U.S. FOOD & DRUG ADMINISTRATION

FDA's Real-World Evidence Program: An Update

Jacqueline Corrigan-Curay, J.D., M.D.
Director, Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
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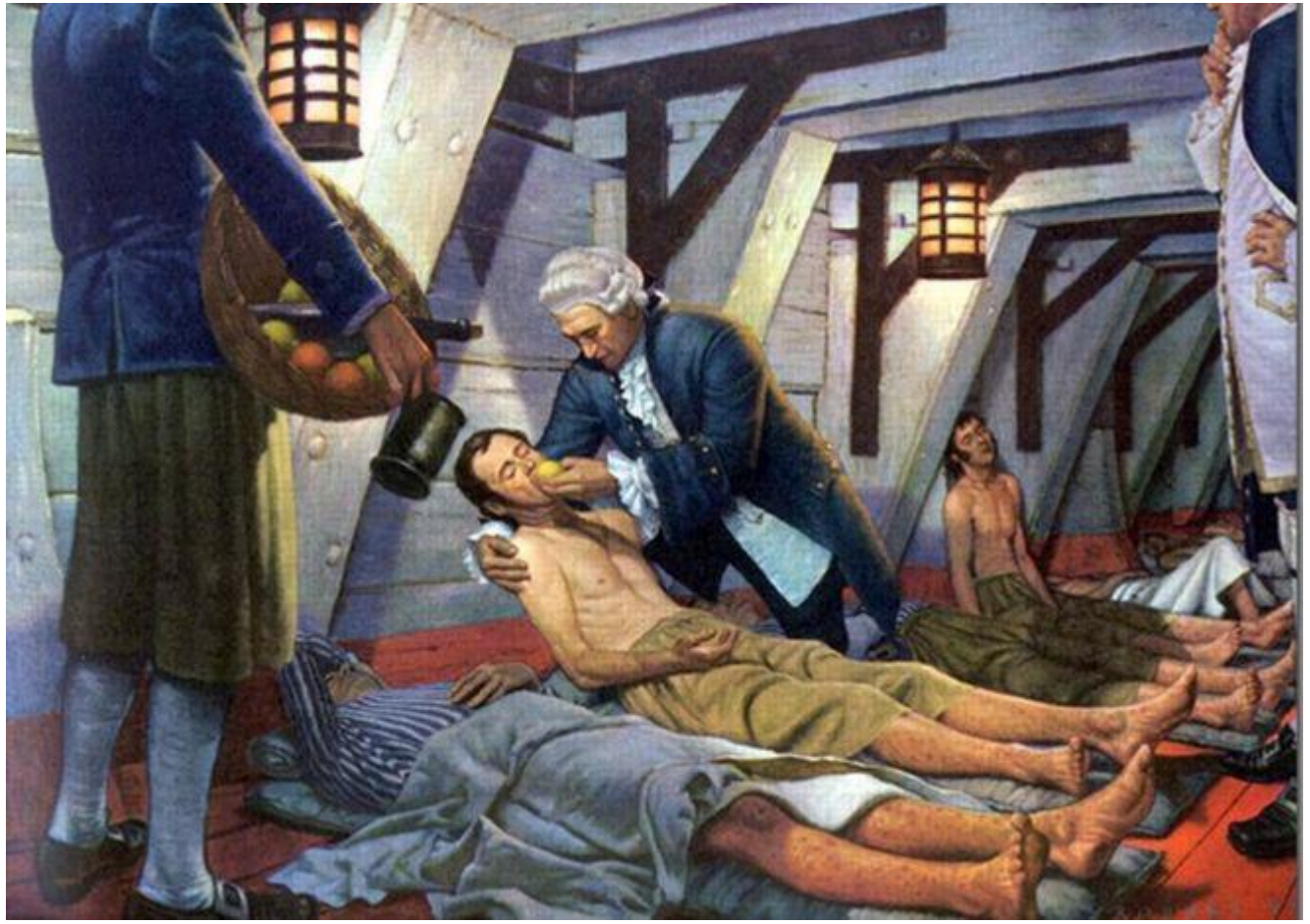
Disclaimer

- **The views and opinions expressed in the following slides are those of the individual presenter and should not be attributed to the FDA.**
- **No relevant financial relationship exists**

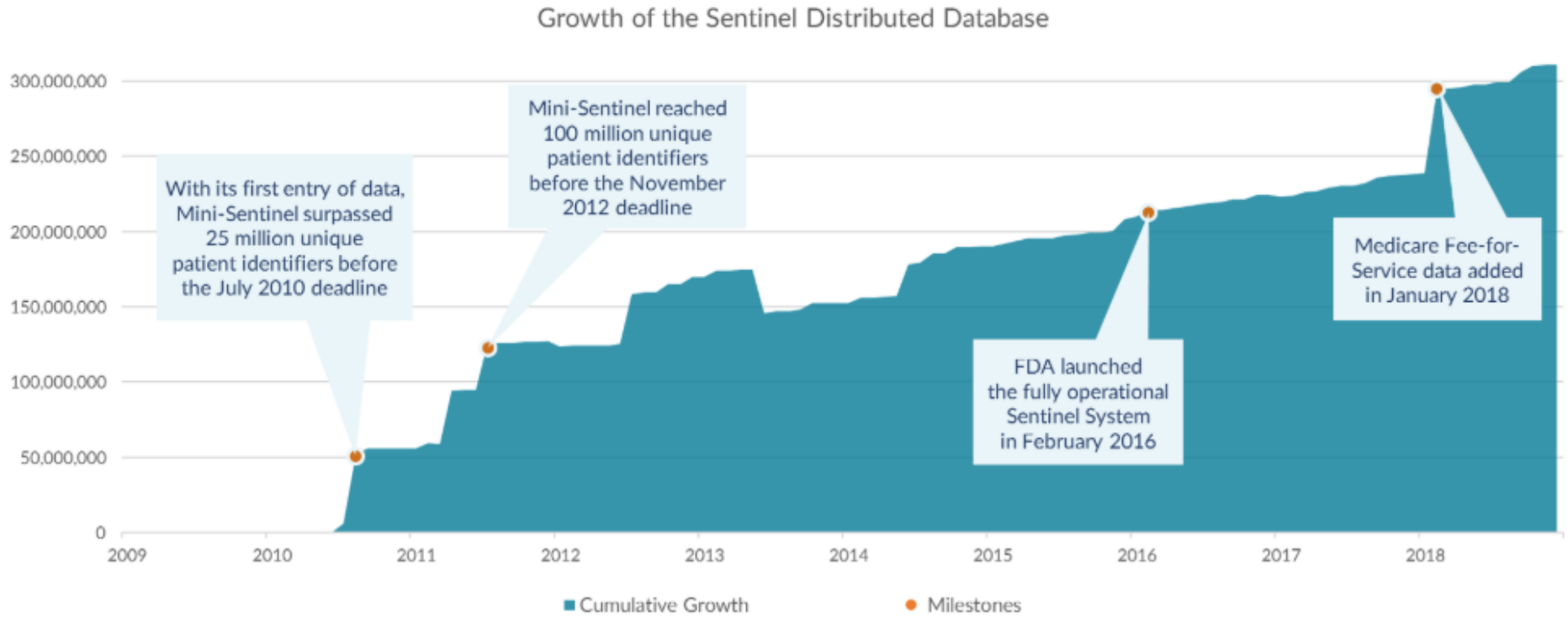
Overview

- Why real-world evidence?
- Mandate and goals
- Program areas
- Demonstration projects

RWE is Not New



Sentinel Initiative

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Perspective

Mini-Sentinel and Regulatory Science — Big Data Rendered Fit and Functional

Bruce M. Psaty, M.D., Ph.D., and Alasdair M. Breckenridge, M.D.

N Engl J Med 2014; 370:2165-2167 | June 5, 2014 | DOI: 10.1056/NEJMp1401664

Share:

310.8 million cumulative patient identifiers between 2000 and 2018

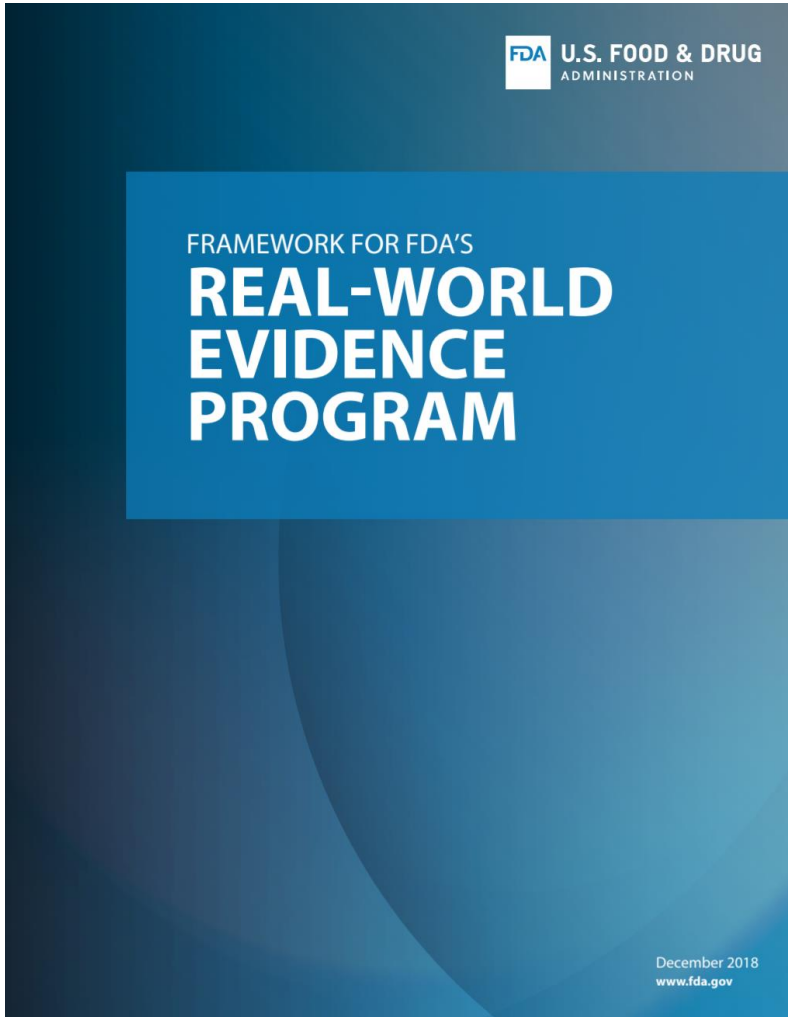
Of members with medical and drug coverage, there are:

- **70.1 million** members are currently accruing new data
- **11.7 billion** pharmacy dispensings
- **15.0 billion** unique medical encounters
- **48.5 million** members with at least one laboratory test result
- **668 million** person-years of data

Why Expand Use of RWD/RWE?

- Increased digitization of health care data provides 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, long-term but infrequent outcomes
- Lower resource intensity – more questions answered
- Understand how medications are used in practice and value

21st Century Cures – A Path forward for RWE



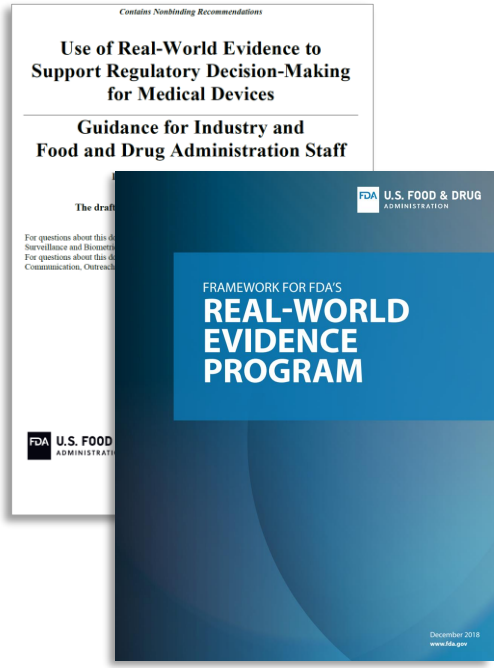
Scope of RWE Program Under 21st Century Cures Act

Under the Cures Act, FDA's RWE Program must evaluate the potential use of RWD to generate RWE of product effectiveness to help support approval of new indications for drugs approved under FD&C Act Section 505(c) or to help to support or satisfy postapproval study requirements. FDA's RWE Program will also apply to biological products licensed under section 351 of the Public Health Service Act.

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

Definitions

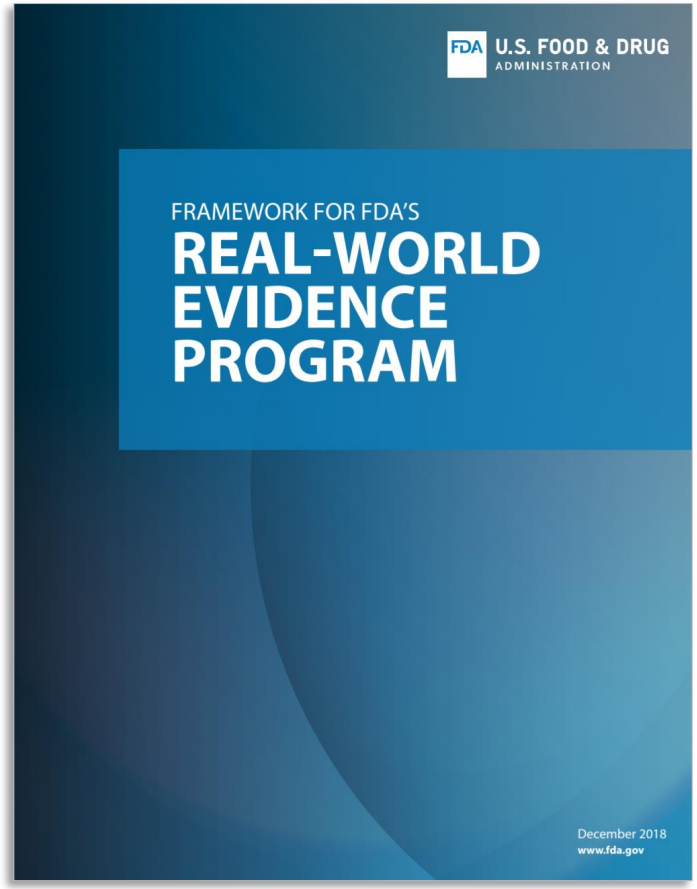
Real world evidence means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than *traditional clinical trials*

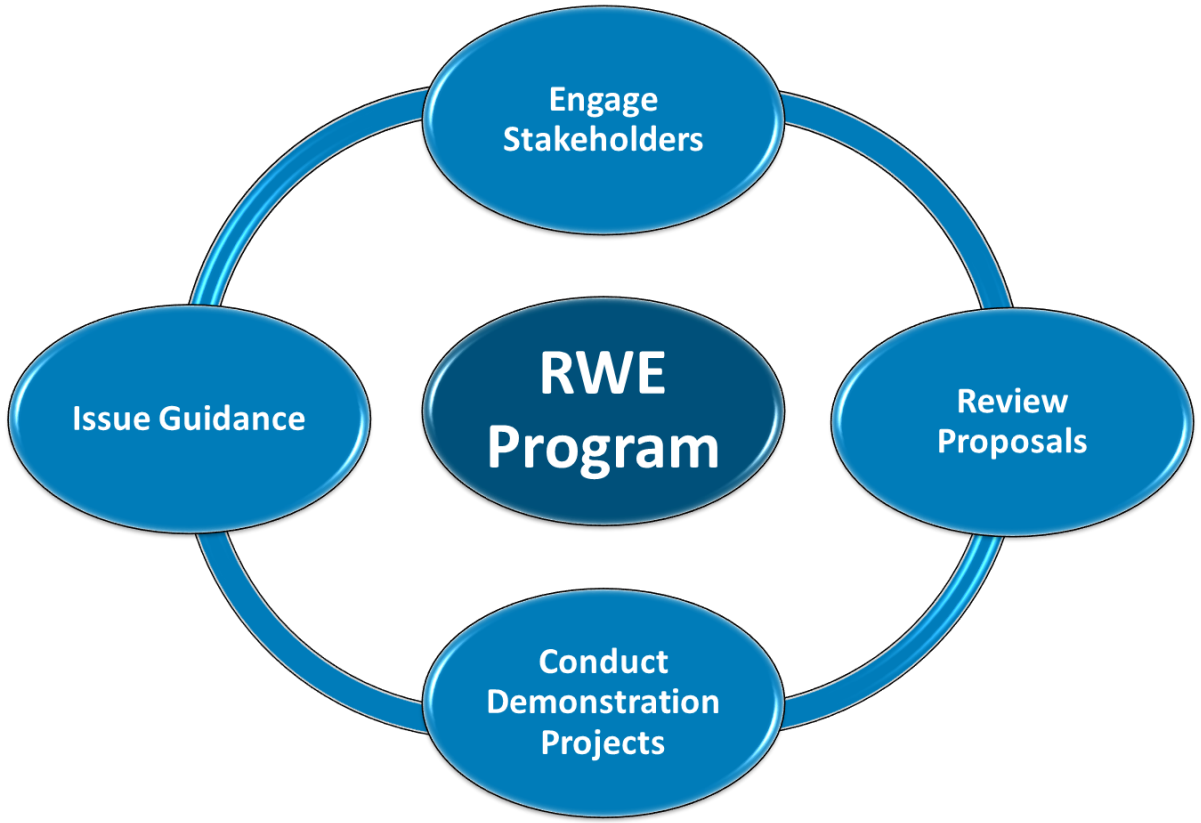


Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

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.

FDA Real-World Evidence Program





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

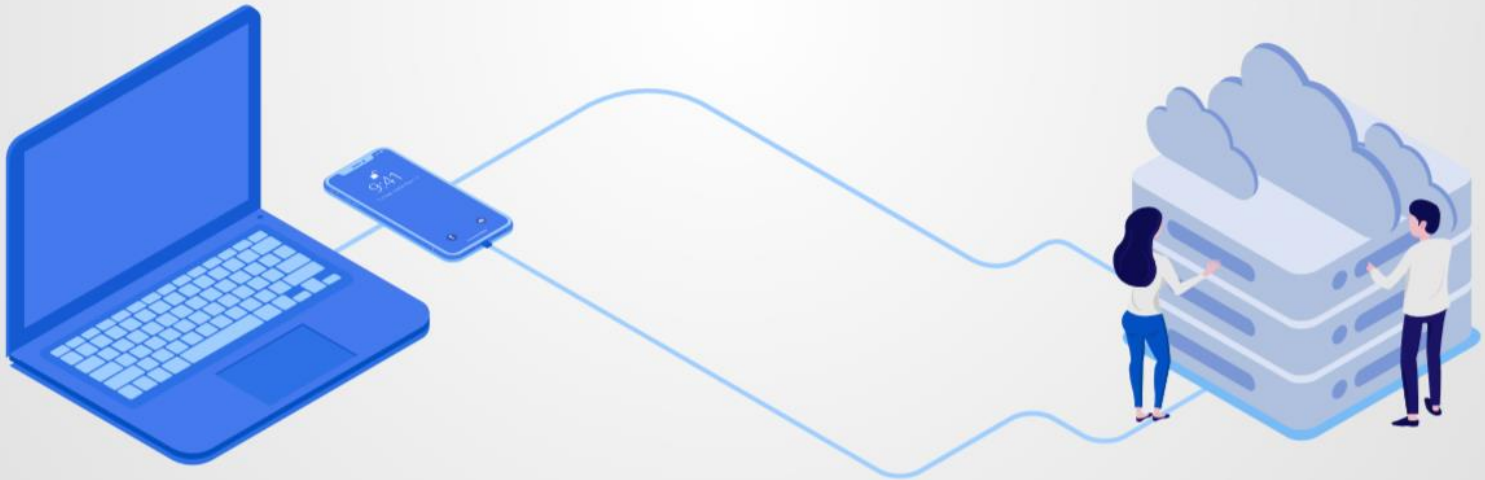
RWD and Technology

AI case study: IBM Watson & Mayo clinic

Watson uses AI to analyze unstructured information and pull out insights from the data

The system generated a **ranked list of relevant trials** for each patient **without making clinicians read through EMRs** or long lists of eligibility criteria

Study results showed **80% increase in enrollment** for breast cancer study using Watson Clinical Trial matching system



From a presentation by Hadas Jacoby Adani (Cato Research). http://cato.com/marketing/2018/CATO-Big-Data-RWE-and-AI-made-simple.pdf

Different Products and Standards, But Coordination

Contains Nonbinding Recommendations

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or CDRHClinicalEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

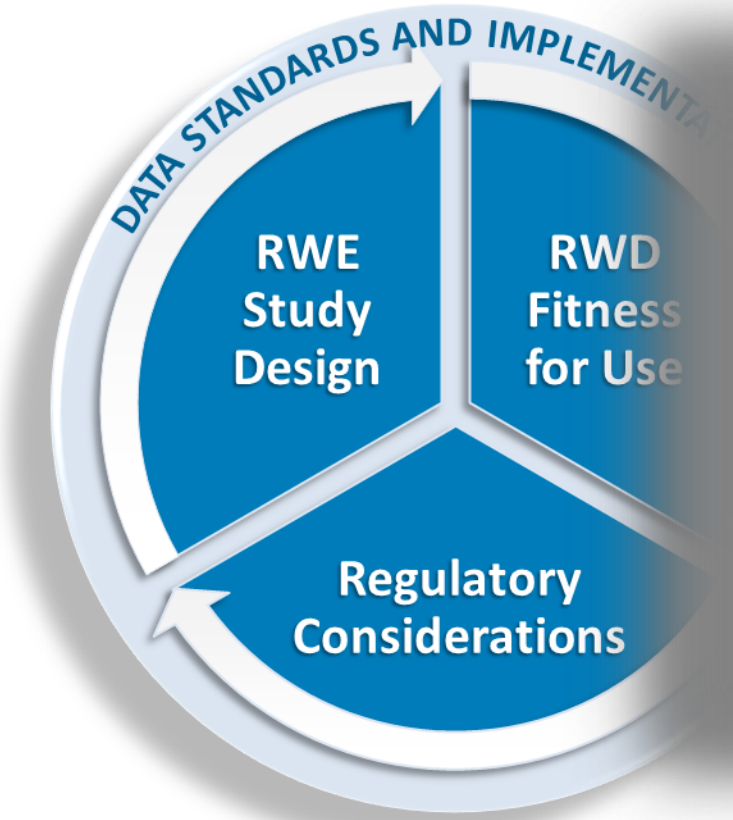
- **FDA guidance document which describes the potential use of RWE throughout the total product lifecycle for devices**
  - **Draft issued prior to 21st Century Cures Act**
- **Definitions of Real World Data and Real World Evidence are harmonized with the FDA Framework**
- **CDRH, CBER, and CDER are coordinating as the 21st CC RWE program proceeds**

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

Benchmark

- Substantial evidence standard unchanged
  - 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 RWD/RWE for Use in Regulatory Decisions



Consider:

Clinical

- Whether the RWD are fit for use
- trial or study design
- rate RWE can provide
- entific evidence to
- lp answer the
- uestion
- study conduct meets
- requirements

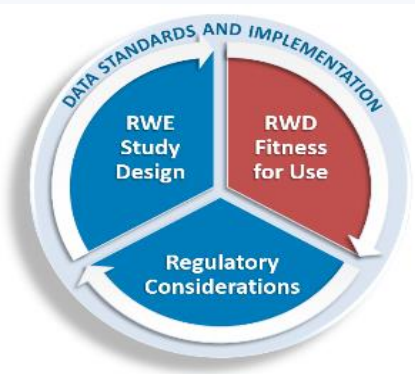
Demonstration Projects

- Relevancy
- Quality
- Linkage

- Common data models
- Mobile technologies

- Randomized trials
- Assessment of observational studies

RWD FIT FOR USE



RWD Fitness for Use

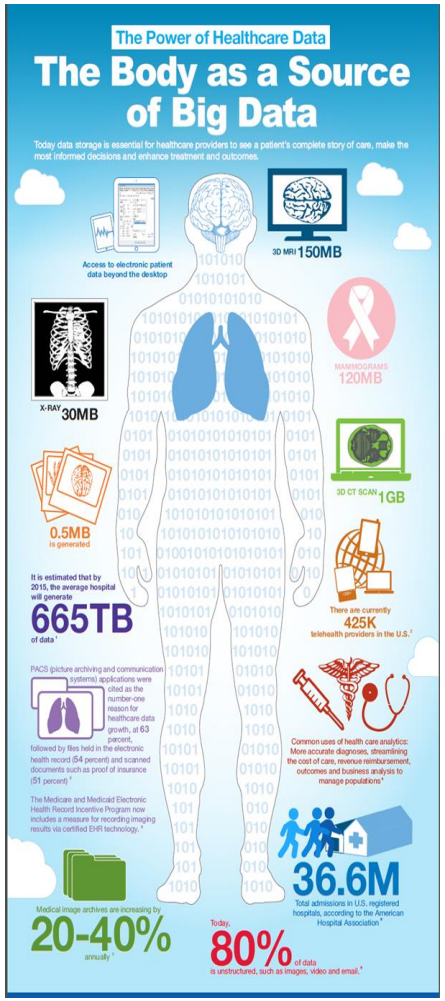
- **Data reliability (data accrual and data quality control) and relevance**
  - **Data must be collected and maintained in a way that provides an appropriate level of reliability**
  - **Data must be suitable to address specific regulatory question of interest - relevance**
- **FDA does not endorse 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**

Is RWE Ready for Regulatory Use?

Biomarker

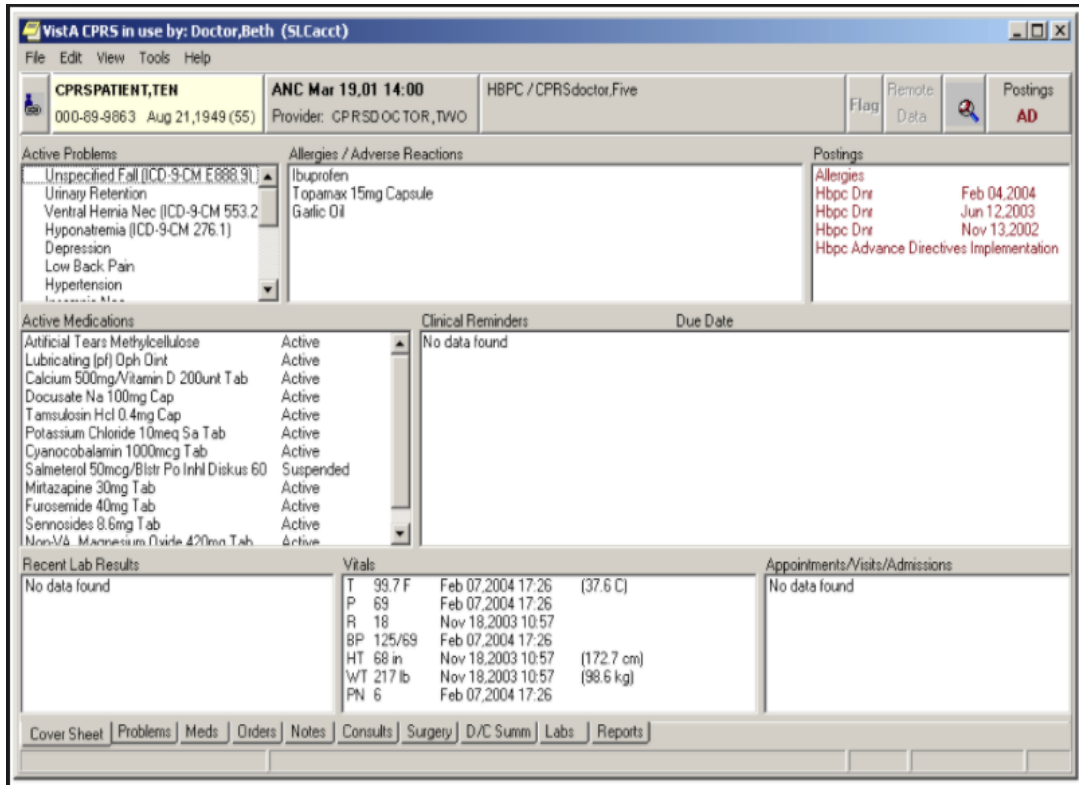
Clinical endpoint

Type of endpoint	Studies %	Examples of endpoints measured
Chemistry	21%	HBA1c, pregnancy test, GFR
Hematology	4%	Severe neutropenia Apheresis yield > 5 million CD34+ cells/kg
Pathology	1%	Increase/decrease of parabasal cells; biopsy proven acute rejection, clearing of anterior chamber cells
Microbiology	9%	Sustained virological response, plasma viral load, conversion to negative sputum
Imaging +/- (survival, clinical signs)	10%	Bone mineral density; vertebral fractures, spleen volume, progression free survival
Physiological/ functional measurement	10%	6 minute walk, normal sinus rhythm, FEV1, sleep studies
Clinical event /clinical sign	13%	Death, hospitalization, MACE, MS relapse, Lice free head
CRO/PRO	31%	Toronto western spasmodic torticollis rating scale, Hamilton depression rating scale, Rheumatology scale ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score



EHR – Opportunity and Challenge

- **While 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 does not = consistency/ complete documentation**
  - **Clinical outcome measures for drug approvals may not be used or consistently recorded in practice**



Role of Unstructured Data

Table 1. Comparison of cohorts generated using structured electronic health record data only versus structured electronic health record data supplemented with abstracted unstructured data.

Goal	Structured data only	Structured and unstructured data
Recent LC patients	ICD-9 code of 162.x with at least two visits ≥2013 (n = 26,630)	ICD-9 code of 162.x with at least two visits ≥2013 (n = 26,630)
NSCLC patients	Patients without an administration for etoposide (n = 23,235)	Patients with confirmed NSCLC (n = 21,445)
Advanced NSCLC patients	Patients with a diagnosis for secondary metastases (ICD9 196.x–198.x) (n = 4382)	Patients with a confirmed diagnosis of advanced NSCLC (n = 10,826)
Patients with an advanced diagnosis date after 2013	Patients with a first diagnosis for secondary metastases ≥2013 (n = 3562)	Patients with a confirmed date of advanced diagnosis ≥2013 (n = 8324)
Squamous cell NSCLC patients	Unable to distinguish	Patients with a confirmed diagnosis of squamous cell carcinoma (n = 2092)

LC: Lung cancer; NSCLC: Non-small-cell lung cancer.

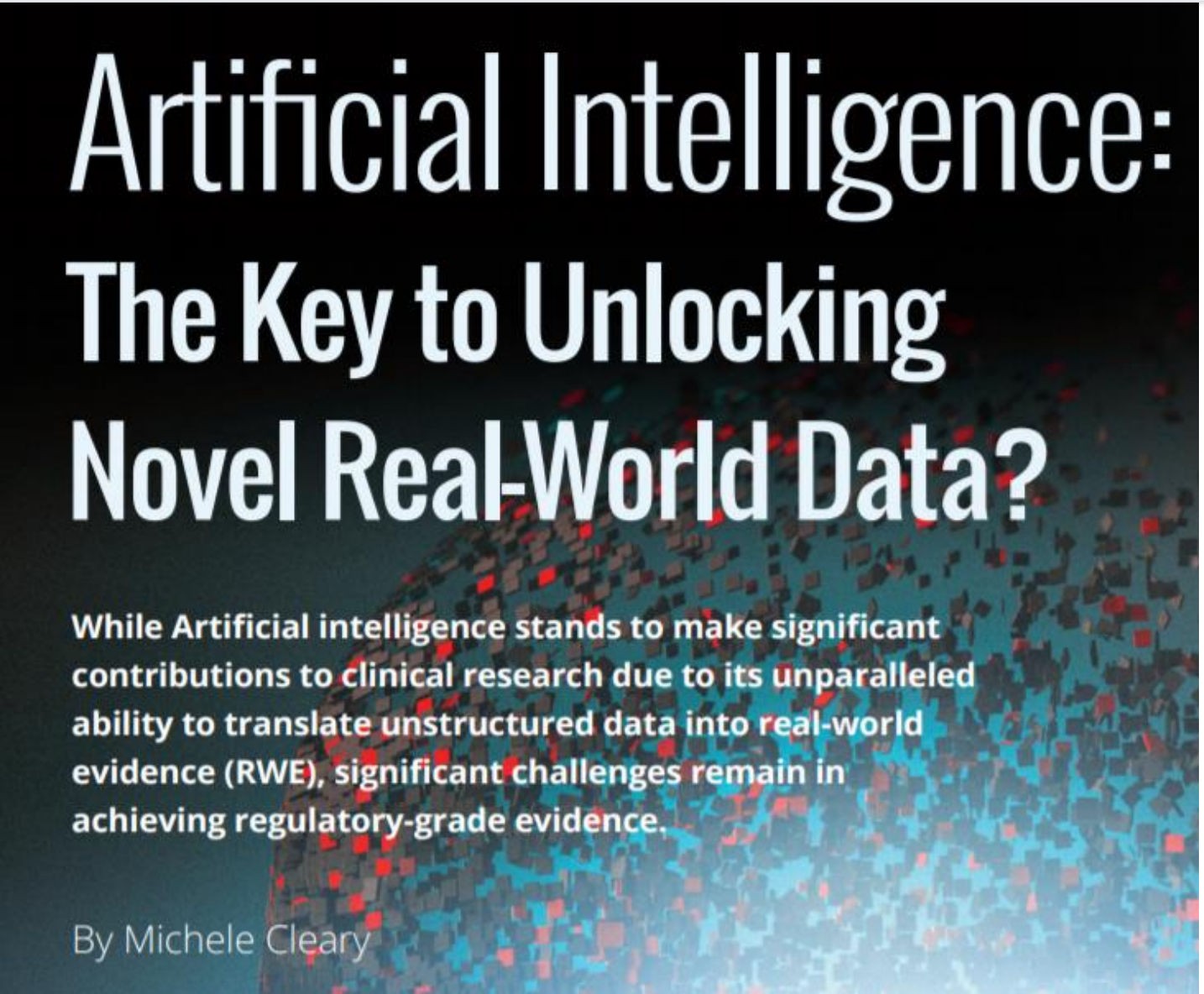
Opportunities and challenges in leveraging electronic health record data in oncology

Marc L Berger*,1, Melissa D Curtis, Gregory Smith, James Harnett1 & Amy P Abernethy

Future Oncol. (2016) 12(10):1262–74

Future ONCOLOGY

Can AI help us produce evidence from RWD



For example:

- Structuring large data sets
- Connecting and merging data sources
- Analyzing data and flagging potential trends
- Identifying potential biases and confounders

Alignment of Demonstration Projects with the Framework

Understanding EHRs in the Context of Clinical Trials

- Harmony- Outcomes Ancillary Study
- One Source - ISpy

HARMONY-Outcomes Ancillary Study

- **Collaboration with Duke Clinical Research Institute and Glaxo SmithKline**
- **Supported by FDA**
- **Assessed 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

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**

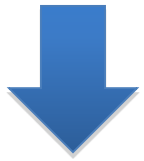
Courtesy of Dr. Laura Esserman and Susan Dubman

Common EHR Data Structure

mCODE™

Minimal Clinical Oncology Data Elements

Data standards to improve the quality and usability of EHR data

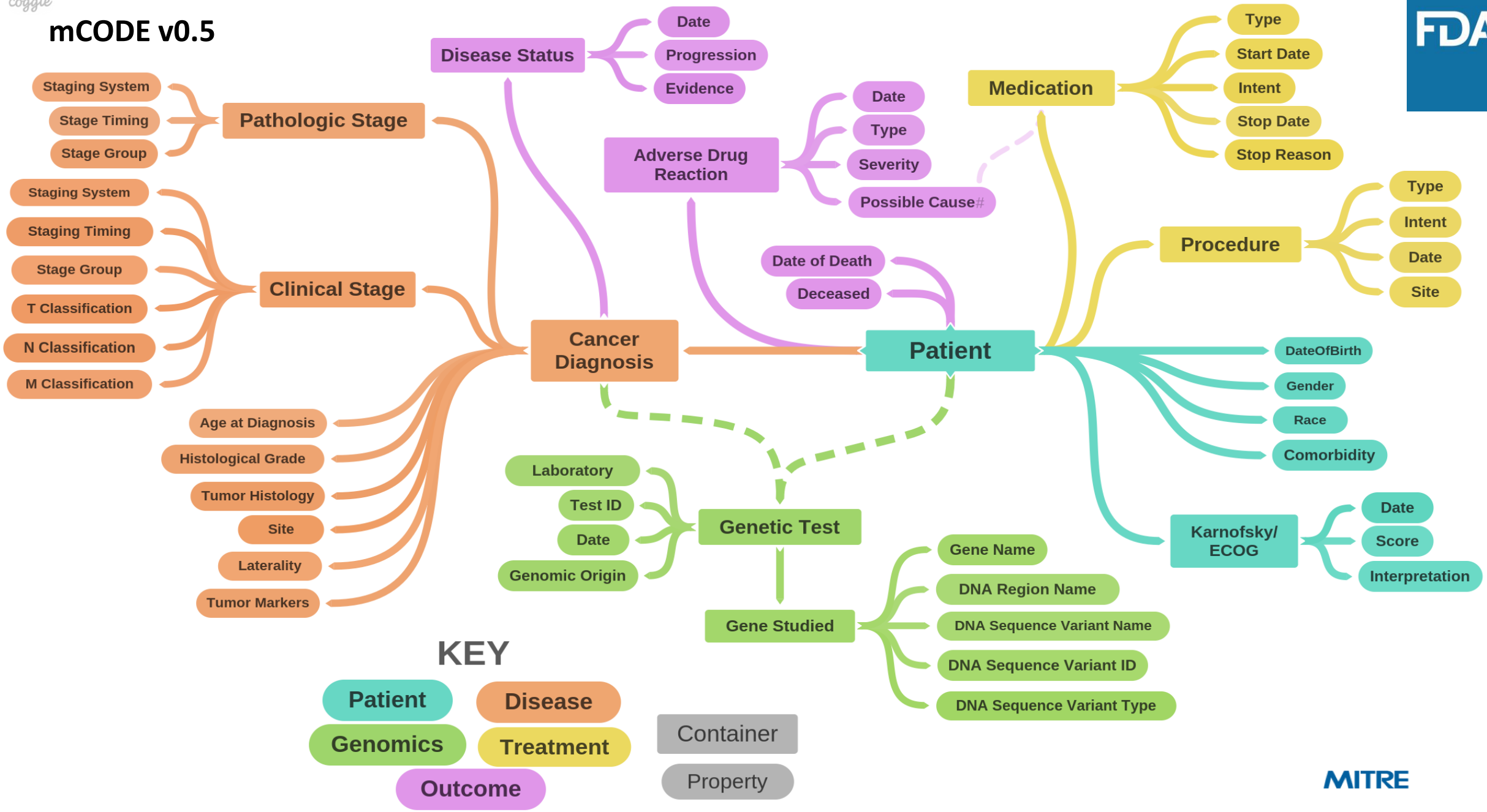


Collection of clinical trials data using the EHR

Courtesy of ASCO/MITRE

coggle

mCODE v0.5



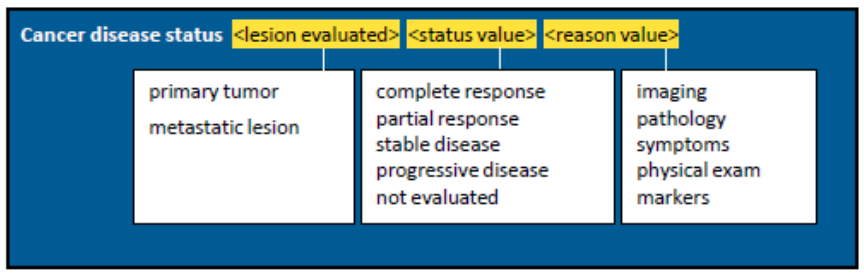
ICARE: Develop and validate mCODE-based outcome measures embedded in the EHR

Disease Status

Clinical Assessment

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

Question Format

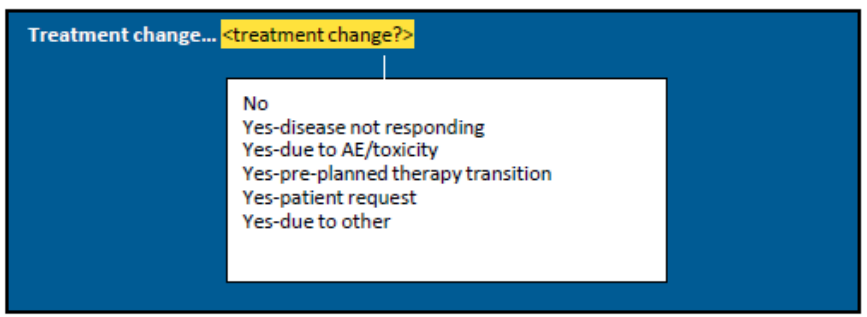


Treatment change

Clinical Assessment

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

Question Format



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

MITRE

FDA

NCI National Clinical Trials Network
a National Cancer Institute program

ASCO
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Patient-Generated Health Data (Digital Health Tools)

Alignment of Demonstration Projects with the Framework

Use of Mobile Technologies to Enhance RWD

- Trial in Juvenile Idiopathic Arthritis
- Inflammatory Bowel Disease Registry
- Mobile devices and novel endpoints

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

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)

- **Use the MyStudies app to support:**
  - **Collection of primary outcome (uveitis) from ophthalmology appointments (also reminders for appointments)**
  - **Potential support for the Childhood Arthritis & Rheumatology Research Alliance (CARRA) Registry**

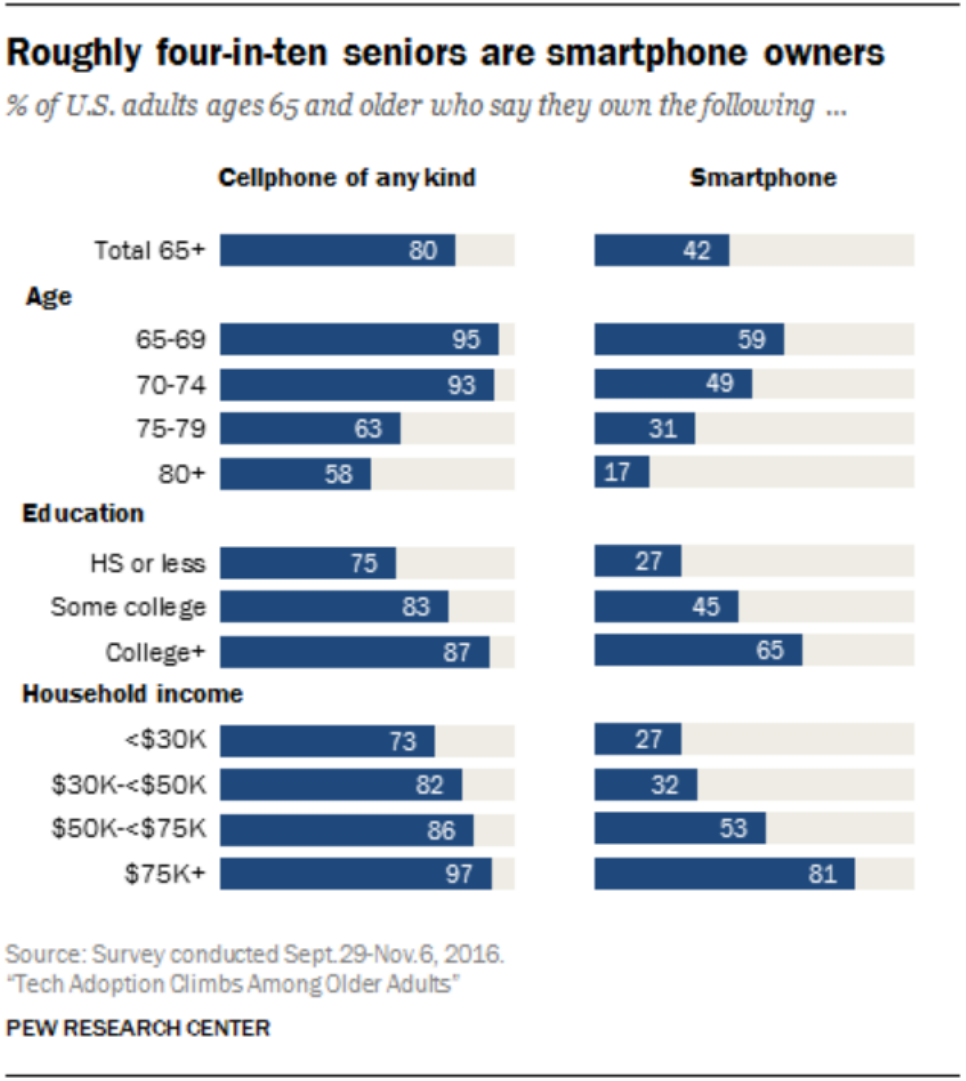
CARRA
Childhood Arthritis and Rheumatology Research Alliance

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**

Ensure Digital Technology Does not Limit Diversity

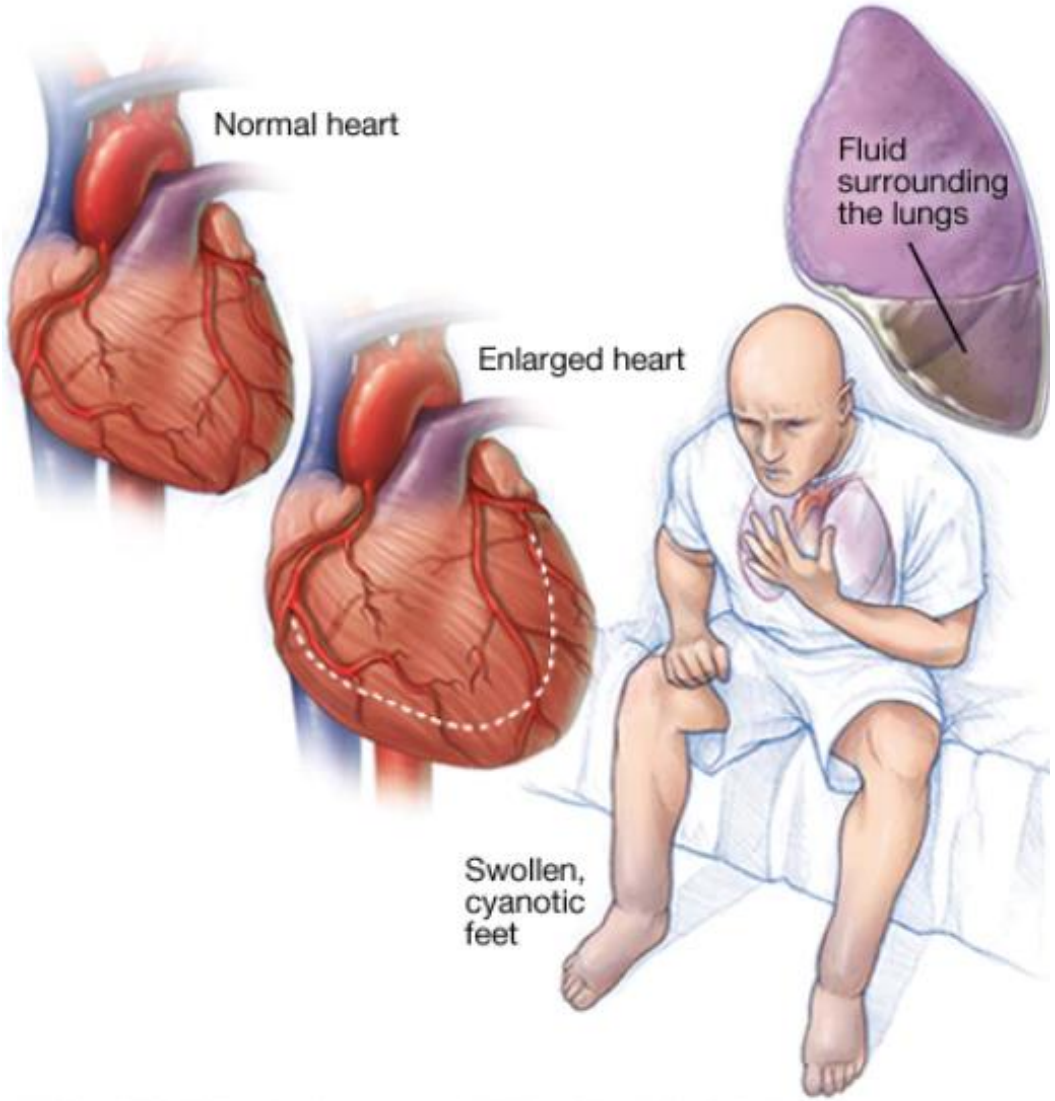


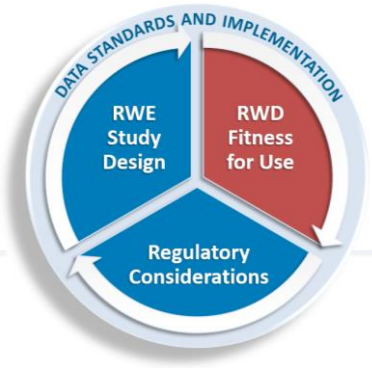
% of U.S. adults who own the following devices

	Any cellphone	Smartphone	Cellphone, but not smartphone
Less than high school graduate	92%	66%	25%
High school graduate	96%	72%	24%
Some college	96%	85%	11%
College graduate	98%	91%	7%
Less than $30,000	95%	71%	23%
$30,000-$49,999	96%	78%	18%
$50,000-$74,999	98%	90%	8%
$75,000+	100%	95%	5%

Exploring Wearable Sensors for Patients with Heart Failure

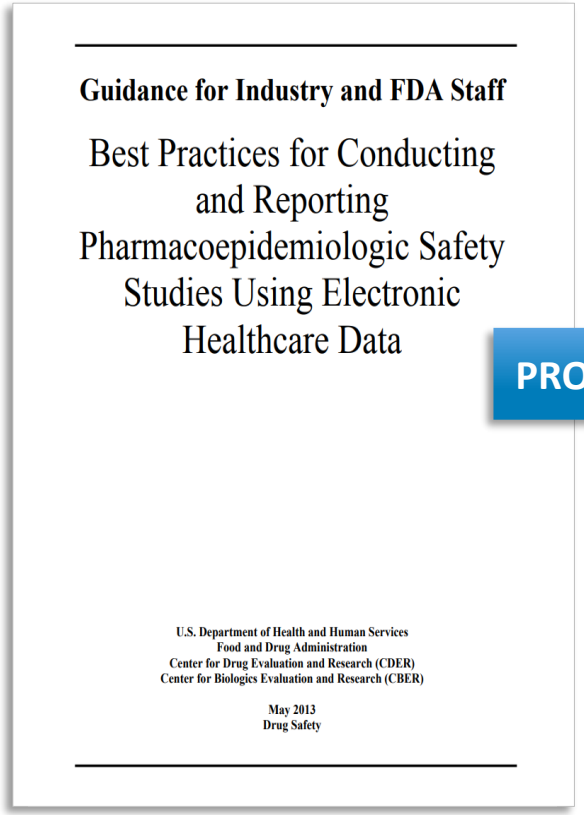
- To evaluate the feasibility and performance of two novel wearable and smartphone-based mobile health platforms for real-world surveillance of surrogate endpoints for heart failure drug approvals in 150 patients
- Novel health platforms will measure ECG data, heart rate, respiratory rate, accelerometer data, steps, activity, and sleep





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

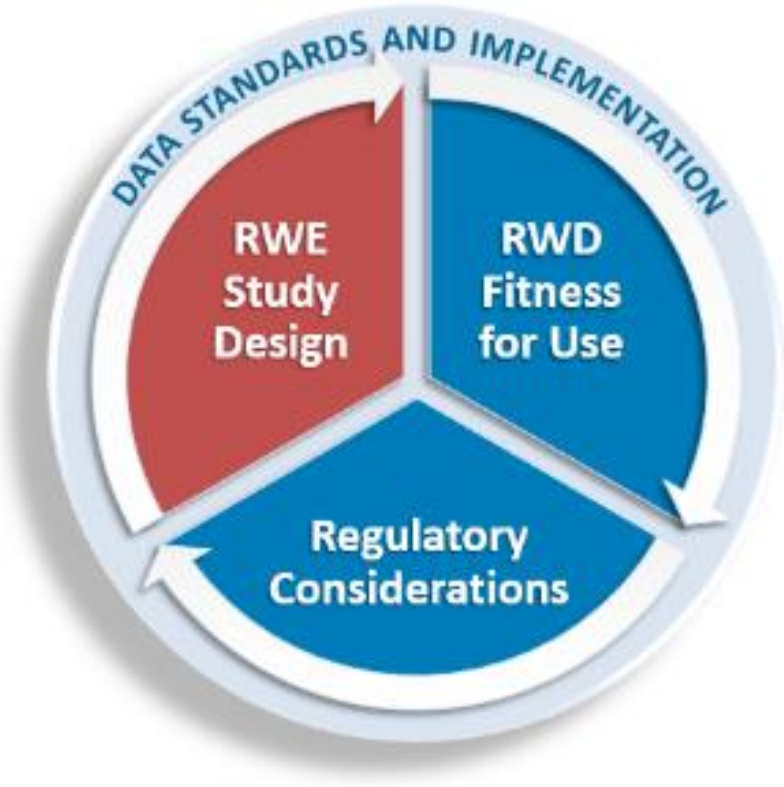
Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

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

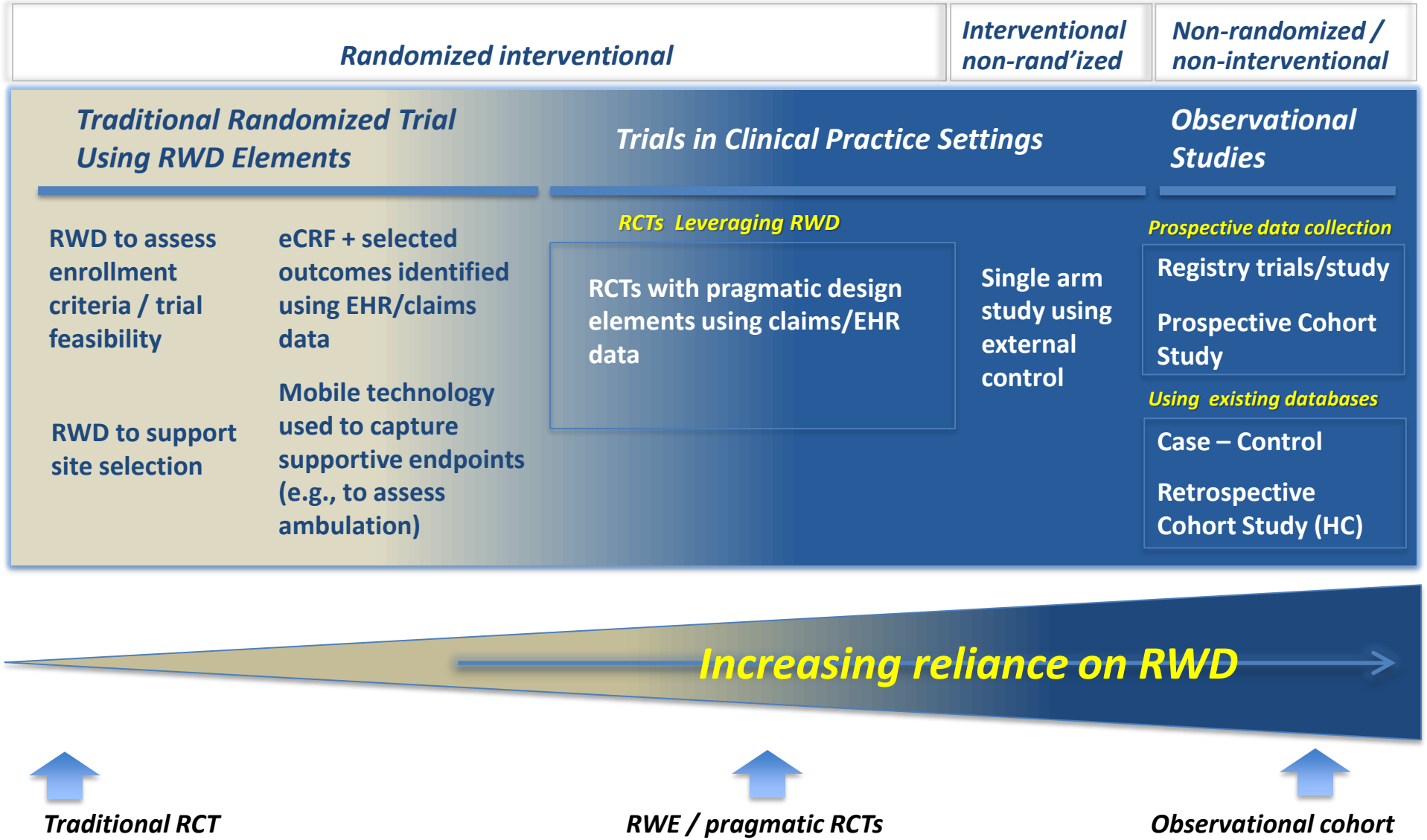
PROGRAM ITEMS:

- **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**

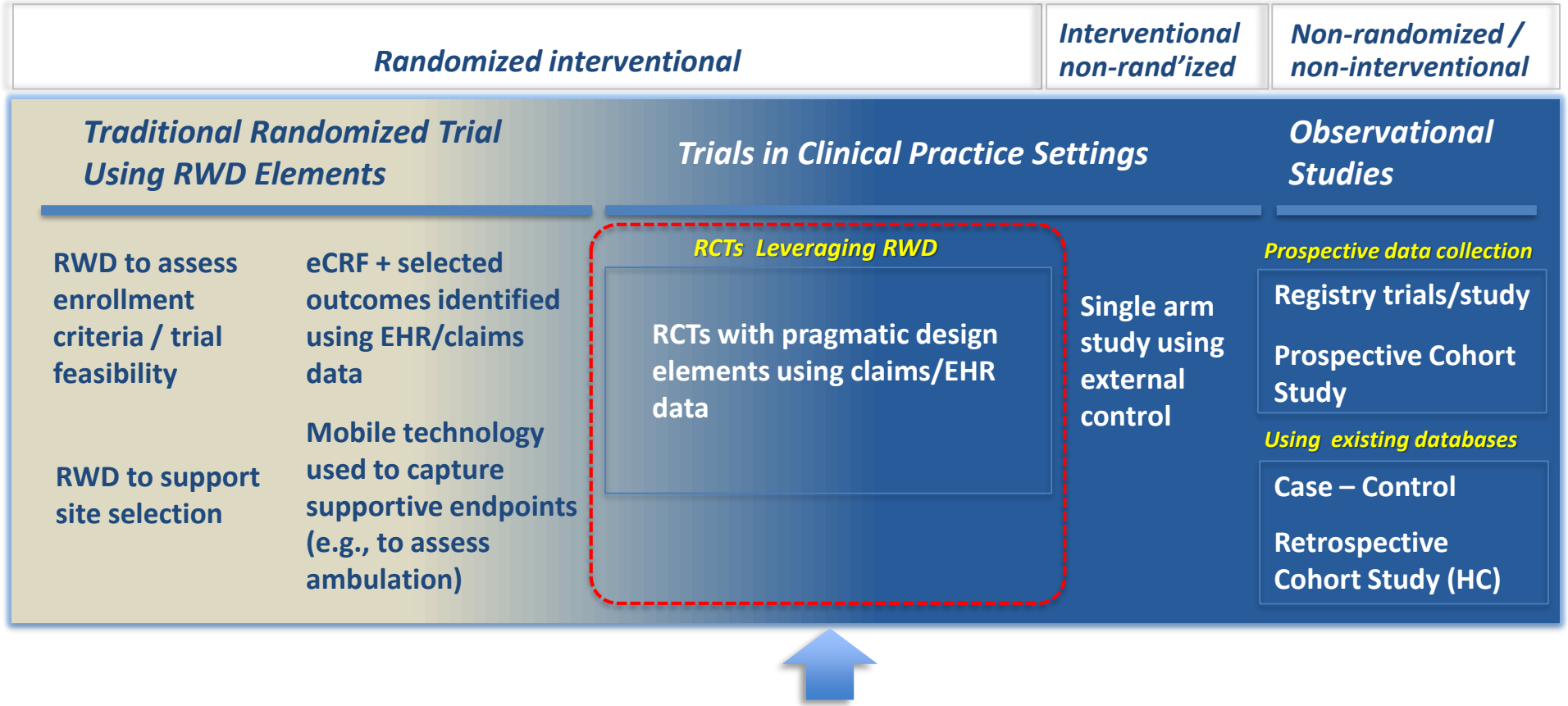


RWE STUDY DESIGN

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



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



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Leveraging Randomized Clinical Trials to Generate Real-World Evidence for Regulatory Purposes

July 11, 2019 - 8:30 am to July 12, 2019 - 1:00 pm

Register now

The Westin Washington, D.C. City Center - National Ballroom
1400 M Street NW
Washington, DC 20005

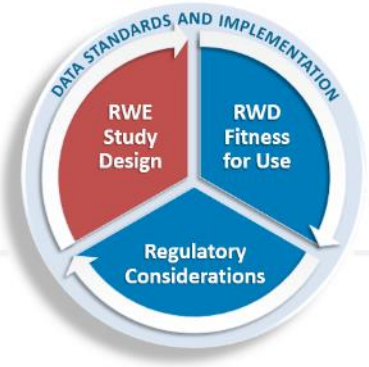
Contact Info

Event Manager
margolisevents@duke.edu

Description

There are emerging opportunities to leverage real world data (RWD) and resultant real-world evidence (RWE) in support of supplemental approval or labeling actions based on substantial evidence of effectiveness as envisioned in 21st Century Cures and PDUFA VI. As part of implementation efforts for this legislation, the U.S. Food and Drug Administration (FDA) published a strategic framework to guide the development of a new program for regulatory uses of RWD and RWE. The Framework suggests the potential integration of clinical trials into the healthcare system by using randomized designs to generate RWE for regulatory submissions.

https://healthpolicy.duke.edu/events/leveraging-randomized-clinical-trials-generate-real-world-evidence-regulatory-purposes

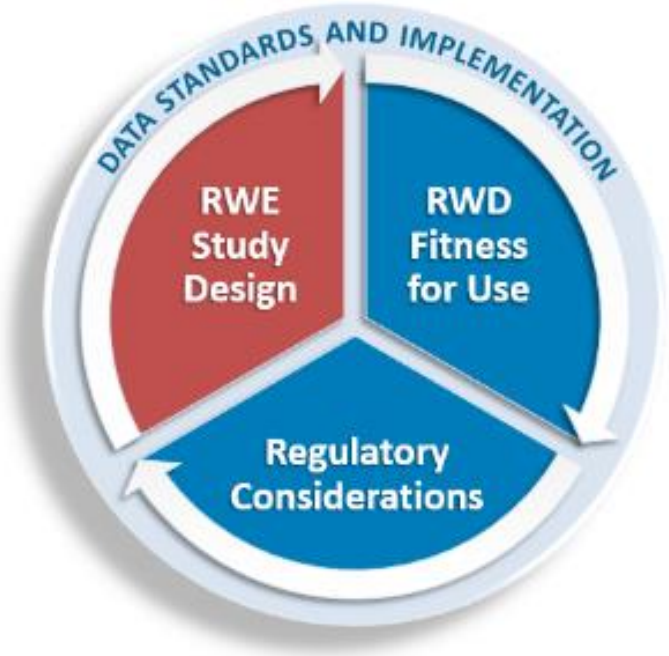


Potential for Study Designs Using RWD to Support Effectiveness

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

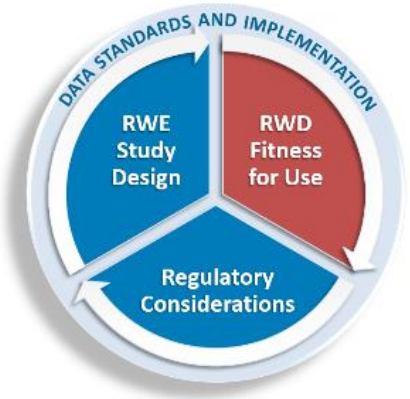
- **What is the question we are trying to answer and is this the best setting?**
- **How will RWD be captured in these settings?**
  - **What is the impact on lags in data capture**
- **Is blinding necessary?**
- **Bridging between regulatory endpoints and clinical practice**
- **Site inspections and monitoring**
- **Statistical analysis**

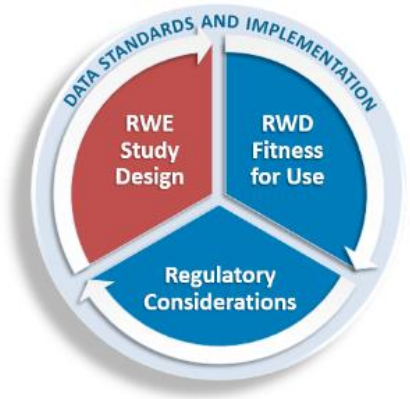
Alignment of Demonstration Projects with the Framework



RELIANCE Trial – PCORI – FDA Catalyst

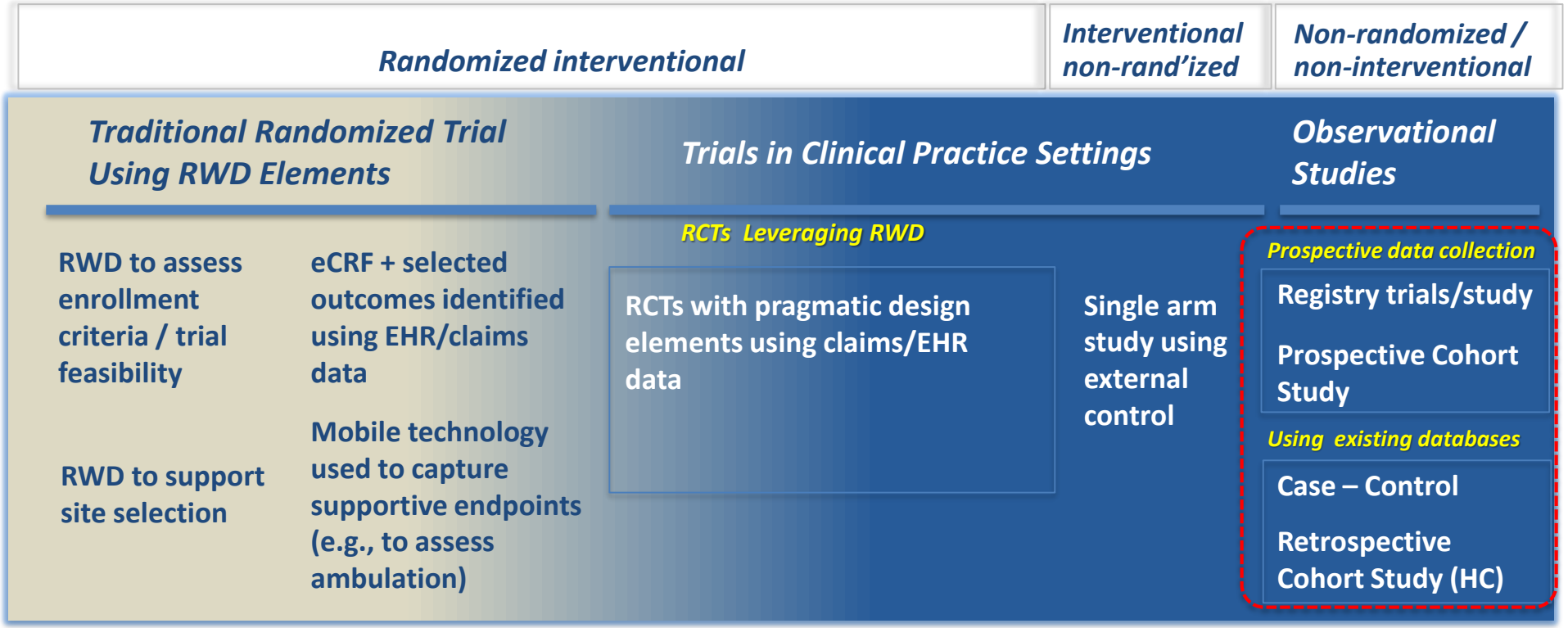
RELIANCE Trial



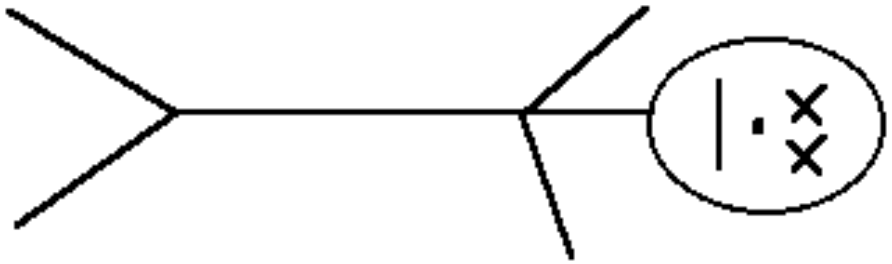


- **RofLumilast or Azithromycin to prevent COPD Exacerbations**
  - Randomized "real world" trial; 1,600 adults in each arm
  - Azithromycin - macrolide with anti-inflammatory properties
  - Roflumilast - noncorticosteroid anti-inflammatory; phosphodiesterase type 4 inhibitor
- **Primary outcomes**
  - 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

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



Observations Can Be Compelling



RWE Informs Effectiveness when Fit-for-Use

DRUG	INDICATION	STATUS	DATA
Lutathera *(lutetium 177 dotate)*	GEP-NET Gastropanc. Neuroendo 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)*	Treatment of MTX toxicity	Approved 2012	▪ Approval based on open-label, **NIH compassionate Use Protocol**
Uridine Triacetate	Treatment of 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)*	Treatment of 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	Treatment of NAGS deficiency	Approved 2010	▪ Retrospective, non-random, un-blinded **case series of 23 patients** compared to **historical control group**
Myozyme (alglucosidase alfa)	Treatment of Pompe disease	Approved 2004	▪ Open-label, non-randomized study of 18 patients compared to **historical control group of 62 untreated patients**
Refludan®	Anti-coagulation in heparin-induced thrombocytopenia	Approved 1998	▪ Two non-randomized, open-label multicenter trials using **historical control comparator group from HIT Registry**

Bold = RWE

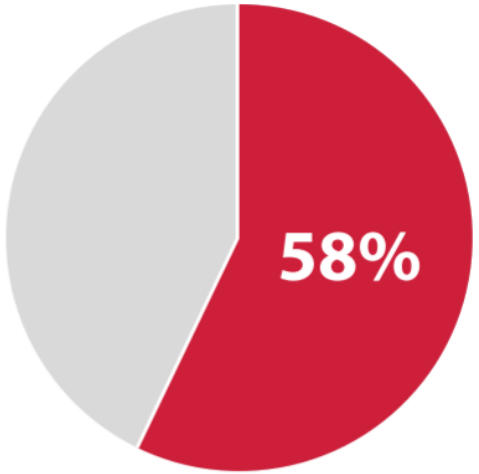
NOT EXHAUSTIVE

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

Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses – Subpart E

Appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness, especially when there is a lack of available therapy.

Recognize physicians and patients are generally willing to accept greater risks or side effects.



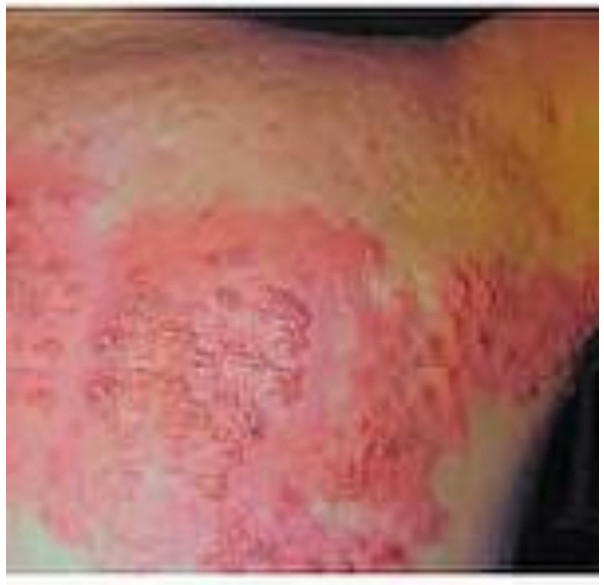
34 of CDER's 59 novel drugs (58%) were approved to treat rare or "orphan" diseases.

21 CFR 312.80

MERCK Zostavax for Herpes Zoster (HZ)

Pre-approval efficacy trials:

- **Shingle Prevention Study (SPS)**
  - **Double-blind, placebo-controlled (DBPC) RCT 38,000 individuals > 60**
  - **Median follow-up 3.1 years - reduction in HZ incidence 51%**



- **ZOSTAVAX Efficacy and Safety Trial (ZEST)**
  - **DBPC RCT of 22,200 individuals 50-59 years of age**
  - **Median follow-up 1.3 years - reduction in HZ incidence 70%**

MERCK Zostavax for Herpes Zoster (HZ) *(cont.)*

Post Marketing Commitment to study long-term efficacy in ages 50-59

- Prospective observational study run by Kaiser Permanente Northern California
- Data on 1.3 million members, with over 350,000 individuals who received Zostavax and 100,000 individuals with more than 5 years follow up post vaccination
- Study is ongoing and will continue through 2023

Clinical studies section of labeling updated:

- In assessing effectiveness adjustments made for calendar time, age, sex, race/ethnicity, healthcare resource utilization, comorbid conditions, and immunocompromise status
- Vaccine effectiveness (VE) against HZ for 50-59 over first 3 years following vaccination was 60%
- For individuals 60-69, 70-79 and 80 or older average VE against 49%, 46% and 44% respectively.

Methods Matter

JAMA The Journal of the American Medical Association

Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

Cardwell et al.
JAMA, August 11, 2010—Vol 304, No. 6

Among patients in the UK General

incident esophageal or gastric cancer.

BMJ

Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort

Jane Green, clinical epidemiologist,[1] Gabriela Czanner, statistician,[1] Gillian Reeves, statistical epidemiologist,[1] Joanna Watson, epidemiologist,[1] Lesley Wise, manager, Pharmacoepidemiology Research and Intelligence Unit,[2] Valerie Beral, professor of cancer epidemiology[1]

BMJ 2010;341:c4444

The risk of oesophageal cancer increased with 10 or more prescriptions for oral bisphosphonates and with prescriptions over about a five year period. In Europe

about 2 per 1000 with five years' use of oral bisphosphonates.

Studies utilising the **same datasource**, over a **very similar time** period with the **same drug** of interest and the **same outcome** delivered opposing results

Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey

Lars G Hemkens,[1,2] Despina G Contopoulos-Ioannidis,[3,4] John P A Ioannidis[1,4-6]

Correction notice to paper "Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey"

Lars G Hemkens , Despina G Contopoulos-Ioannidis , John P A Ioannidis

BMJ

We fully acknowledge this important issue and have performed re-analyses to evaluate whether the summary ROR estimates are different when no selective inversion ("coining") is employed to make the initial RCD study OR <1.

Therefore, the results are remarkably similar in these additional analyses with modest differences in the exact estimates (from 1.25 to 1.58) and with 6 re-analyses giving actually a somewhat higher summary ROR than our original analysis and 1 re-analyses giving a somewhat lower summary ROR than our original analysis that had shown a summary ROR of 1.31. The results of the 2 re-analyses that include all 16 clinical questions (ROR 1.34 and 1.39) have even more remarkable similarity to the summary ROR reported in our original article [1]. Therefore, we trust that our results and conclusions remain unaltered.

Published Observational Studies on Multiple Disease States

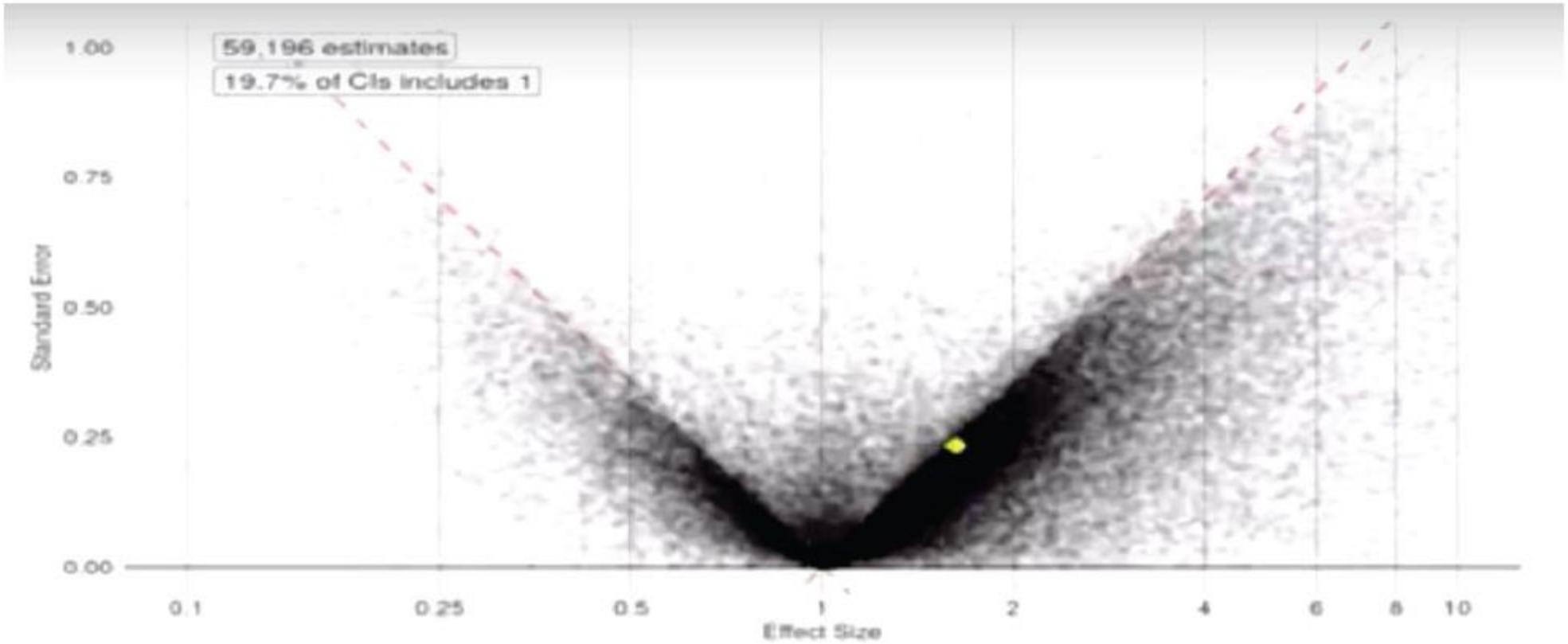


FIGURE 5-4 Effect estimates from published observational studies on all disease states, all treatments, and all causal effects.
NOTE: CI = confidence interval.

From Presentation by Patrick Ryan, Senior Director and Head, Epidemiology Analytics, Janssen Research & Development , reproduced from: *Examining the impact of real-world evidence on medical product development: Proceedings of a workshop series*. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/25352.

Efforts to Enhance Transparency

Transparency about study design and analysis <u>before</u> execution is critical for ensuring confidence in the result

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

1. *A priori*, determine and declare that a study is a Hypothesis Evaluation Treatment Effectiveness (HETE) study or an Exploratory study based on conditions outlined below
2. Post a HETE study protocol and analysis plan on a public study registration site prior to conducting the study analysis.
3. Publish HETE study results with attestation to conformance and/or deviation from the study protocol and original analysis plan. Possible publication sites include a medical journal, or a publicly available web-site.
4. Enable opportunities to replicate HETE studies (i.e., for other researchers to be able to reproduce the same findings using the same data set and analytic approach). The ISPE companion paper lists information that should be reported in order to make the operational and design decisions behind a RWD study transparent enough for other researchers to reproduce the conduct of the study.
5. Perform HETE studies on a different data source and population than the one used to generate the hypotheses to be tested unless it is not feasible (e.g., another data set is not available)
6. Authors of the original study should work to publicly address methodological criticisms of their study once it is published.
7. Include key stakeholders (patients, caregivers, clinicians, clinical administrators, HTA/payers, regulators, manufacturers) in designing, conducting, and disseminating HETE studies.

RCT Duplication Demonstration Projects

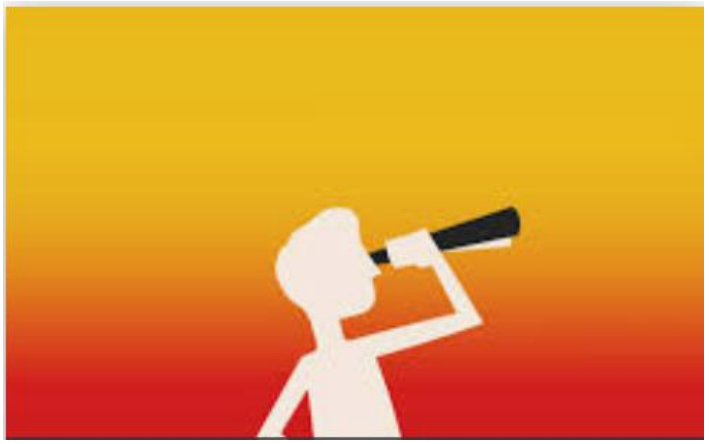
- **Substantial assessment of the comparability of randomized and non-randomized designs to understand if non-interventional designs could provide credible evidence of drug effect**
  - **Comparable results with similar clinical questions?**
  - **Reasons for differences?**
- **Goal: approximately 30 retrospective trial replications 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/

Real World Data Sources

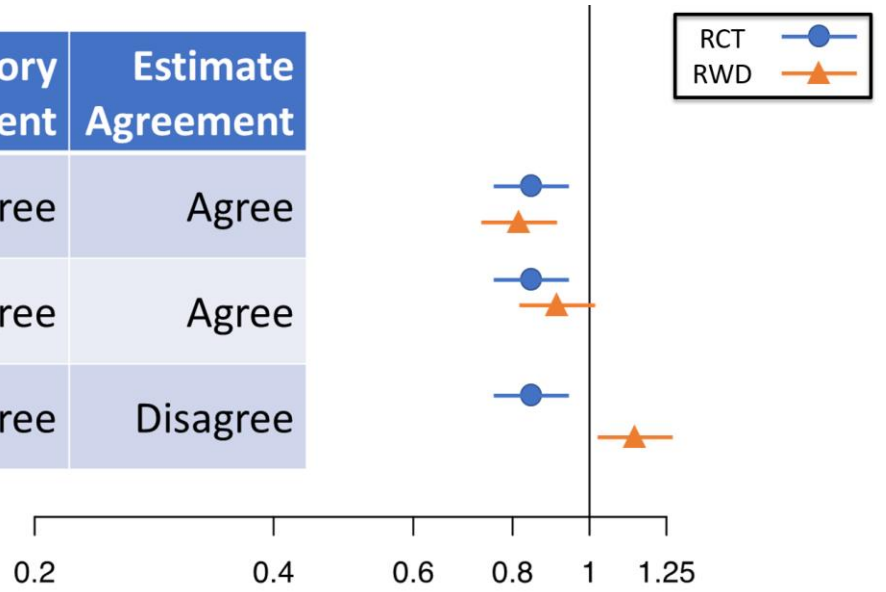
- **Early logistical decision that replication of large amount of trials with a short timeline would benefit from the highly structured nature of claims**
- **Retrospective**
  - **Optum© Clinformatics® Data Mart from 2004 through September 2017**
  - **Truven MarketScan from 2006 through December 2017**
  - **Medicare Parts A, B, and D across varying time ranges for select therapeutic areas with continuing data accrual**
  - **No Laboratory Values**
- **Prospective**
  - **will include laboratory values if needed for endpoint**

Implementation Process

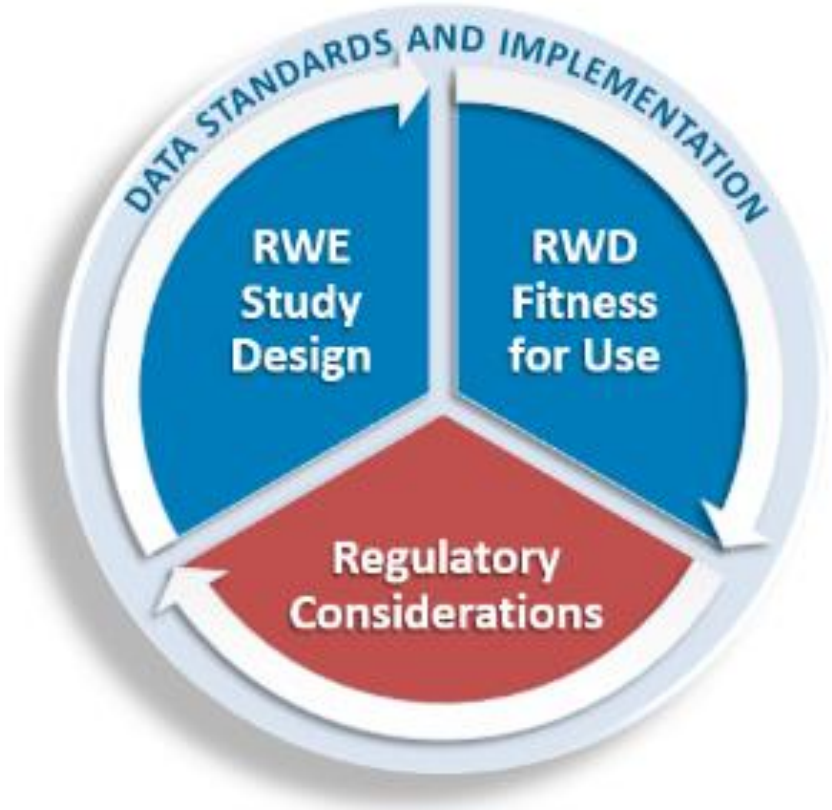
1. Prospective engagement with FDA during protocol development and initial feasibility and power calculations
2. FDA review of final definitions of cohort identification, exposure, outcome, and covariates
3. While blind to differential outcome, final power analyses and covariate balance checks are completed – joint go/no go decision
4. Study protocol registered on ClinicalTrials.gov
5. Analyze outcome data and calculate effect measures
6. Document findings
7. Apply prespecified measures of agreement
8. Audit trail visible to FDA throughout the process – FDA sub-team may at its option engage in additional post-hoc sensitivity analyses for training purposes

Evaluating Agreement

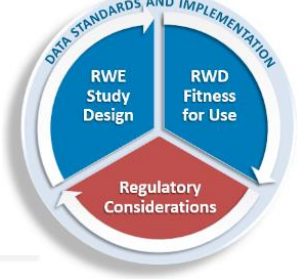
Regulatory Agreement	Estimate Agreement
Agree	Agree
Disagree	Agree
Disagree	Disagree



- **"Regulatory Decision" Agreement (RA): RWD study would have come to the same conclusion as RCT based on statistical significance of effect estimate**
  - **Same significance finding (reject / do not reject H_0)**
  - **Same non-inferiority margin required when applicable**
- **Estimate Agreement (EA): RWD effect estimate lies within the 95% CI from the RCT**

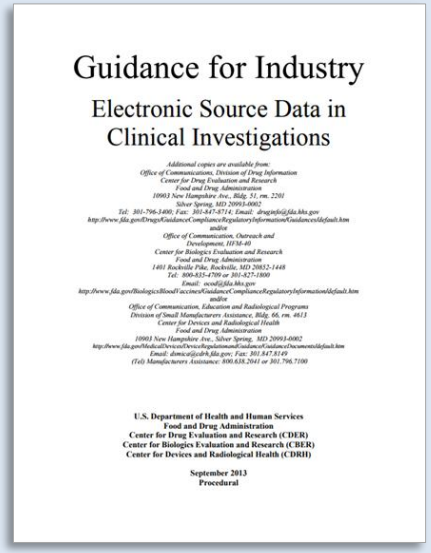


REGULATORY CONSIDERATIONS



Regulatory Considerations in Increasingly Digital World

eSource



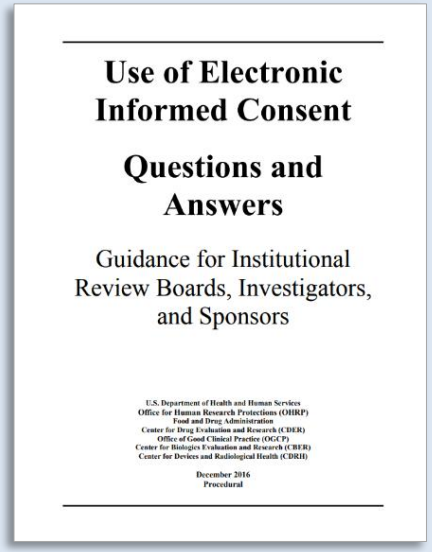
Guidance for Industry

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

E-Informed Consent



Use of Electronic Informed Consent

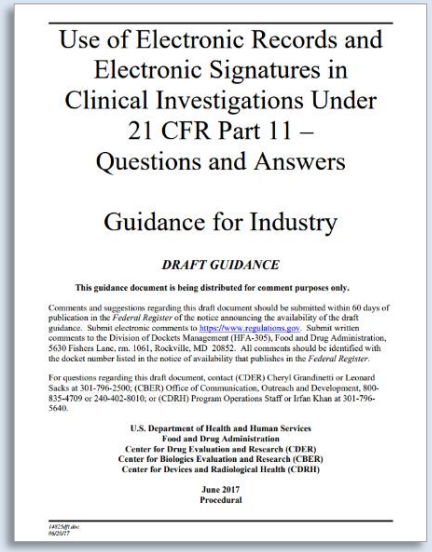
Questions and Answers

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

E-Records & e-Sig



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

Guidance for Industry

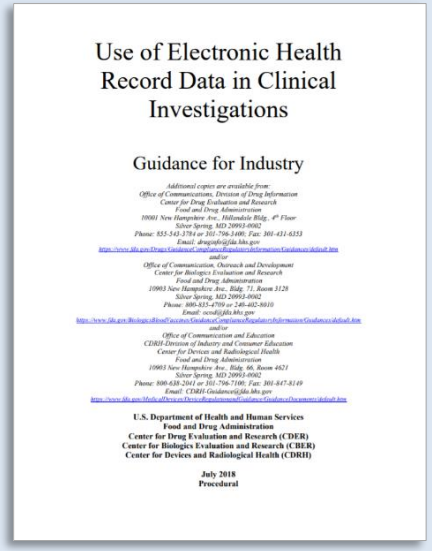
DRAFT GUIDANCE

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

EHR



Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

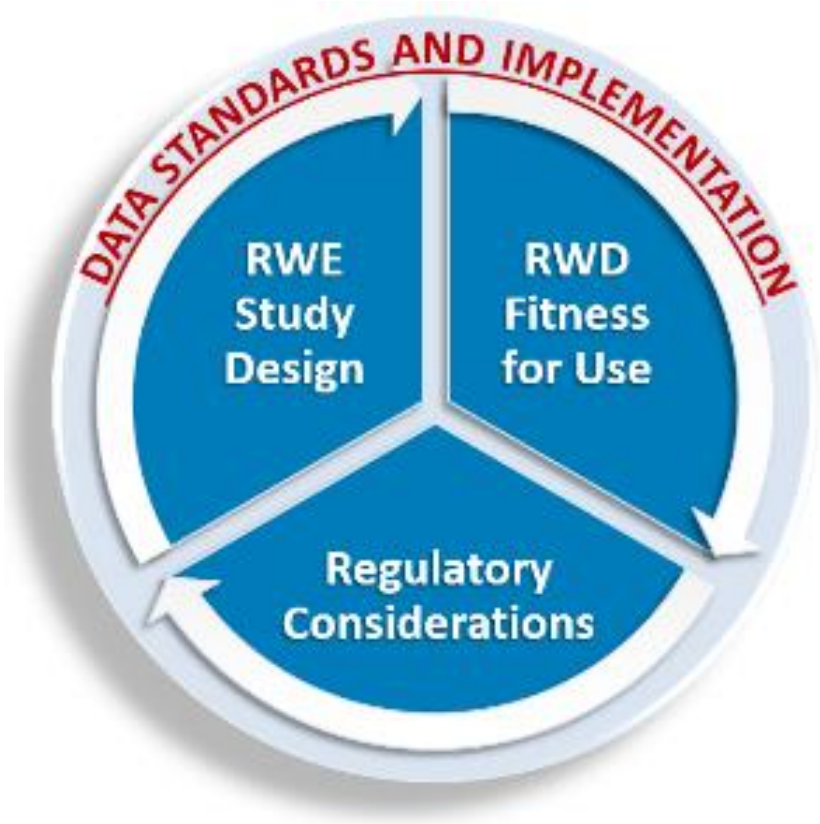
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

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

FDA

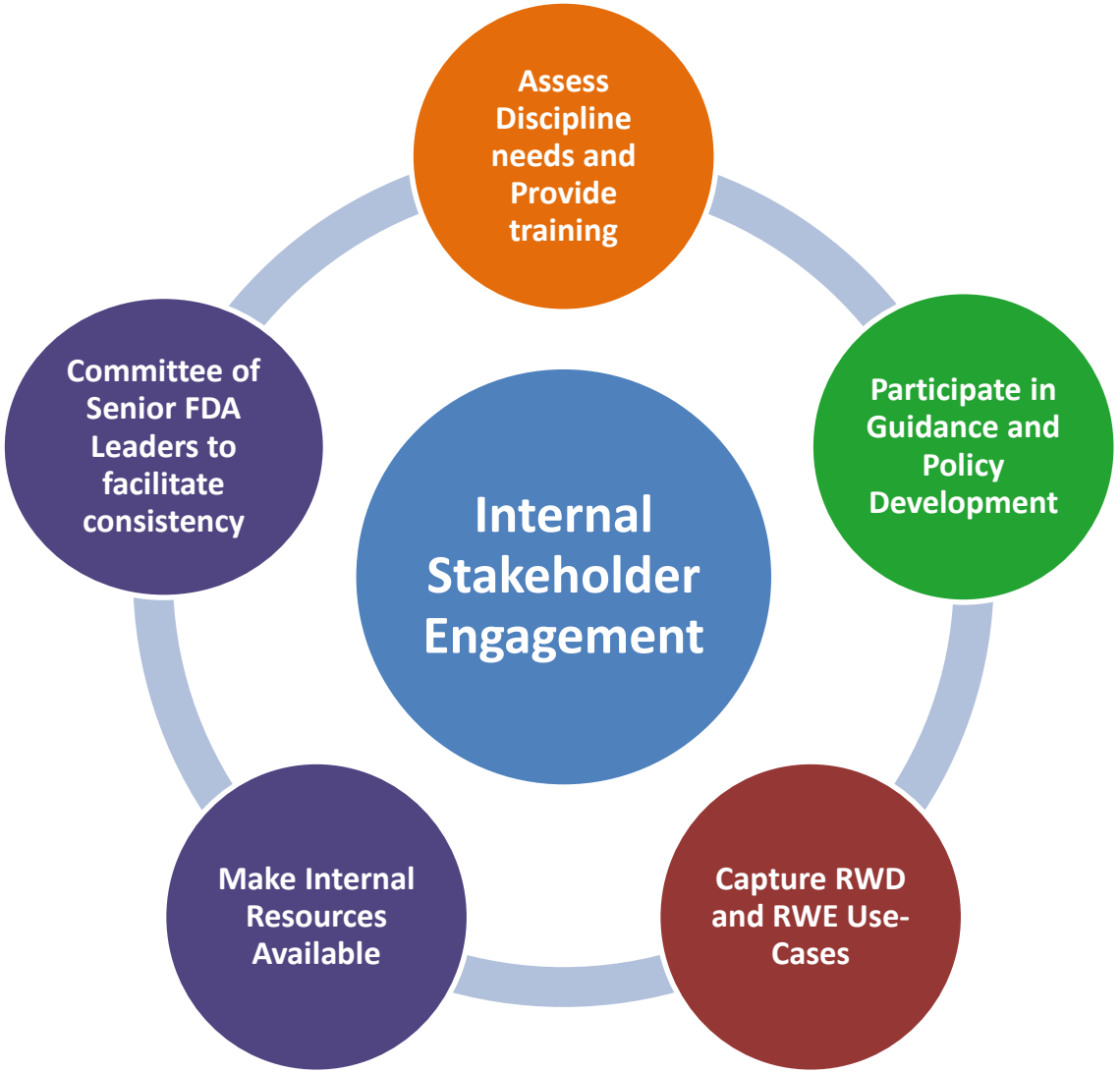
Identify **gaps** between RWD/ RWE data standards and existing systems

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

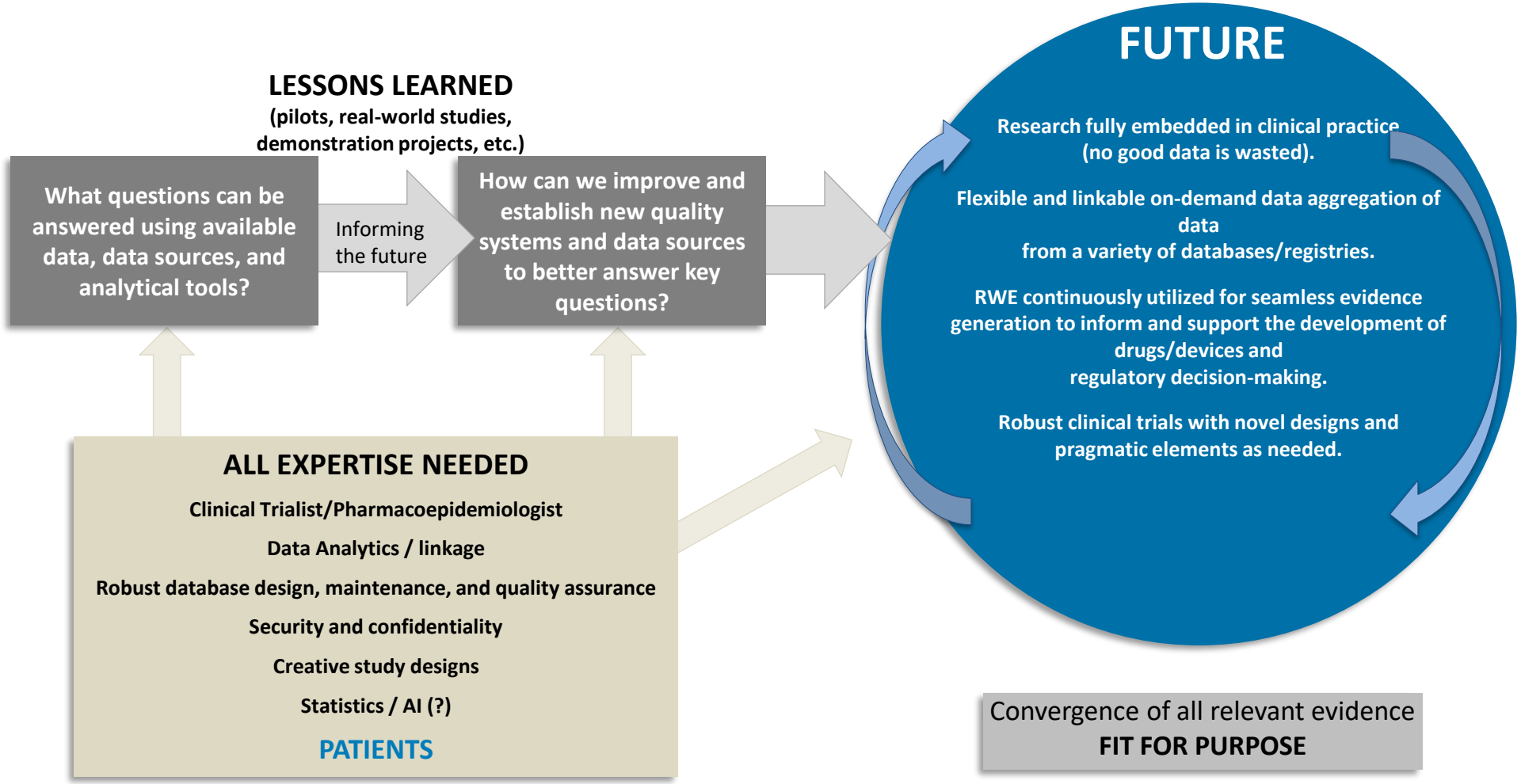
Collaborating with Stakeholders to adopt or develop standards and implementations strategies

RWD Submission Standard

Internal Stakeholder Engagement



Creative Thinking & All Expertise Needed



U.S. FOOD & DRUG ADMINISTRATION

CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION