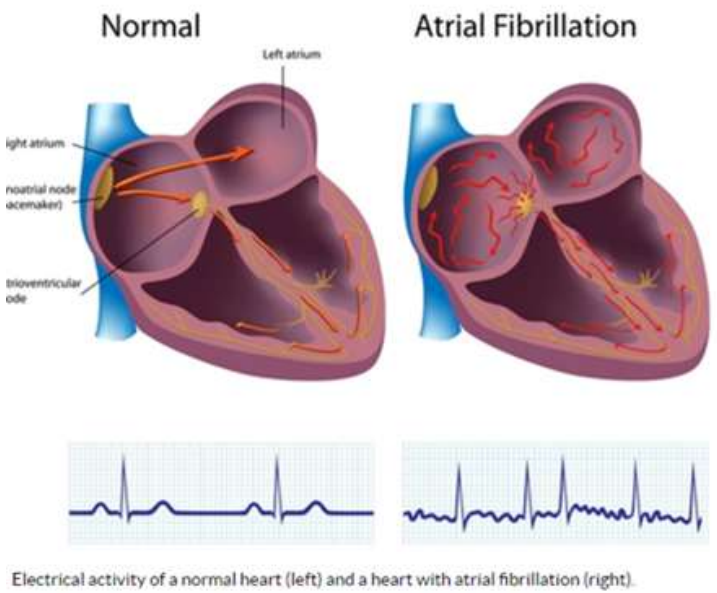
Demonstration Project

- **SPARC Inflammatory Bowel Disease cohort within the IBD Plexus research exchange platform**
  - Provider based recruitment of individuals >18 years of age with a confirmed IBD diagnosis from academic and community sites

- **FDA-Catalyst will align with the registry by providing support from the My Studies App**

Demonstration Project – *Impact AFib – Large Randomized Trial*

- Implementation of an individually randomized controlled trial within the FDA-Catalyst distributed database environment
- Test the ability of an education intervention to increase the appropriate use of oral anticoagulants in a patient population with atrial fibrillation (afib) at high risk of stroke
- Intervention materials include letter from health plan to describe project, patient brochure (additional information on AF and OACs), and patients pocket card (tool to facilitate conversation between patients and providers)
- Enrollment of approximately 80,000 individuals in the early and late intervention arm
- Protocol available at:



Electrical activity of a normal heart (left) and a heart with atrial fibrillation (right).

https://www.sentinelinitiative.org/FDA-catalyst/projects/implementation-randomized-controlled-trial-improve-treatment-oral-anticoagulants-patients

Demonstration Project

RELIANCE

pcori

FDA

- **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

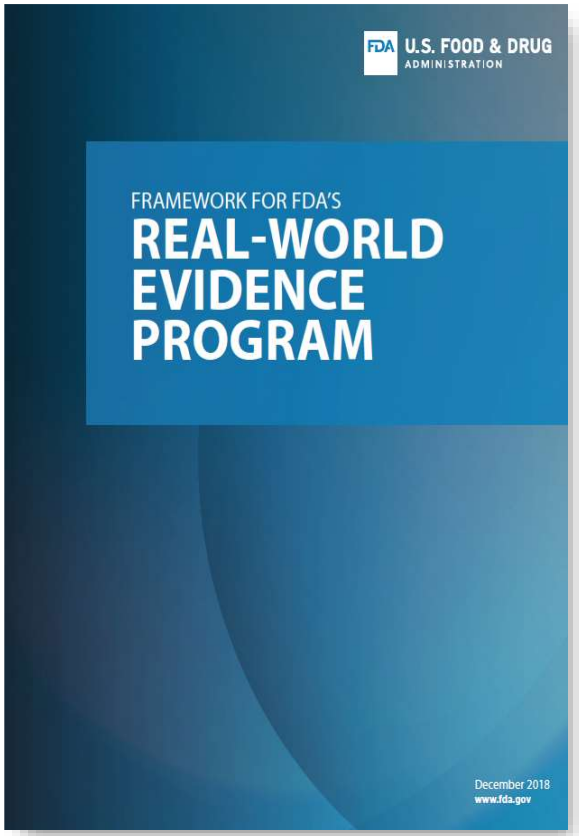
Demonstration Project: *Assessment of Non-Interventional Designs*

- **Attempted duplication of results of phase 3 & 4 RCTs over three years to provide empirical evidence base that could inform our level of confidence in high quality non-interventional designs**
- **FDA reviewers and researchers from the Brigham and Women's Hospital/Harvard Medical School Division of Pharmacoepidemiology**
  - Selected trials in which claims data are sufficiently fit for purpose in a research environment
    - Oral hypoglycemic, novel oral anticoagulant, antiplatelet, antihypertensive, anti-osteoporosis, asthma, COPD, heart failure, anti-arrhythmic, and lipid lowering medications
  - Concurred with pre-specified measures of agreement
  - Established an implementation process
- **Goal: 30 trials completed by March 2020**

https://www.rctduplicate.org/

Conclusion

- Framework serves as a roadmap for more fully incorporating RWD and RWE into the regulatory paradigm
- RWE remains a top FDA priority
- FDA is committed to understand its full potential
- Multi-stakeholder effort



Acknowledgements

- Khair ElZarrad
- Peter Stein
- David Martin
- Dianne Paraoan
- FDA RWE Committee

Q&A and Resources

Click for:

- FDA Real World Evidence webpage
- Framework for FDA's RWE Program
- FDA MyStudies Application
- PDF of today's slides

- Additional questions on the webinar?

  Email: CDERSBIA@fda.hhs.gov

Open Q&A begins shortly – type in your questions now.

Click Here for Evaluation and Certificate

Learn about other resources from CDER Small Business & Industry Assistance:
Visit Our Website!


FDA
U.S. FOOD & DRUG
ADMINISTRATION