U.S. FOOD & DRUG ADMINISTRATION

Real World Evidence and Personalized Medicine

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FDA

Presenter Disclosure Information

FINANCIAL DISCLOSURE:

No relevant financial relationship exists

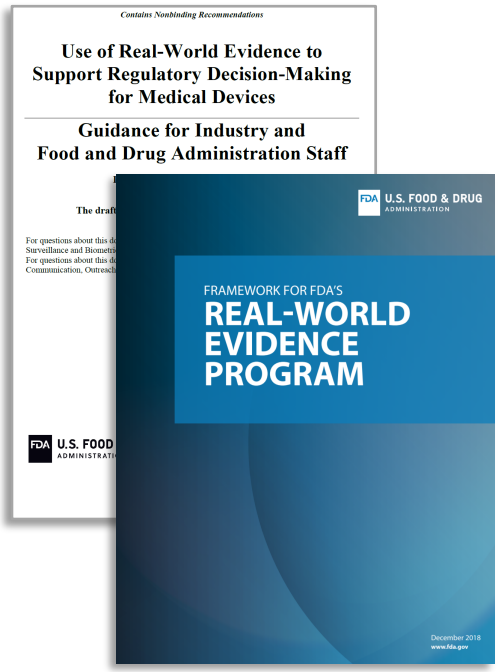
The views expressed herein are those of the author and should not be construed as FDA's views or policies

Overview

- Real world evidence in drug development
- FDA framework for real world evidence
  - Fitness for use
    - EHRs, claims databases, mobile technology
  - Study design
    - Traditional Randomized controlled trials, pragmatic trials, observational studies
  - Regulatory considerations

Real World Evidence

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*



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.

How Can RWE Contribute to Personalized Safety and Efficacy in Drug Development?

- Polymorphisms of target molecules
- Genomic subpopulations
- Metabolomic subpopulations
- Pathologic subpopulations
- Clinical subpopulations

Experience using RWD

- Safety
  - Considerable experience using claims and pharmacy data
  - Capture adverse events in large populations
- Efficacy
  - Limited experience using RWD
  - Small populations with rare inherited diseases and cancers
- Where are the opportunities for RWD/RWE to continue to fill gaps in evidence ?

Evidence of Effectiveness
Adequate and Well-Controlled Studies

- Distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation
- Designs that permit a valid comparison with a control to provide a quantitative assessment of drug effect
- Types of control:
  - (i) *Placebo concurrent control.*
  - (ii) *Dose-comparison concurrent control.*
  - (iii) *No treatment concurrent control.*
  - (iv) *Active treatment concurrent control.*
  - (v) *Historical control.* The results are compared with adequately documented natural history of the disease, historical control designs are usually reserved for special circumstances e.g. diseases with high and predictable mortality, studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

21 CFR 314.126

Clinical RWE of Effectiveness

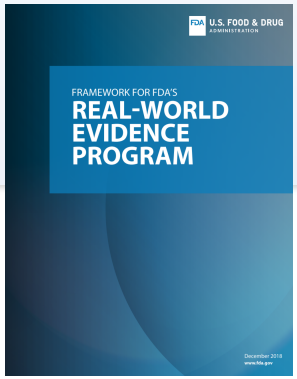
DRUG	INDICATION	STATUS	DATA
Lutathera *(lutetium 177 dotate)*	Gastro-pancreatic Neuroendocrine tumors	Approved 2017	▪ Open label clinical trial ▪ **Analysis of 360 patients in an investigator sponsored, open-label**, single-arm, single institution study of 1214 patients
Voraxaze *(glucarpidase)*	Methotrexate toxicity	Approved 2012	▪ Approval based on open-label, **NIH compassionate Use Protocol**
Uridine Triacetate	5 FU overdose	Approved 2015	▪ Two single-arm, open label expanded access trial of **135 patients compared to case history control**
Defitelio *(defibrotide sodium)*	Severe hepatic Veno-occlusive disorder	Approved 2016	▪ Two prospective clinical trials enrolling 179 patients and **an expanded access study with 351 patients**
Blincynto *(Blinatumomab)*	Acute Lymphoblastic Leukemia	Approved 2014	▪ Single arm trial ▪ Reference group weighted analysis of patient level **data on chart review of 694 patients at EU and US study sites***
Carbaglu carglumic acid	N-acetyl glucosamine synthetase deficiency	Approved 2010	▪ Retrospective, non-random, un-blinded **case series of 23 patients** compared to **historical control group**
Myozyme (alglucosidase alfa)	Pompe's disease	Approved 2004	▪ Open-label, non-randomized study of 18 patients compared to **historical control group of 62 untreated patients**
Refludan®	Heparin-induced thrombocytopenia	Approved 1998	▪ Two non-randomized, open-label multicenter trials using **historical control comparator group from HIT Registry**

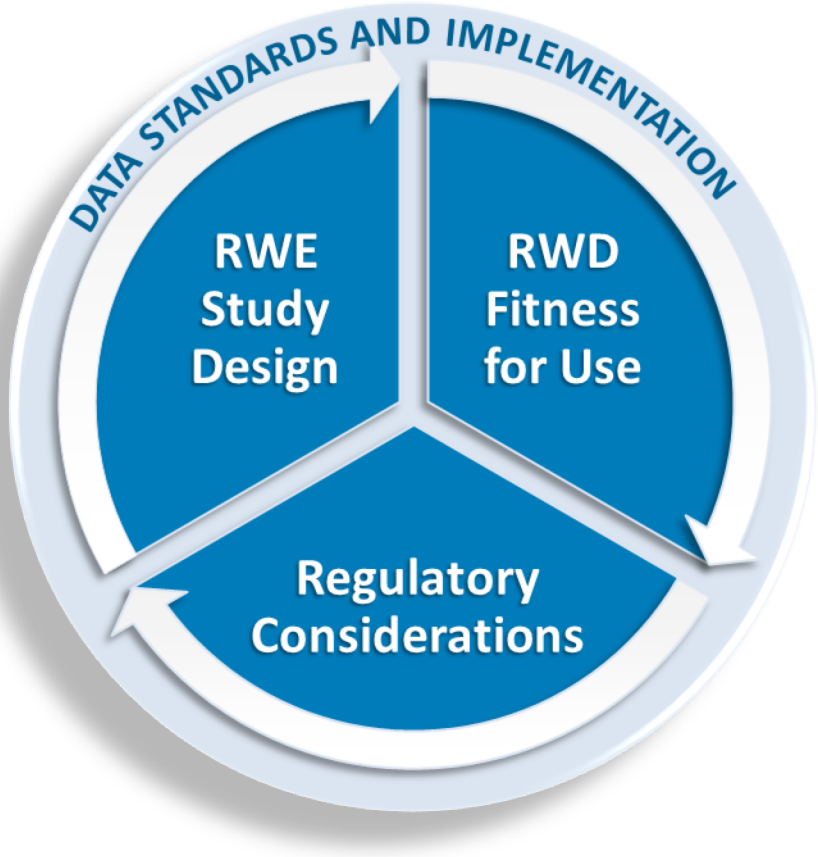
Bold = RWE

NOT EXHAUSTIVE

*https://www.nature.com/bcj/journal/v6/n9/full/bcj201684a.html

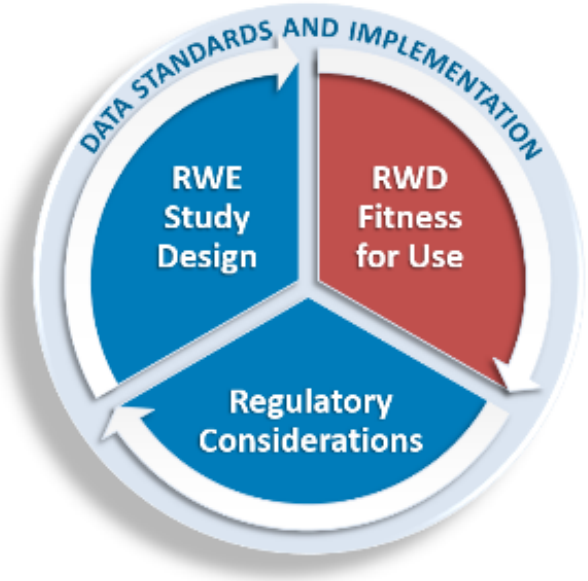
Framework for FDA's RWE Program





Consider:

- **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**



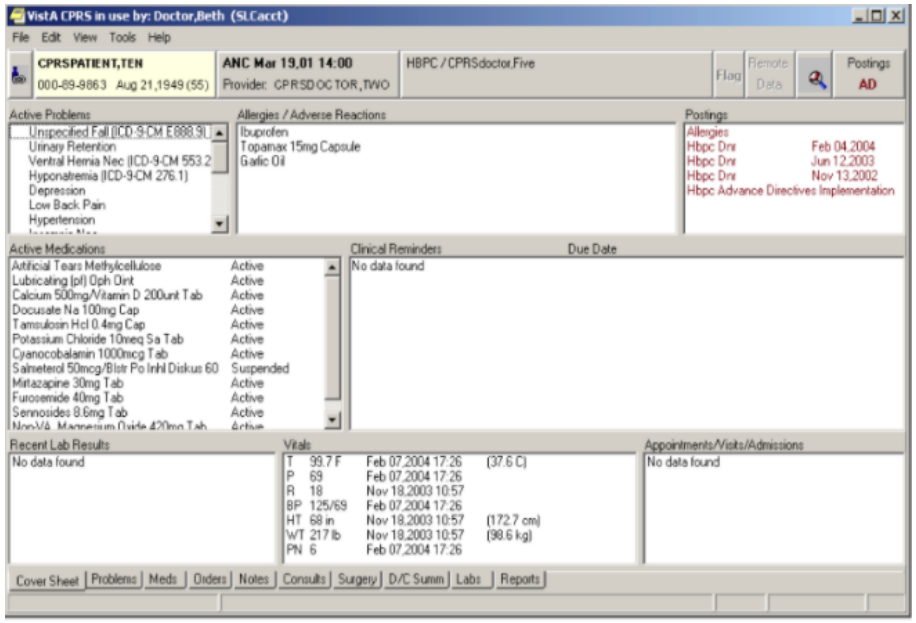
RWD FITNESS FOR USE

RWD - Fitness for Use

- **Reliability**
  - data accrual
  - quality
- **Relevance**
  - address specific regulatory question of interest
- **Completeness**
  - a single source of RWD may not capture all data elements, and multiple integrated data sources may be needed

Sources of RWE- Electronic Health Records

- Potential for a more complete and granular clinical picture
- Challenges
  - Unstructured
  - Lack of data standards
  - Incomplete
  - Not interoperable
  - Clinical outcome measures for drug approvals may not be used or consistently recorded in practice



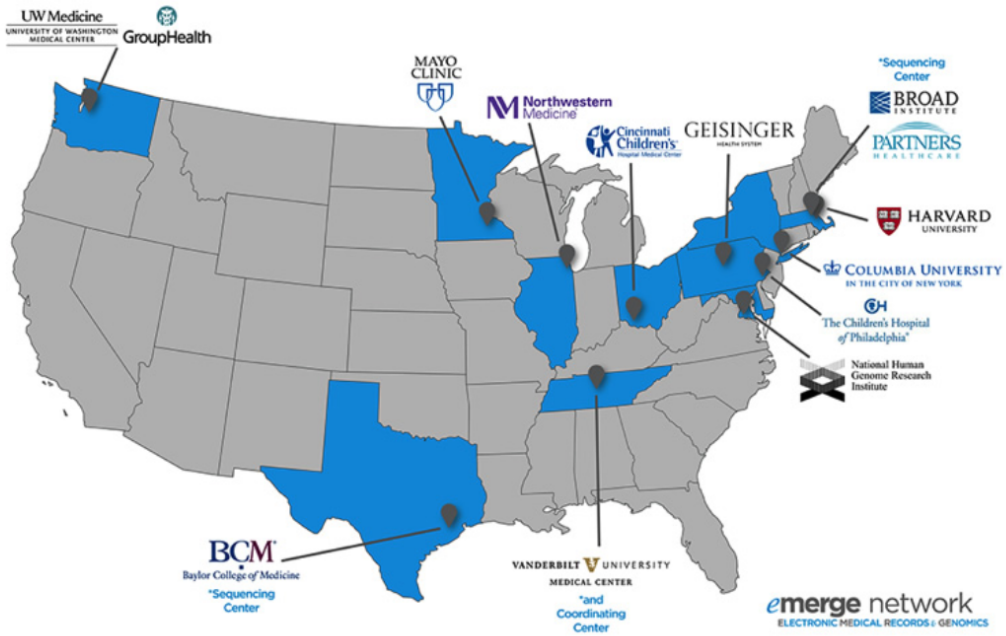
Creating Quality Clinical/Research Records – Design for Multiuse

- **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

Electronic Medical Records and Genomics (eMERGE)

National network organized and funded by the National Human Genome Research Institute (NHGRI) that combines DNA biorepositories with electronic medical record (EMR) systems for large scale, high-throughput genetic research in support of implementing genomic medicine.



Each site combines a biobank or study cohort with extensive genomic data and access to clinical data derived from electronic medical records. Sites are geographically dispersed and have diverse patient populations, including two sites focusing specifically on pediatrics.

https://emerge.mc.vanderbilt.edu/emerge-sites/

Patient-Generated Health Data (Digital Health Tools)

Biosensor as the data originator

e.g., activity trackers, glucose sensors, wireless heart rate monitors

Patient as the data originator

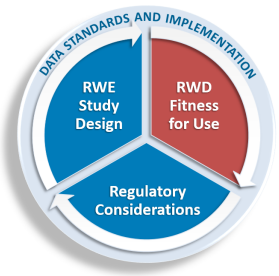
e.g., questionnaires, cognitive tests, coordination tests, episodic accelerometer based tests (six minute walk)

The Mobile Health Universe

- Mobile devices can capture health information directly from patients
- They include
  - cellphones capturing the patient's response to a PRO
  - cellphone cameras capturing the appearance of a lesion
  - customized sensors that measure and transmit physiological information e.g. movement in joints, heartrate irregularities, accelerometers, glucose monitors

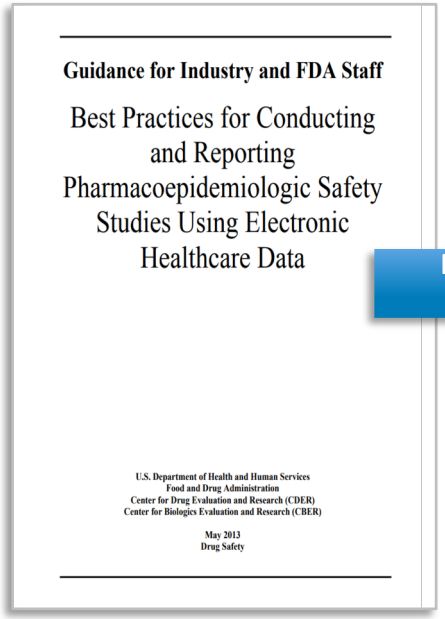
Biosensors and personalized medicine

- Selection of populations for participation in studies
- Identification of functional subpopulations who respond differently to treatment
- Identification of subpopulations at greater risk of adverse events
- Study medication adherence
- Novel endpoints e.g. continuous data measurements



RWD Fitness for Use

Leveraging the principles from the 2013 guidance on electronic health care data and our demonstration projects:



Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

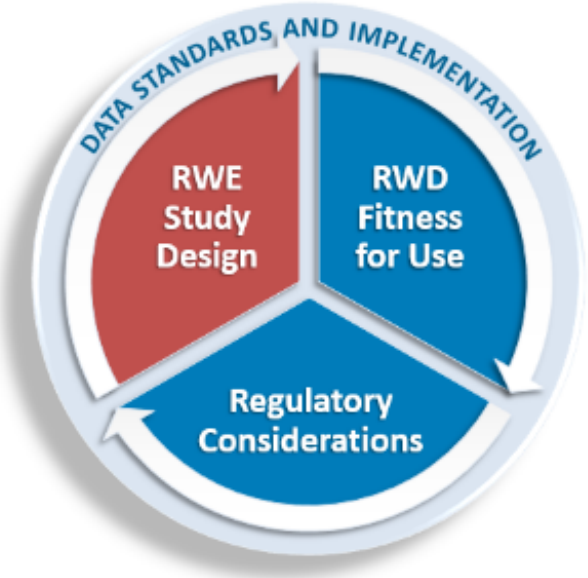
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2013
Drug Safety

PROGRAM ITEMS:

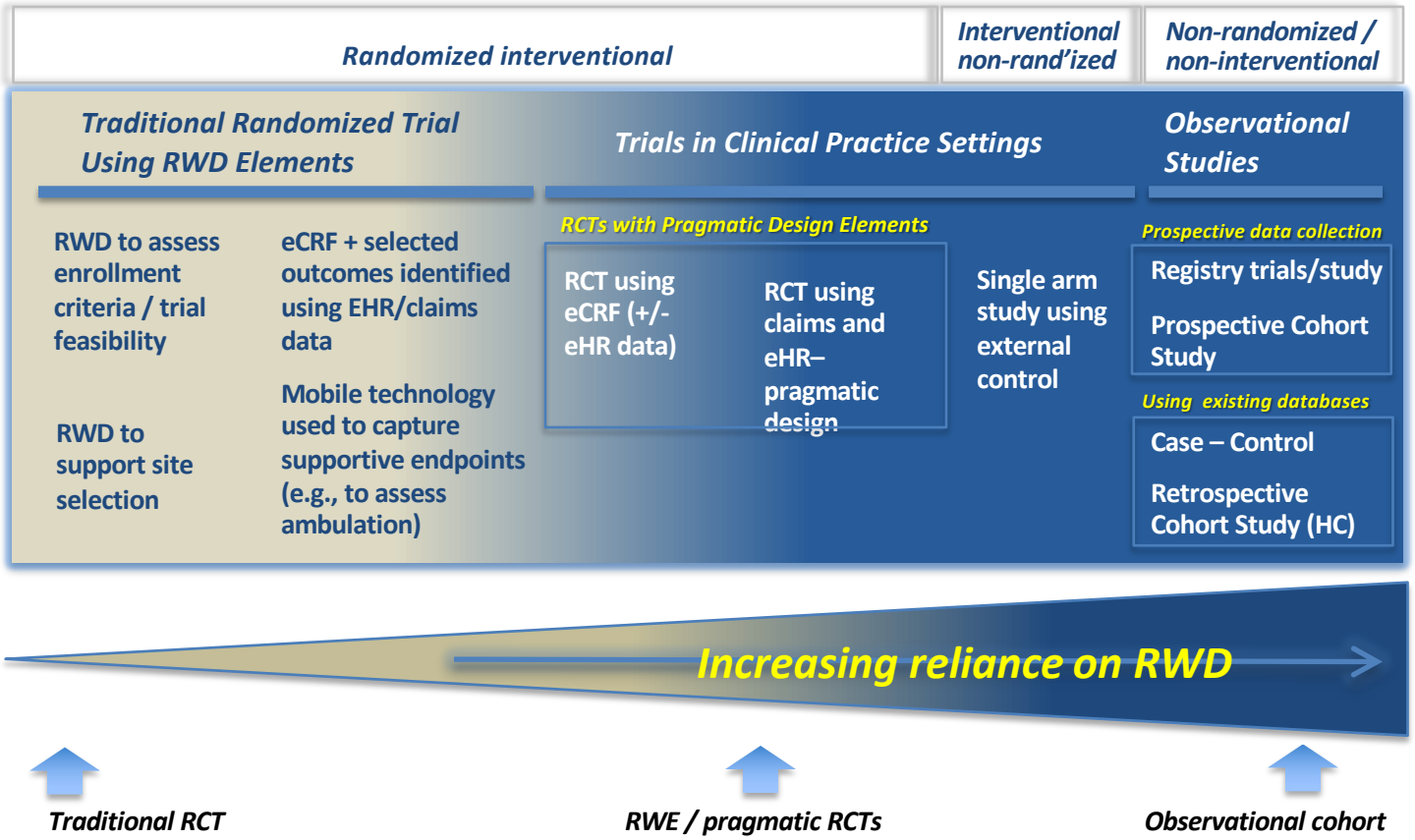
- **How to assess RWD from medical claims and EHRs and registry data to generate RWE regarding drug product effectiveness**
- **The use of mobile technologies, electronic PROs, and wearables to potentially fill gaps**

Sentinel



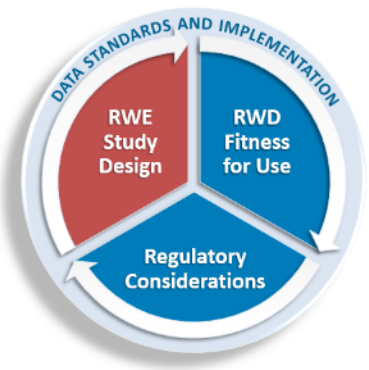
RWE STUDY DESIGN

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



Opportunities to integrate clinical research and eHRs

- Randomized controlled trials using the EHR platform
  - Research module in the EHR
  - Randomization and blinding
  - Dedicated study visits
  - This improves efficiencies, may allow for integration of trial-related and care-related activities
  - Makes some use of existing EHR data
- Pragmatic trials
  - Procedures that are part of health care
  - Data that do not require scheduling e.g. fractures, strokes, MIs
- Observational studies
  - Rely fully on existing data obtained in the course of health care (Real world evidence)



Randomized controlled trials

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?
- Blinding/Masking?
- 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

Pragmatic trials

- Salford lung study
- Randomized, open label comparison of fluticasone/vilanterol versus usual care in 2800 patients with COPD
- Used local EHR and local pharmacists
- 8.4% reduction in COPD exacerbations

Salford lung study

Advantages

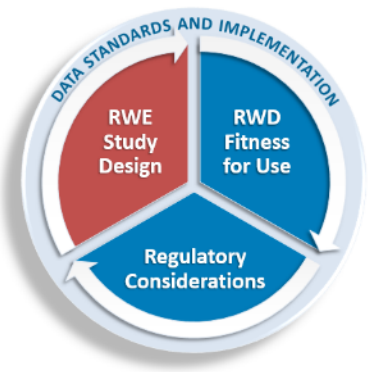
- Real world compliance
- Reduced cost
- Broad population including subgroups

Disadvantages

- Accuracy of diagnosis
- Compliance with treatment
- Confounding therapy
- Outcome bias

Precis criteria for pragmatism

- Eligibility
- Recruitment
- Setting
- Organization
- Flexibility – delivery
- Flexibility - adherence
- Follow-up
- Primary outcome
- Primary analysis



Observational studies

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

Pink Sheet
Pharma intelligence

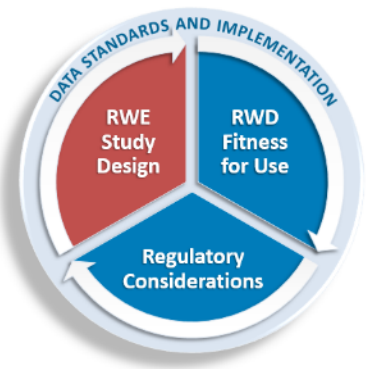
US FDA Is Hesitant About Using Observational Studies In Real-World Evidence Framework

FDA

06 Dec 2018 | ANALYSIS

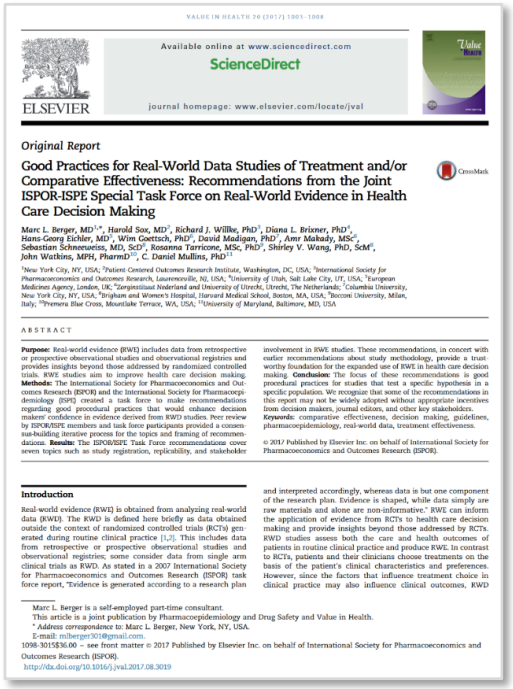
- **Treatment assignment based upon physician judgment, rather than random assignment, creates a challenge for establishing causal inference that must be addressed to support the acceptability of observational studies for effectiveness decisions**

- **Despite literature citing examples where observational and randomized trials have reached similar conclusions about treatment effect there are also examples when effects identified in observational studies could not be reproduced in randomized trials or when the effect sizes differed in direction or magnitude**



Potential for Study Designs Using RWD to Support Effectiveness

FDA



VALUE IN HEALTH 20 (2017) 1003–1008

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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

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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.

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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.
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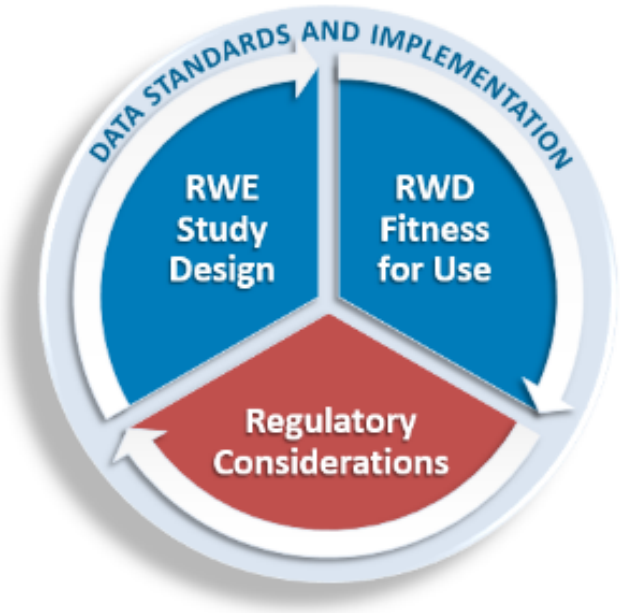
http://dx.doi.org/10.1016/j.jval.2017.08.3019

Observational studies

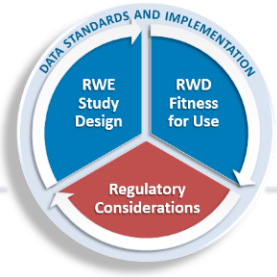
- Multiple different evaluations of the same data set may result in the chance finding of a favorable analysis
- Transparency of study design before analyzing observational data is critical to avoid biased selection of favorable analyses and to ensure methodological rigor
- Replication in different datasets is helpful

PROGRAM ITEM:

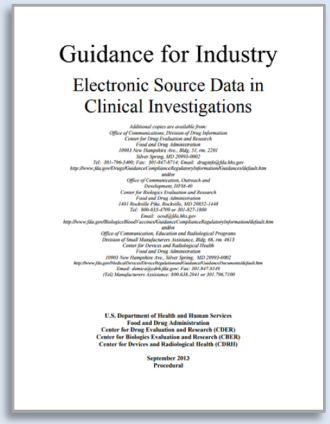
- **Guidance about observational study designs using RWD, including whether and how these studies might provide RWE to support product effectiveness in regulatory decision making**



REGULATORY CONSIDERATIONS



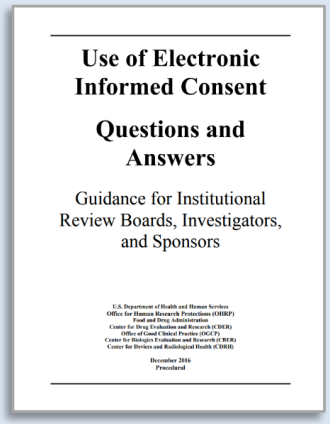
Regulatory Considerations


Guidance for Industry

Electronic Source Data in Clinical Investigations

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)

September 2013
Procedural

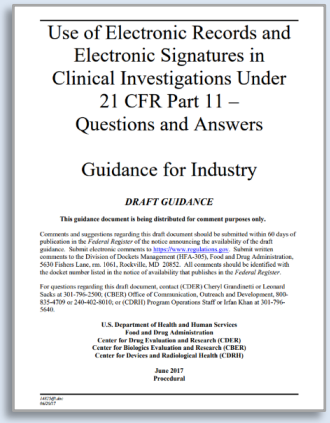

Use of Electronic Informed Consent

Questions and Answers

Guidance for Institutional Review Boards, Investigators, 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

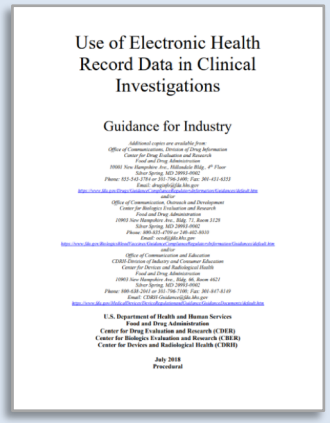
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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)

June 2017
Procedural


Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

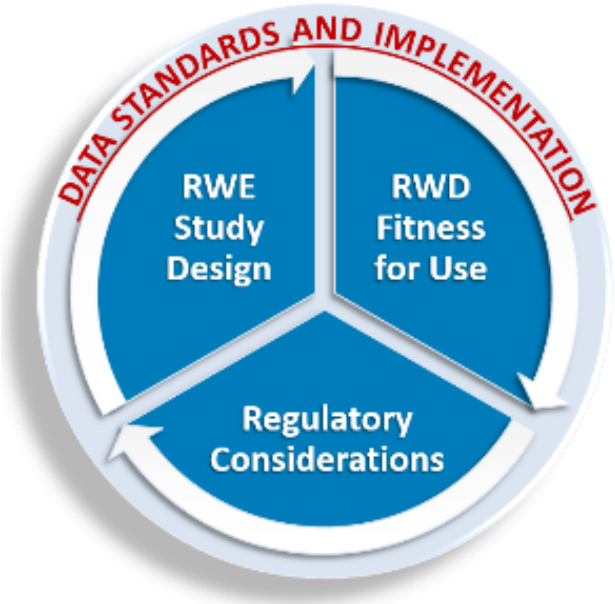
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

July 2018
Procedural

PROGRAM ITEMS:

Develop guidance as needed regarding the applicability of regulatory requirements to use of RWD in RCTs and observational studies, including informed consent and oversight

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



DATA STANDARDS AND IMPLEMENTATION

Data Standards and Implementation

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

Identify and assess data standards and implementation strategies **required** to use RWD/ RWE

Collaborating with Stakeholders to adopt or develop standards and implementations strategies

RWD Submission Standard

Conclusions

- Technology is expanding the reach of RWD with new access to large populations and rare subgroups
  - EHRs, genomic databases, vital statistics, electronic registries, mobile technologies
- We see new opportunities to harness these data sources for personalized medicine
- Ongoing success will depend on adapting these data sources to research
  - Data standards, interoperability, data quality, reliability and confidentiality

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CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov


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RWD/RWE: The Power of Many Benefiting Individual Patients

IMPLEMENTATION OF A RANDOMIZED CONTROLLED TRIAL TO IMPROVE TREATMENT WITH ORAL ANTICOAGULANTS IN PATIENTS WITH ATRIAL FIBRILLATION (IMPACT-AFib) (NCT03259373)

Target Population - Individuals with atrial fibrillation at high risk of stroke

Dx two diagnoses of AF (ICD-9 codes)
Risk CHA_2D_2-VASC: Age, sex, Dx of HTN, heart failure, vascular disease, diabetes

Enrolled 80,000 individuals

FDA Catalyst – part of Sentinel

Demonstration Project:
Assessment of Non-Interventional Designs

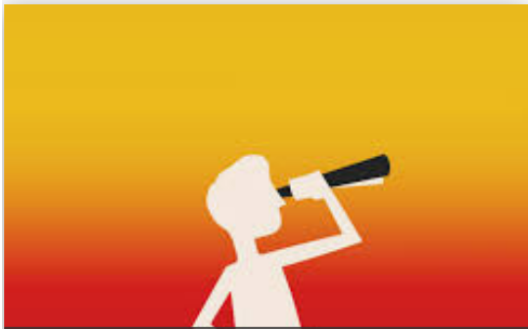
- **Attempted duplication of results of phase 3 & 4 RCTs over three years to provide empirical evidence base that could inform our level of confidence in high quality non-interventional designs**
  - **Comparable results with similar clinical questions?**
  - **Reasons for differences?**
- **FDA reviewers 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/

Demonstration Project: Assessment of Non-Interventional Designs (2)

FDA Expands Real-World Evidence Partnership with Brigham and Women's Hospital and Aetion

RCT DUPLICATE adds new studies to inform FDA - the first to use real-world evidence to predict treatment safety and efficacy



Using the same methods, duplicate the results of 7 additional studies in advance of the RCT results

https://www.rctduplicate.org/