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

May 7, 2019

Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to the Food and Drug Administration.

Financial Conflicts: None

Expectations in Law for Real-World Evidence: The 21st Century Cures Act

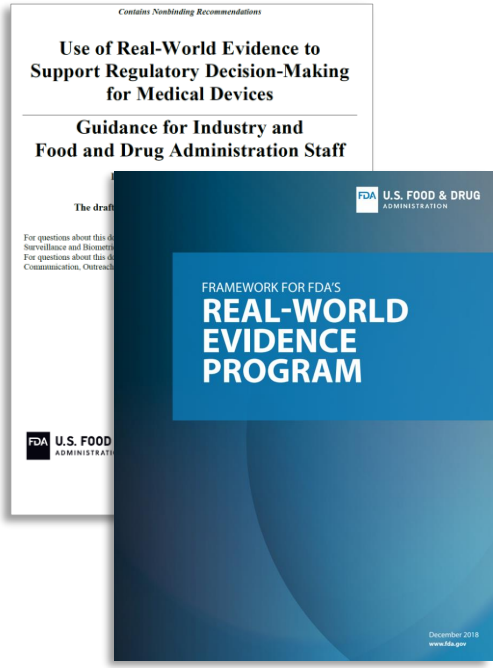
- **FDA shall establish a program *to evaluate the potential use* of real world evidence (RWE) to support:**
  - **Approval of new indication for a drug approved under section 505(c)**
  - **Satisfy post-approval study requirements**
- **Program will be based on a framework that:**
  - **Categorizes sources of RWE and gaps in data collection activities**
  - **Identifies standards and methodologies for collection and analysis**
  - **Describes the priority areas, remaining challenges and potential pilot opportunities that the program will address**
- **Draft Guidance to be issued by 2021**
- **PDUFA commitments aligned with 21st Century Cures Act**

Expanding Indications using RWE: Background and Issues

- The value proposition
- Current uses of RWD/RWE in regulatory decisions in CDER
- A framework for moving forward
- Approaches and demonstration projects

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.

Usual Phase 3 Studies: Value and Limitations

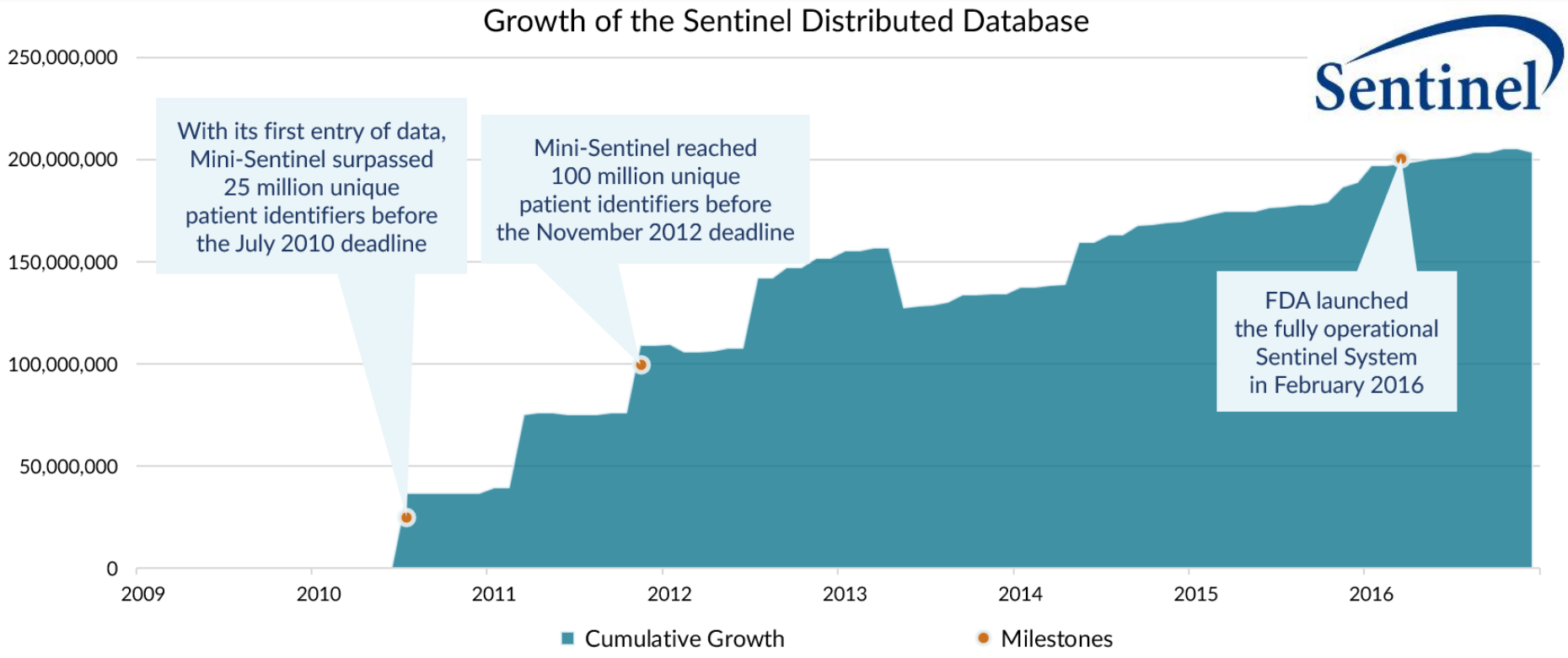
- **Traditional RCTs can provide a precise assessment of efficacy and safety**
  - Potential for valid causal inferences to be drawn
    = *does the drug work – strong internal validity*
  - Well-characterized response (standardized endpoints) in patients with the disease (standardized diagnosis) responsive to treatment (enhanced adherence, exclusion criteria)
    = effect size in patients in trial – *issue of external validity*
  - Reliable data set upon which to base regulatory decisions

- **But have limitations:**
  - Resource intensive, long time to complete
  - Selected population vs post-approval use – internal validity vs external validity/ generalizability
    - Limitations: fewer who are older, with multiple co-morbidities, on many concomitant medications

Why expand use of RWD/RWE?

- **Much broader and more diverse patient experience vs traditional Phase 3 clinical studies**
  - **Includes settings and patients who will use drug post-approval (vs more restricted population in Phase 3 program)**
  - **Patients with broader age, racial/ethnic, co-morbid disease, disease severity, concomitant medication – much wider experience vs Phase 3 trials**
- **Very large sample sizes – potential for detection of infrequent events, drug-drug interactions**
- **Lower resource intensity – utilizing practice data vs extensive trial infrastructure**
  - **Non-blinded studies reducing costs associated with drug supply chain, storage; and resources associated with providing blinded drug supplies to patients**

Sentinel Initiative



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.

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**

Considerable Experience with RWD and Methods

Pharmacoepidemiol Drug Saf. 2018;27:30–37

Some Use in Effectiveness

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**

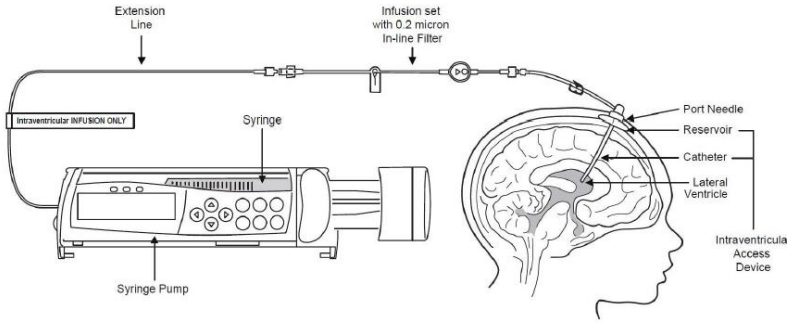
Bold = RWE

NOT EXHAUSTIVE

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

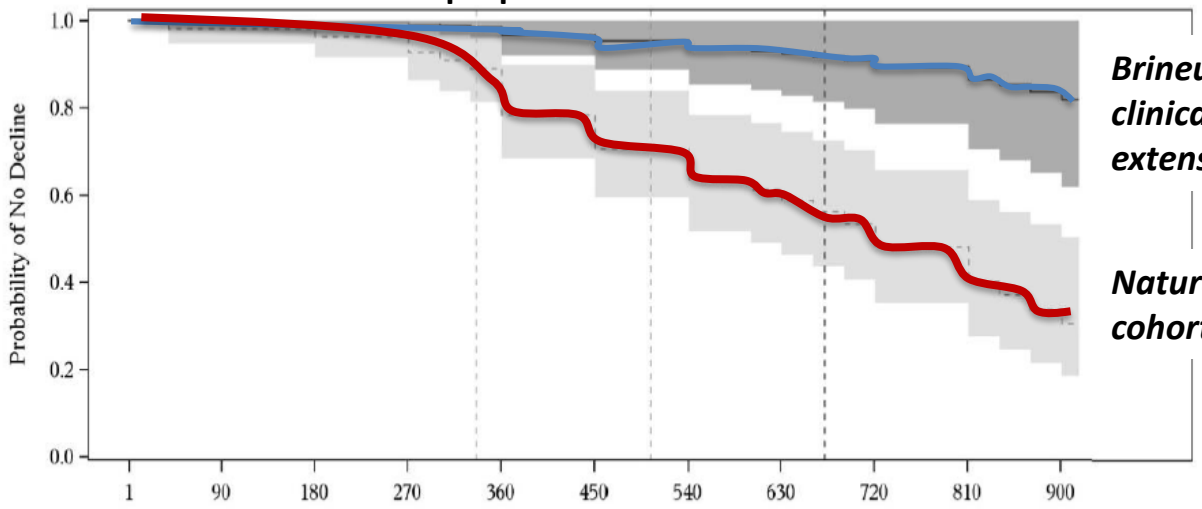
Use of RWE in Regulatory Approval: The Example of Brineura for CLN2

- CLN2 (a neuronal ceroid lipofuscinoses) - rare inherited disorder of CNS (~2–4 of every 100,000 live births in US)
- Deficiency tripeptidyl peptidase-1 enzyme
- Late infantile form onset 2 - 4 years - language delay, seizures, ataxia; progressive, fatal disease
- Brineura (cerliponase alfa) - a recombinant human TPP1



Delivered into CSF through port

Estimated Time to Sustained 2-category decline or Zero score
Cox proportional hazards model



Brineura single arm clinical study / extension (n=22)

Natural history cohort (n=42)

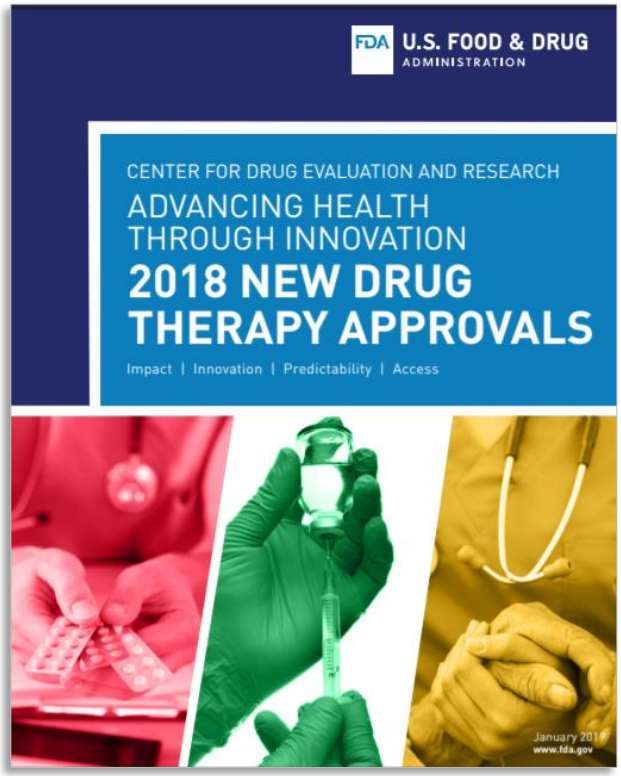
Clinical evidence from single arm study, comparison to natural history cohort (nonconcurrent)

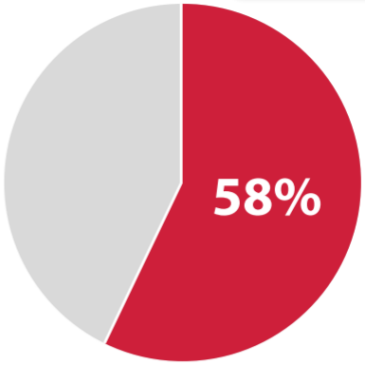
Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses – Subpart E

Establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists

Appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness.

Recognize physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses.

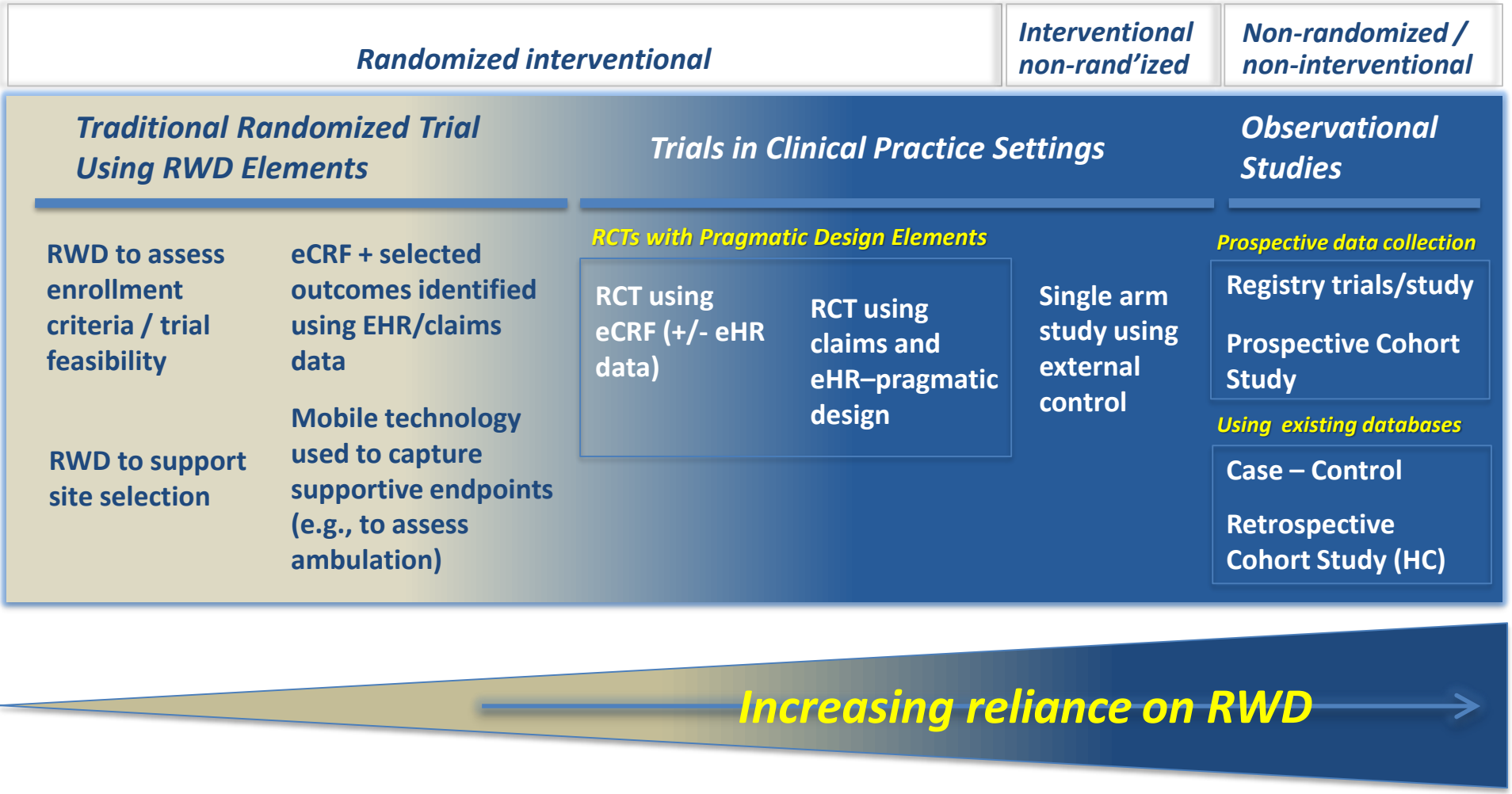




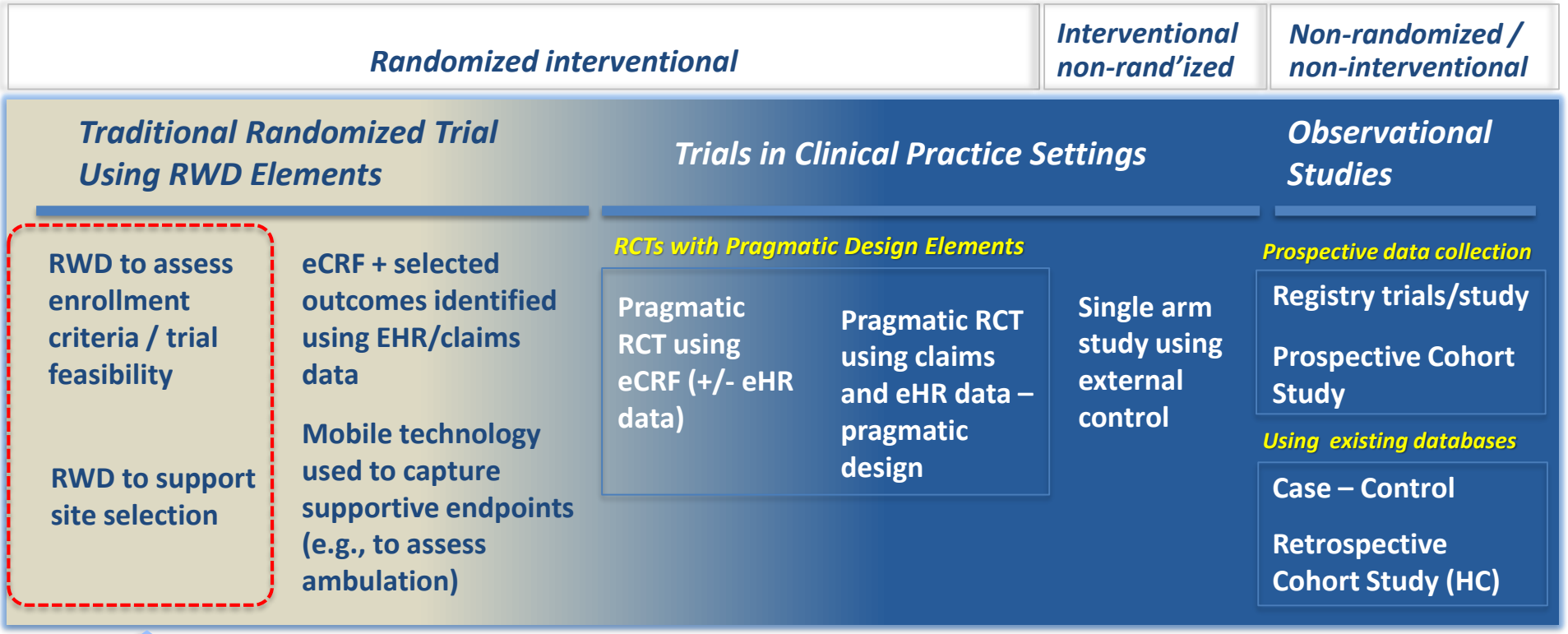
34 of CDER's 59 novel drugs (58%) were approved to treat rare or "orphan" diseases.

21 CFR 312.80

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

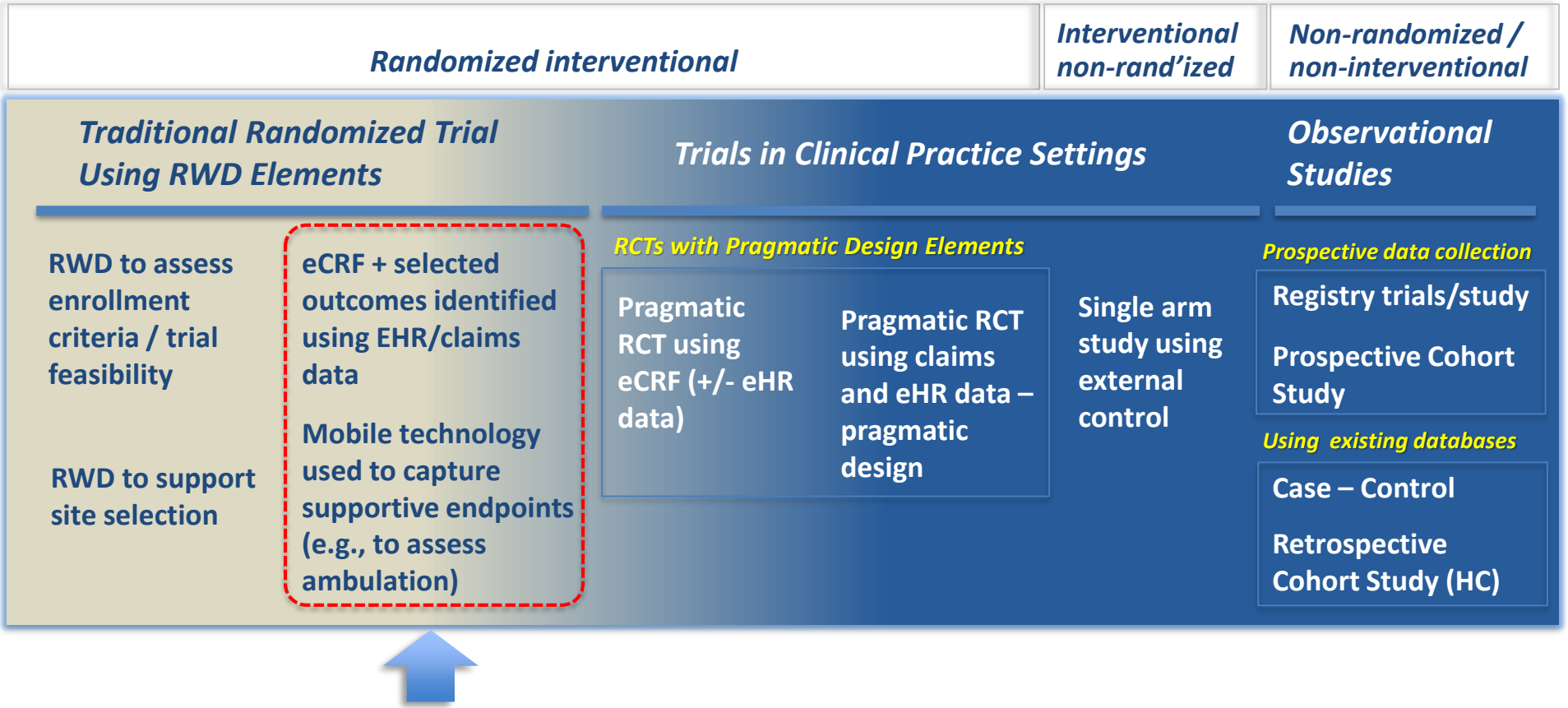


Wide Spectrum of Potential Uses of RWD / RWE in Clinical Studies



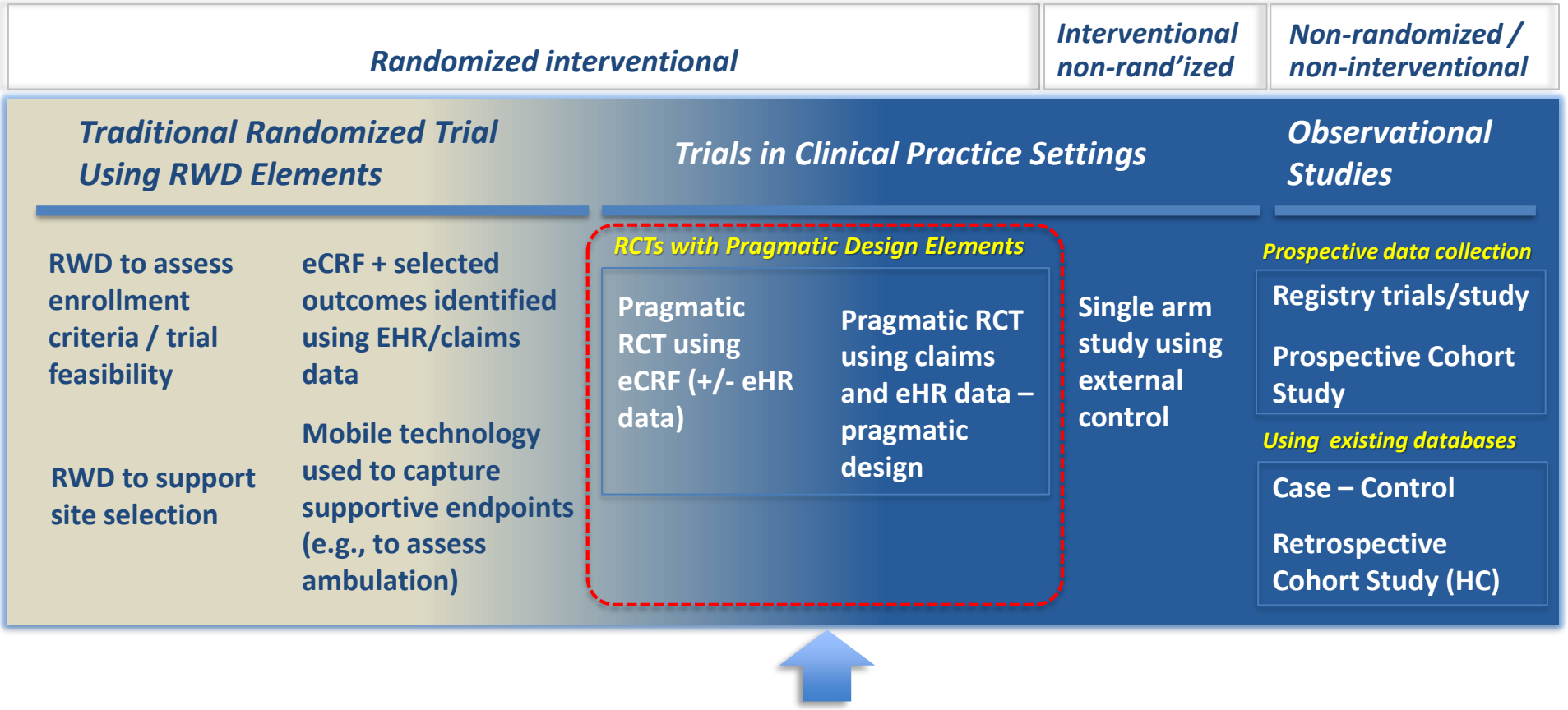
- Already common practice
- Increases trial efficiency, ability to target desired patient populations

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



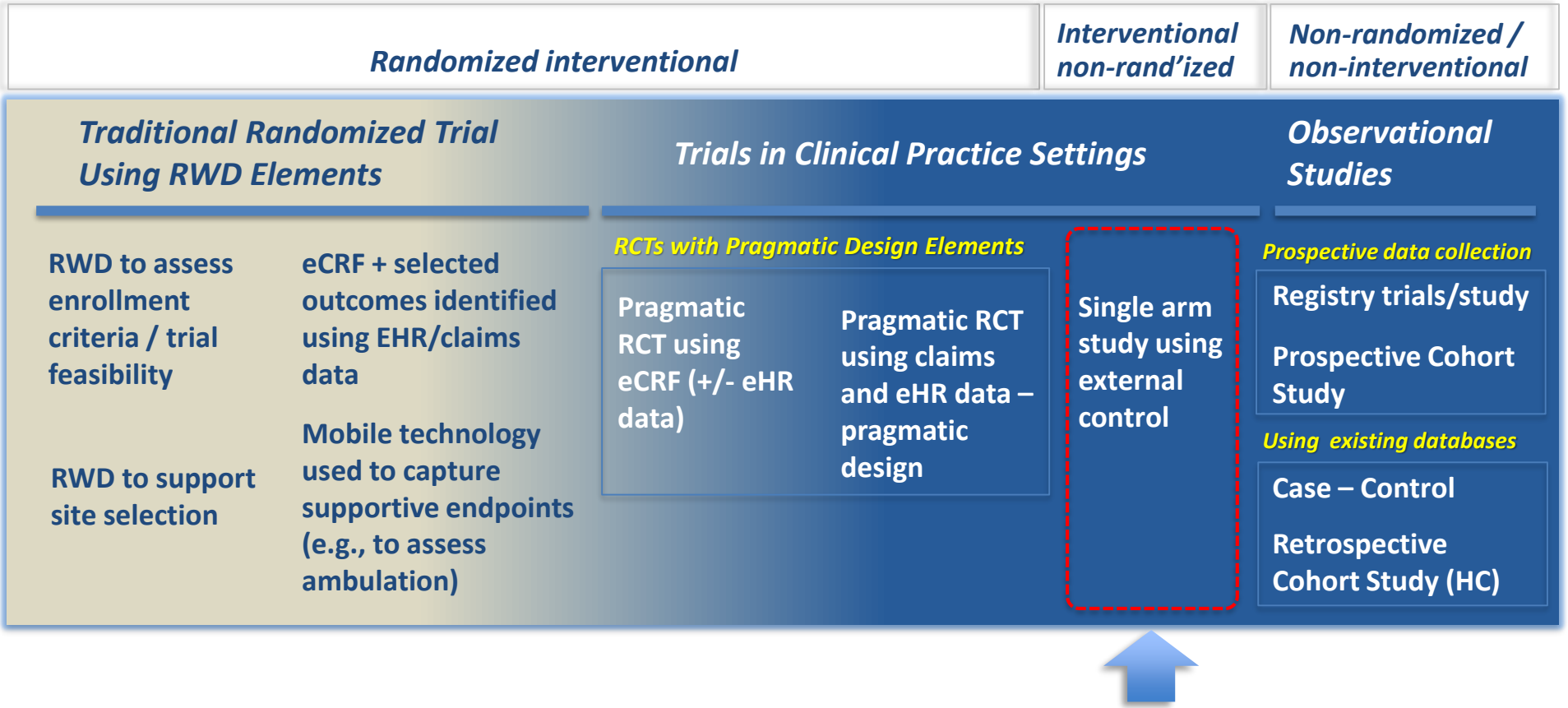
- Rise in mobile technology offers new endpoints ("COAs")
- Correspondence of EHR/Claims and traditional collection methods may support further inroads into RWE generation

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



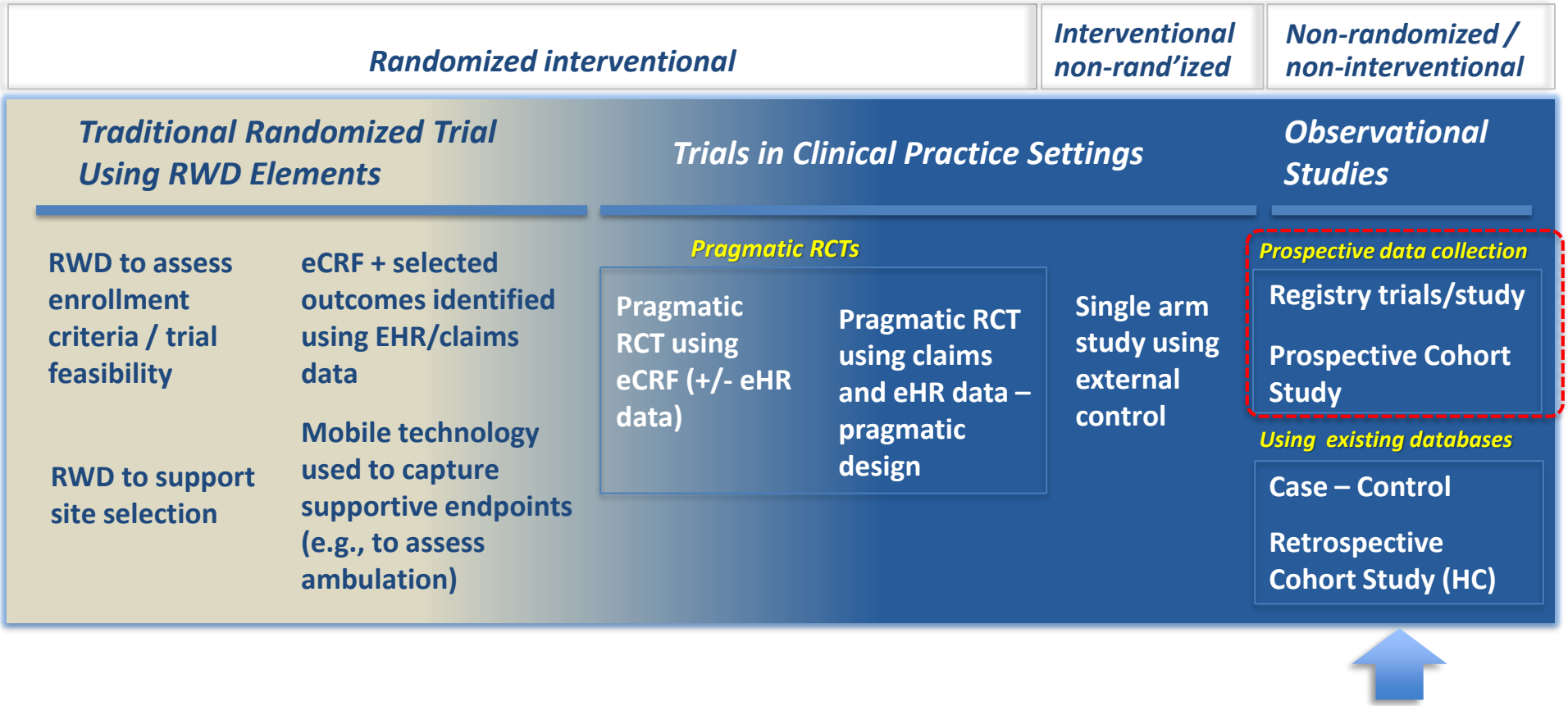
- Limitations of claims databases may be addressed by linking to EHR for richer covariates, more options for trial endpoints

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



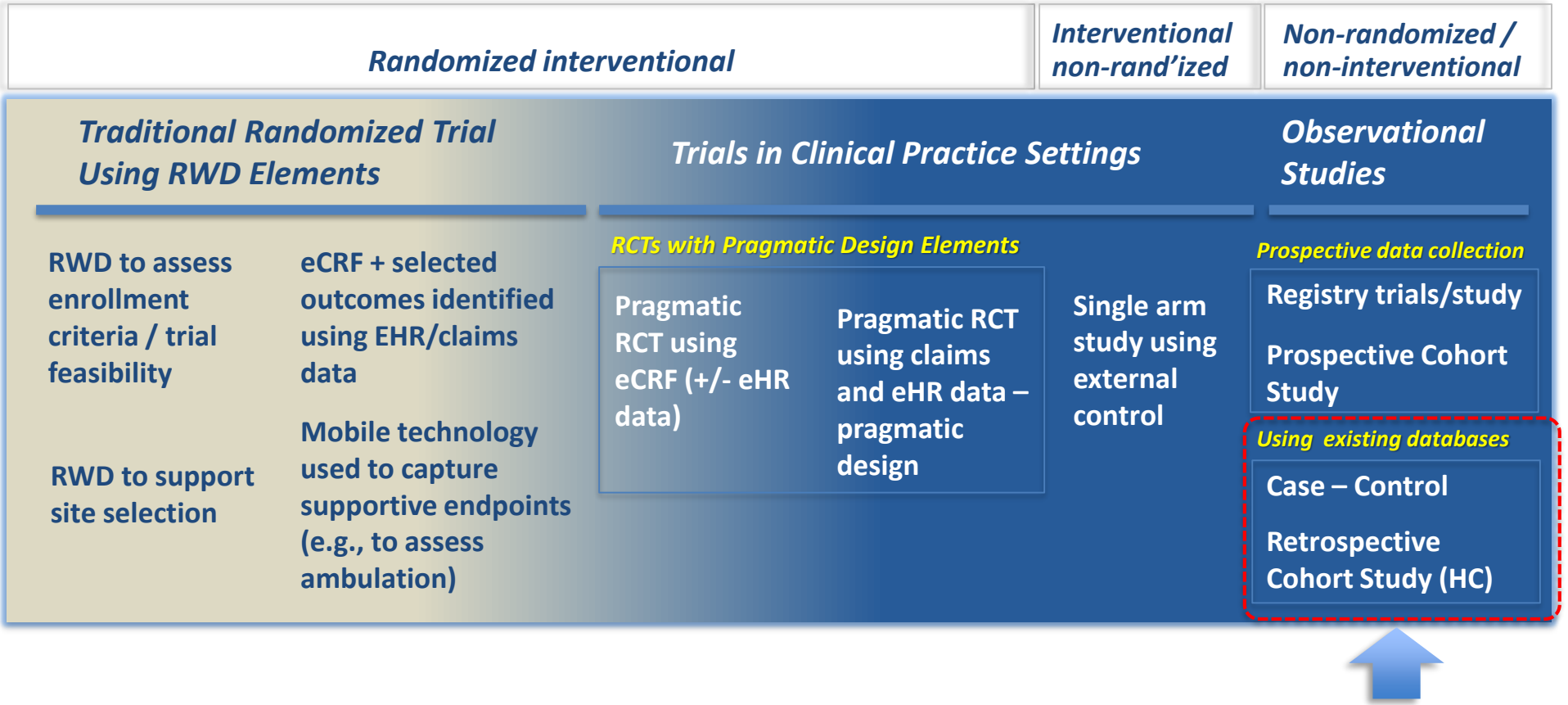
- Commonly applied to rare diseases, oncology
- Requires well-defined natural history, covariate rich external control dataset
- Objective endpoints, substantial drug effect

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



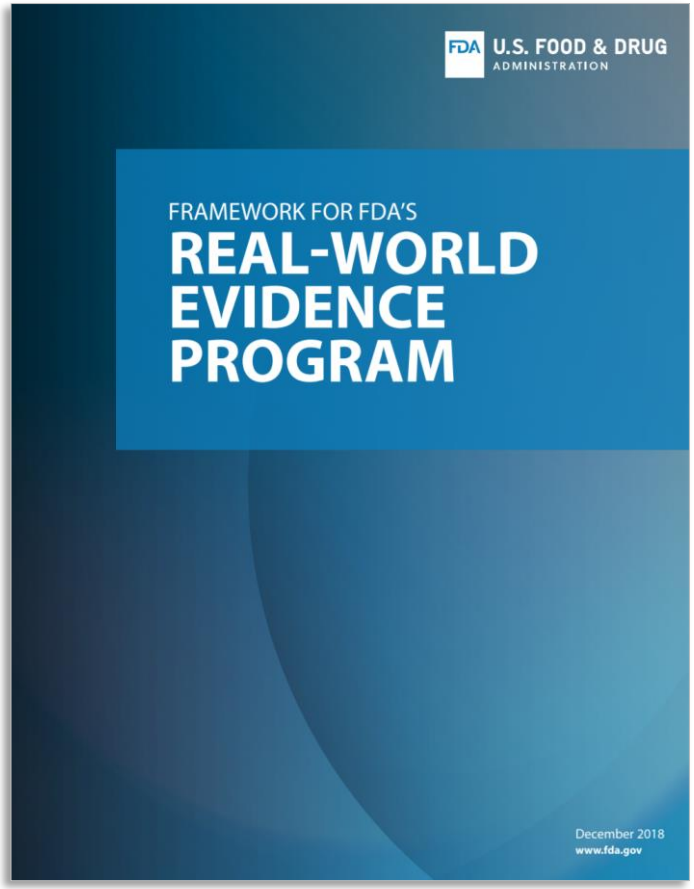
- Prospective studies allow better population and endpoint definition
- Challenging to conduct, assure representative patient population, consistent collection of endpoints

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



- Challenges to drawing causal inferences
- Limitations on comparisons, endpoints
- Requires robust pre-specification
- Data quality and traceability issues

FDA Real-World Evidence Program



- **Outlines FDA's plan to implement the RWE program**
- **Focus on adding or modifying an indication, comparative effectiveness, and comparative safety**
- **Multifaceted program**
  - **Internal processes**
  - **Guidance development**
  - **Stakeholder engagement**
  - **Demonstration projects**

Postmarketing Evaluation (Phase IV)

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

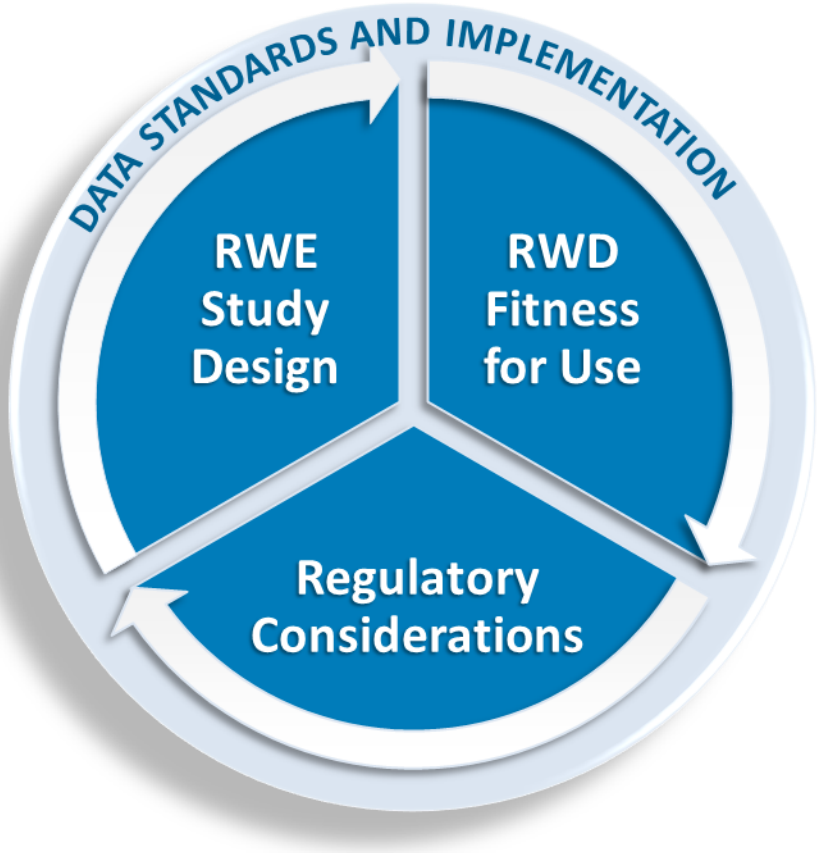
- FDA guidance document which describes the potential use of RWE throughout the total product lifecycle for devices
  - Draft issued prior to 21st Century Cures Act
- Definitions of Real World Data and Real World Evidence are harmonized with the FDA Framework
- CDRH, CBER, and CDER are coordinating as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

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

Benchmark

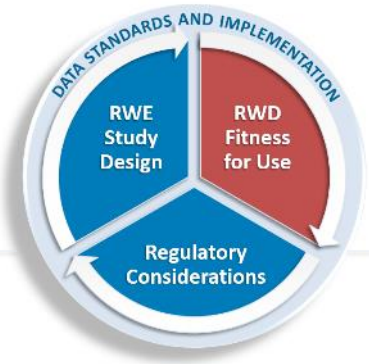
- Substantial evidence standard unchanged
  - Goal is to distinguish the effect of the drug from other influences such as spontaneous change in disease course, placebo effect, or bias
  - Common practices:
    - Probabilistic control of confounding through randomization
    - Blinding
    - Controlled/standardized outcome assessment
    - Adjudication criteria
    - Audits

Framework for Evaluating RWD/RWE for Use in Regulatory Decisions



Consider:

- **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**

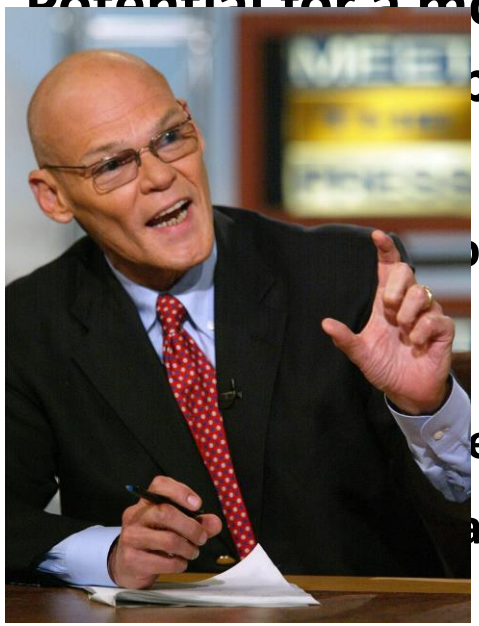


RWD Fitness for Use

- **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 - 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**
  - **How to integrate data sources and address duplication**

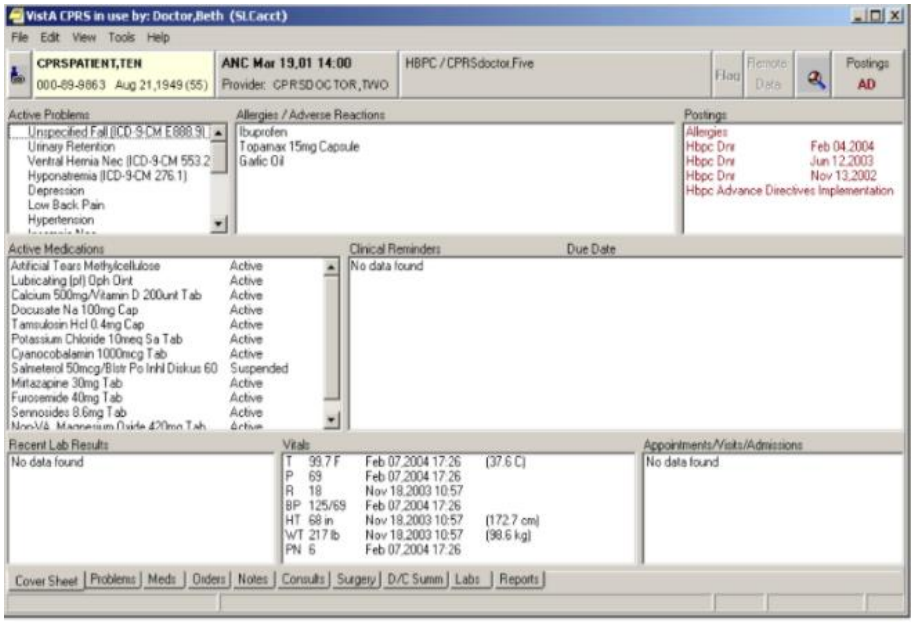
EHRs: Potential and Challenge

Potential for a more complete and [illegible]picture; challenges



[illegible]logy/ radiology and [illegible] are often [illegible] (80%) and images [illegible]essary

[illegible]ata ≠ Standardized



- **Typing ≠ consistency/complete documentation**
- **Interoperability**
- **Clinical outcome measures for drug approvals may not be used or consistently recorded in practice**

It's the data . . .

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.

Future ONCOLOGY

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

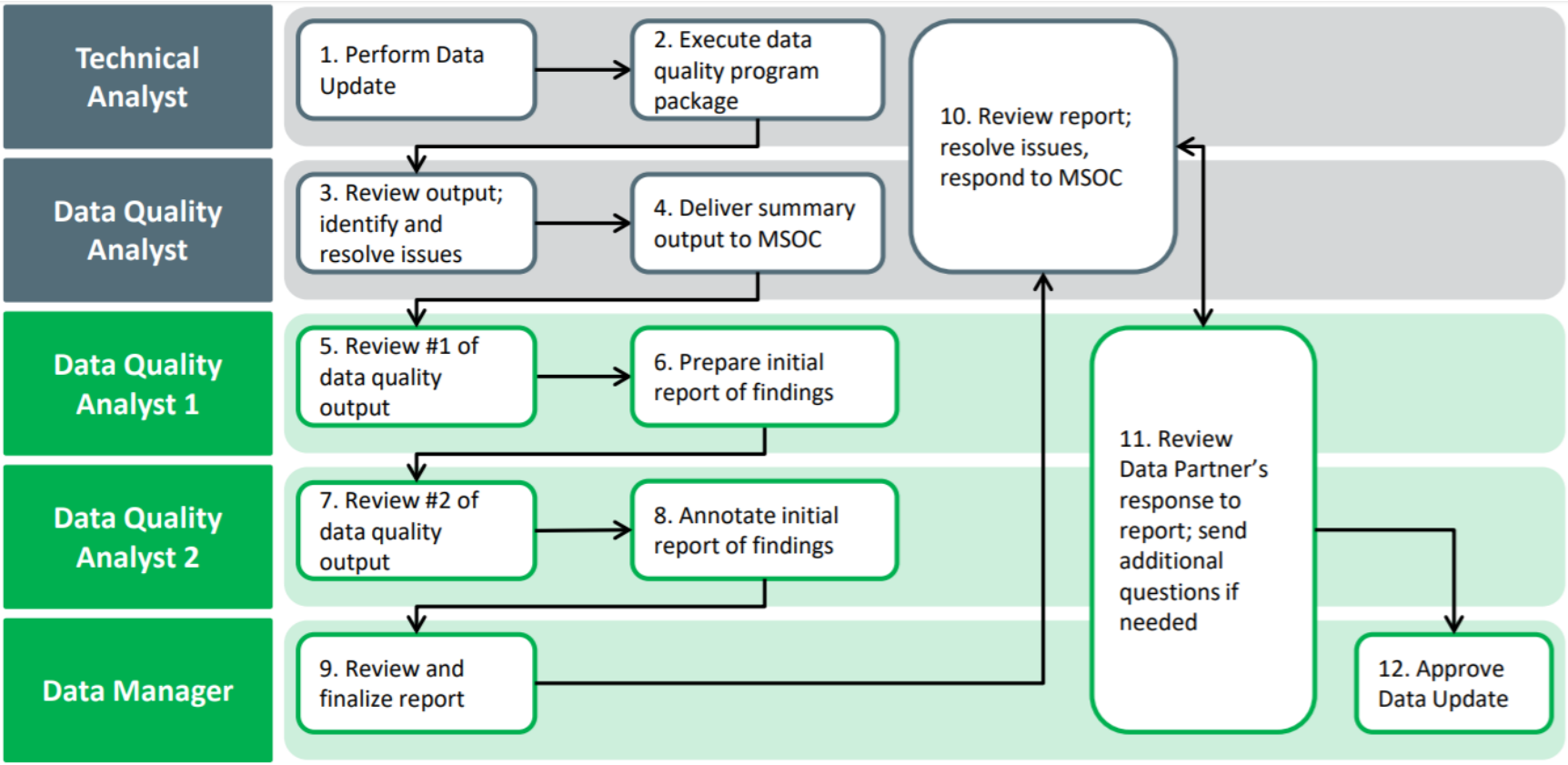
Endpoints in FDA Registrational Trials 2007–2015

Type of Endpoint	% of NDA	Examples of Endpoints Measured
Chemistry data	11	HBA1c, pregnancy test, GFR
Hematology	6	Severe neutropenia Apheresis yield > 5 million CD34+ cells/kg
Pathology	2	Increase/decrease of parabasal cells; biopsy proven acute rejection, clearing of anterior chamber cells
Microbiology	6	Sustained virological response, plasma viral load, conversion to negative sputum
Imaging +/- (survival, clinical signs)	17	Bone mineral density; vertebral fractures, spleen volume, progression free survival
Physiological/ functional measurement	9	6 minute walk, normal sinus rhythm, FEV1, sleep studies
Clinical event /clinical sign	19	Death, hospitalization, MACE, MS relapse, Lice free head
CRO/PRO	30	Toronto western spasmodic torticollis rating scale, Hamilton depression rating scale, Rheumatology scale ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score

Assessing RW Endpoints

- **What is the frequency and consistency of the assessment?**
  - **Is it different than the comparator**
- **How do we translate a regulatory endpoints into a RW endpoint?**
- **For studies without treatment assignment how much do we need to worry about patient/provider bias?**
  - **"I prescribed it and therefore expect it to work"**
  - **"My doctor prescribed it and therefore it should work"**

Sample Sentinel Process for Data Quality Assurance



Patient-centric RWD

Alignment of Demonstration Projects with the Framework

Understanding EHRs in the Context of Clinical Trials

- Harmony- Outcomes Ancillary Study
- One Source - ISpy

Use of Mobile Technologies to Enhance RWD

- Trial in Juvenile Idiopathic Arthritis
- Inflammatory Bowel Disease Registry

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/

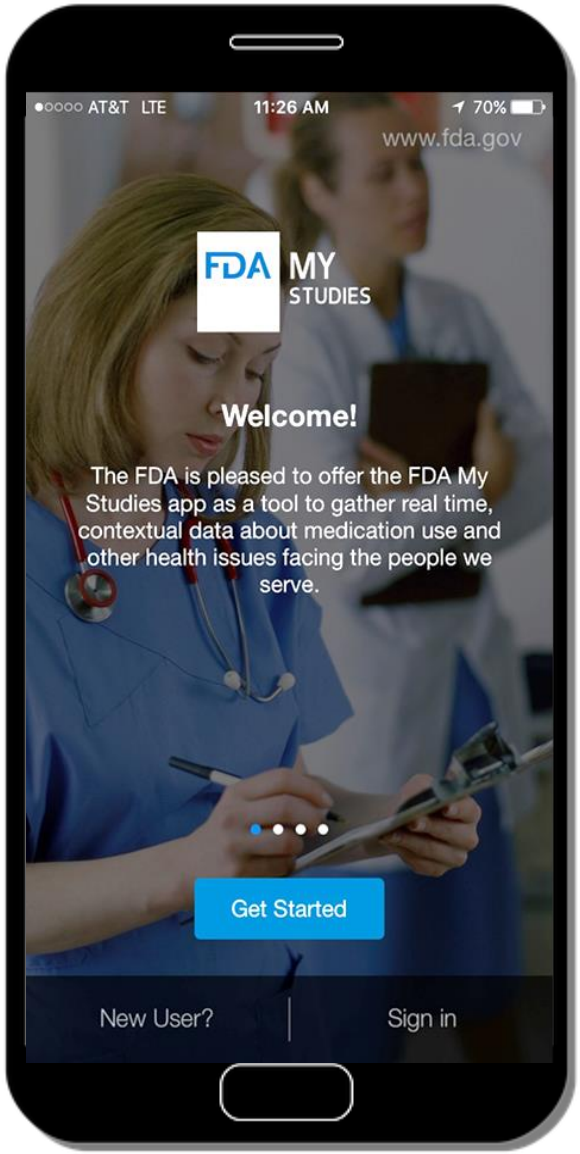
Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus – NCT02465515

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

FDA My Studies



- **Mobile App**
  - **Standard frameworks - ResearchKit (iOS), ResearchStack (Android)**
  - **Gateway capability**
- **Web-based configuration portal**
- **Secure Storage Environment**
  - **21 CFR Part 11 and FISMA complaint**
  - **Partitioned for distributed research**
- **One "e-CRO" has successfully re-purposed the app in a test environment. Eleven groups have downloaded full code/resources from GitHub**
- **FDA SBIA webinar scheduled for May 9**
- **App integral to two new demonstration projects**

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm636494.htm

Demonstration Project

- **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**

pcori

LimitJIA

CARRA
Childhood Arthritis and Rheumatology Research Alliance

Table 1: Primary Inclusion and Exclusion Criteria

Inclusion Criteria:	Exclusion 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	• 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)

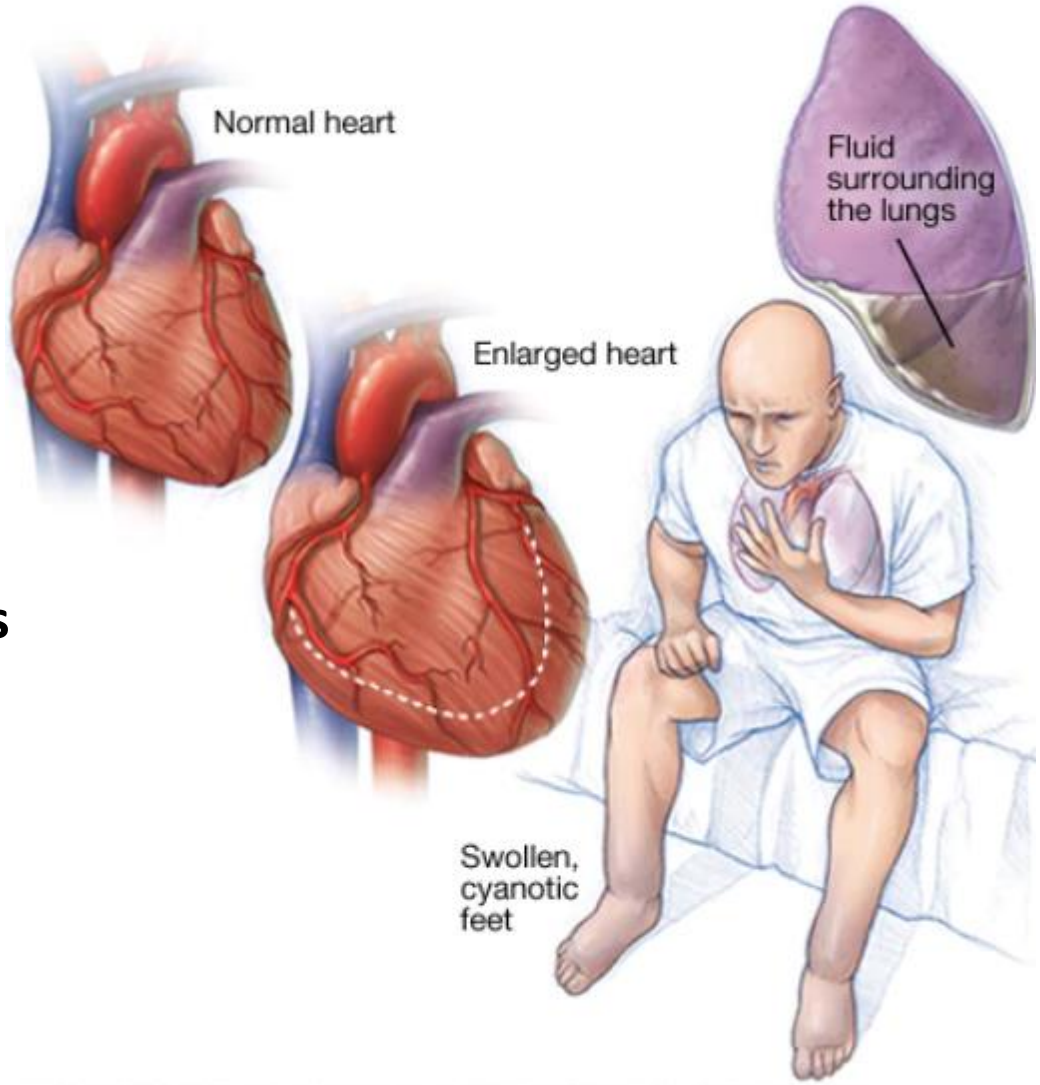
Demonstration Project

- **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**

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**



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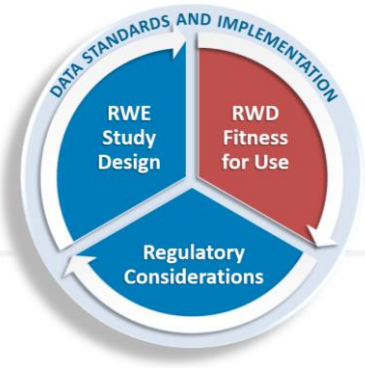
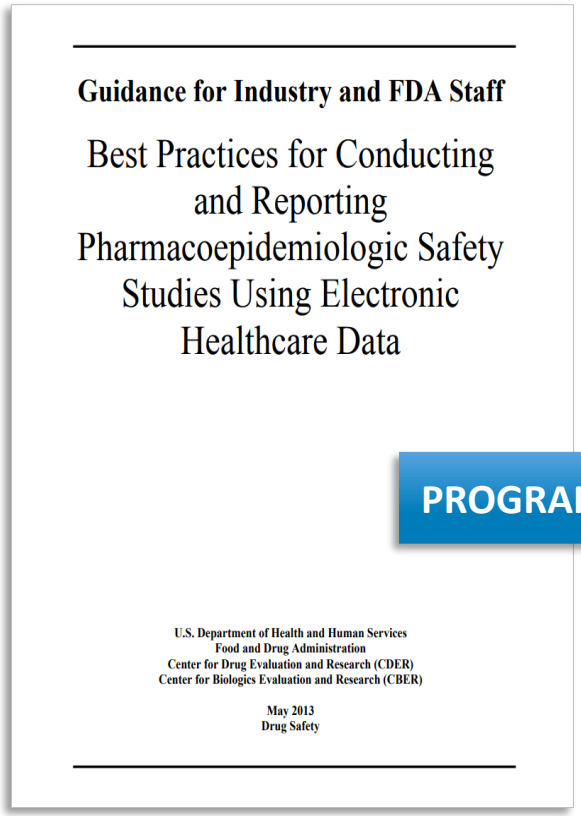


RWD Fitness for Use

As we move forward FDA will leverage the principles from the 2013 guidance on electronic health care data and our demonstrations:



Guidance for Industry and FDA Staff

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

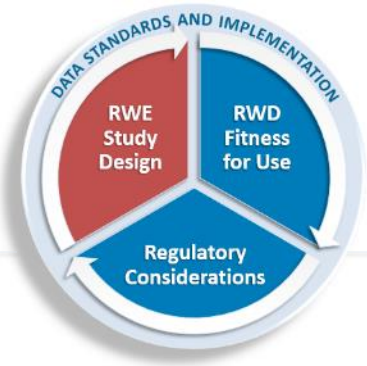
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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



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?
- How will RWD be captured in these settings?
  - Impact on lags in data capture
- Blinding/Masking?
- Bridging between regulatory endpoints and clinical practice
- Site inspections and monitoring

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

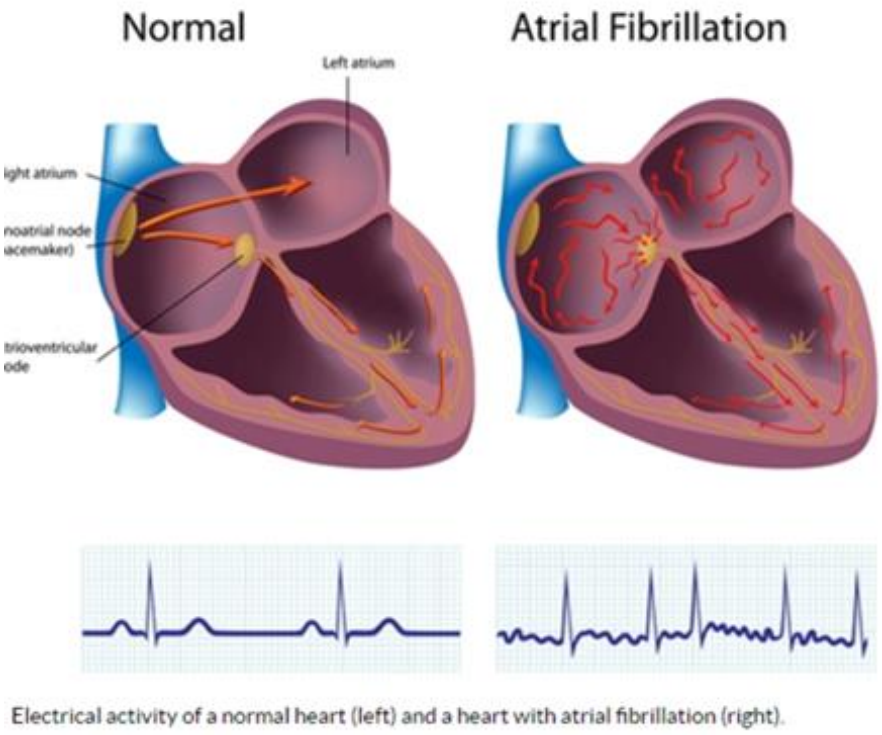
Alignment of Demonstration Projects with the Framework

IMPACT-AFIB – FDA Catalyst

RELIANCE Trial – PCORI – FDA Catalyst

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**
- **Enrollment of approximately 80,000 individuals in the early and late intervention arm**
- **Protocol available at:**

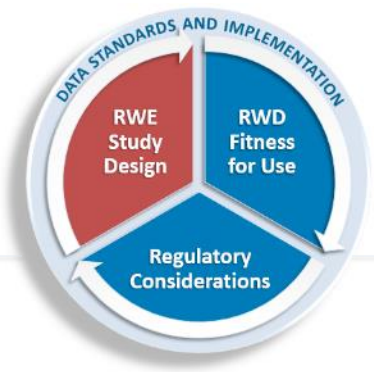


Electrical activity of a normal heart (left) and a heart with atrial fibrillation (right).

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

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
    - Enrollment files: all cause mortality
    - Inpatient claims files: all cause hospitalization for fee for service
    - Part C (Medicare Managed Care): new data source – will request if feasible
    - Part D: medication dispensing



Potential for Study Designs Using RWD to Support Effectiveness

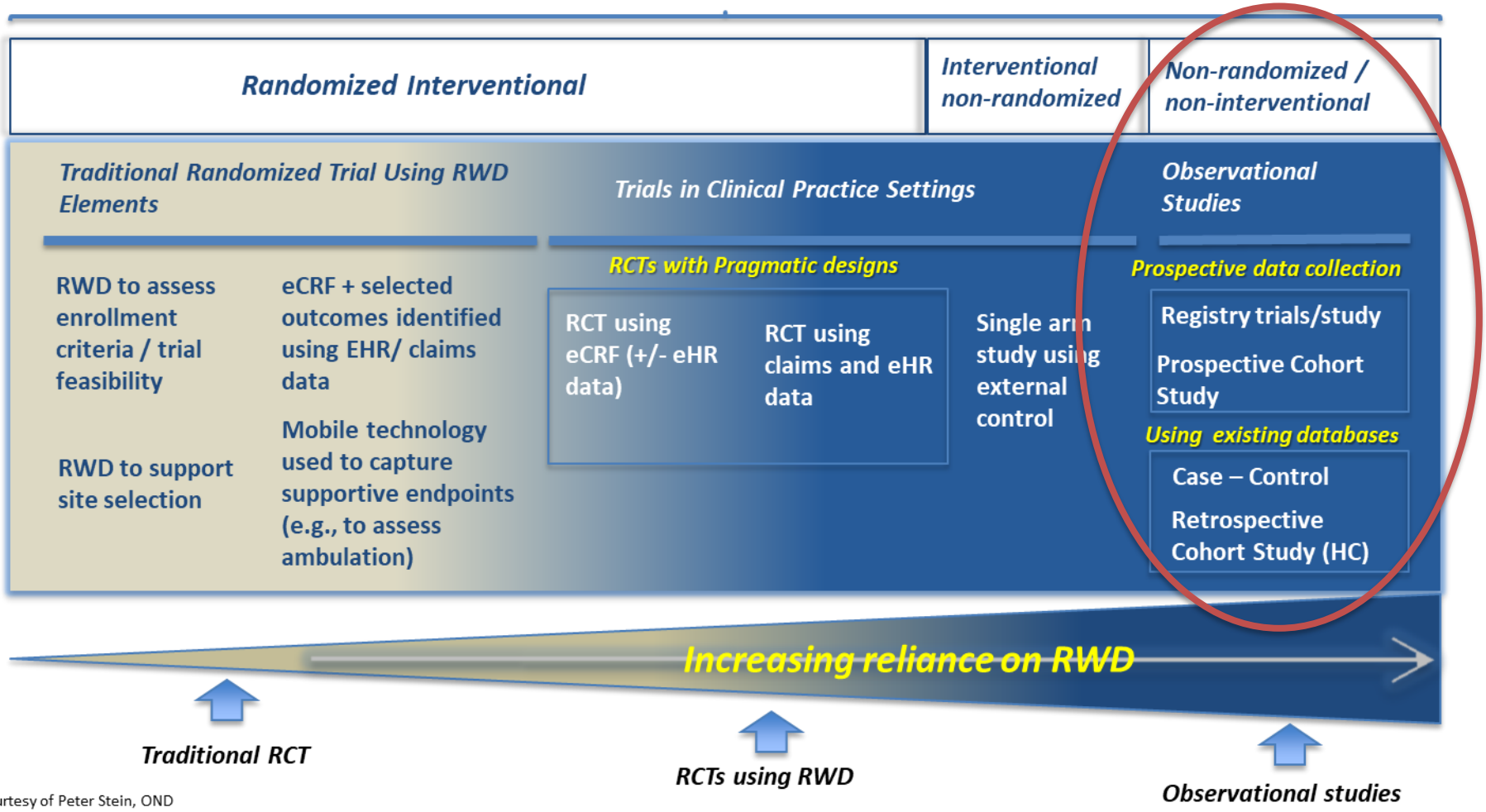
FDA

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**

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

Different challenges and opportunities for each approach



Courtesy of Peter Stein, OND

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**

Observational Studies and Treatment Effects?

RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES, AND THE HIERARCHY OF RESEARCH DESIGNS

JOHN CONCATO, M.D., M.P.H., NIRAV SHAH, M.D., M.P.H., AND RALPH I. HORWITZ, M.D.

N Engl J Med 2000;342:1887-92

TABLE 2. TOTAL NUMBER OF SUBJECTS AND SUMMARY ESTIMATES FOR THE EFFECT OF FIVE INTERVENTIONS ACCORDING TO THE TYPE OF RESEARCH DESIGN.

CLINICAL TOPIC	TYPE OF STUDY	META-ANALYSIS*	TOTAL NO. OF SUBJECTS	SUMMARY ESTIMATE (95% CI)†
Bacille Calmette–Guérin vaccine and tuberculosis	13 Randomized, controlled	Colditz et al.[14]	359,922	0.49 (0.34–0.70)
	10 Case–control	Colditz et al.[14]	6,511	0.50 (0.39–0.65)
Mammography and mortality from breast cancer	8 Randomized, controlled	Kerlikowske et al.[15]	429,043	0.79 (0.71–0.88)
	4 Case–control	Kerlikowske et al.[15]	132,456	0.61 (0.49–0.77)
Cholesterol levels and death due to trauma	6 Randomized, controlled	Cummings and Psaty[16]	36,910	1.42 (0.94–2.15)
	14 Cohort	Jacobs et al.[17]	9,377	1.40 (1.14–1.66)
Treatment of hypertension and stroke	14 Randomized, controlled	Collins et al.[18]	36,894	0.58 (0.50–0.67)
	7 Cohort	MacMahon et al.[12]	405,511	0.62 (0.60–0.65)
Treatment of hypertension and coronary heart disease	14 Randomized, controlled	Collins et al.[18]	36,894	0.86 (0.78–0.96)
	9 Cohort	MacMahon et al.[12]	418,343	0.77 (0.75–0.80)

*Meta-analyses that included either randomized, controlled trials or observational studies are cited.

†CI denotes confidence interval.

The results of well-designed observational studies (with either a cohort or a case–control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic.

misleading.

Sacks, L. Letter to Editor, NEJM Volume 343 Number 16 · **1195**

Cochrane Library

Cochrane Database of Systematic Reviews

ıcare outcomes assessed with observational study
ıs compared with those assessed in randomized trials
ew)

r A, Horvath HT, Bero L 2014

ʌational studies are misleading (just as
ıg), but that no one has devised a
re useful from those that are

Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

Christopher J. Cooper, M.D., Timothy P. Murphy, M.D., Donald E. Cutlip, M.D., Kenneth Jamerson, M.D., William Henrich, M.D., Diane M. Reid, M.D., David J. Cohen, M.D., Alan H. Matsumoto, M.D., Michael Steffes, M.D., Michael R. Jaff, D.O., Martin R. Prince, M.D., Ph.D., Eldrin F. Lewis, M.D., Katherine R. Tuttle, M.D., Joseph I. Shapiro, M.D., M.P.H., John H. Rundback, M.D., Joseph M. Massaro, Ph.D., Ralph B. D'Agostino, Sr., Ph.D., and Lance D. Dworkin, M.D., for the CORAL Investigators*

n engl j med 370;1 nejm.org January 2, 2014

Unmeasured Confounders in Observational Studies Comparing Bilateral Versus Single Internal Thoracic Artery for Coronary Artery Bypass Grafting: A Meta-Analysis

Mario Gaudino, MD; Antonino Di Franco, MD; Mohamed Rahouma, MD; Derrick Y. Tam, MD; Mario Iannaccone, MD; Saswata Deb, MD; Fabrizio D'Ascenzo, MD; Ahmed A. Abouarab, MD; Leonard N. Girardi, MD; David P. Taggart, PhD; Stephen E. Fremes, MD

J Am Heart Assoc. 2018;7:e008010. DOI: 10.1161/JAHA.117.008010

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.

Methods Matter

JAMA The Journal of the American Medical Association

Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

Cardwell et al.

Among patients in the UK General Practice Research Database, the use of oral bisphosphonates was not significantly associated with incident esophageal or gastric cancer.

JAMA, August 11, 2010—Vol 304, No. 6

BMJ

BMJ 2010;341:c4444

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]

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 and North America, the incidence of oesophageal cancer at age 60–79 is typically 1 per 1000 population over five years, and this is estimated to increase to about 2 per 1000 with five years' use of oral bisphosphonates.

Special considerations for observational studies

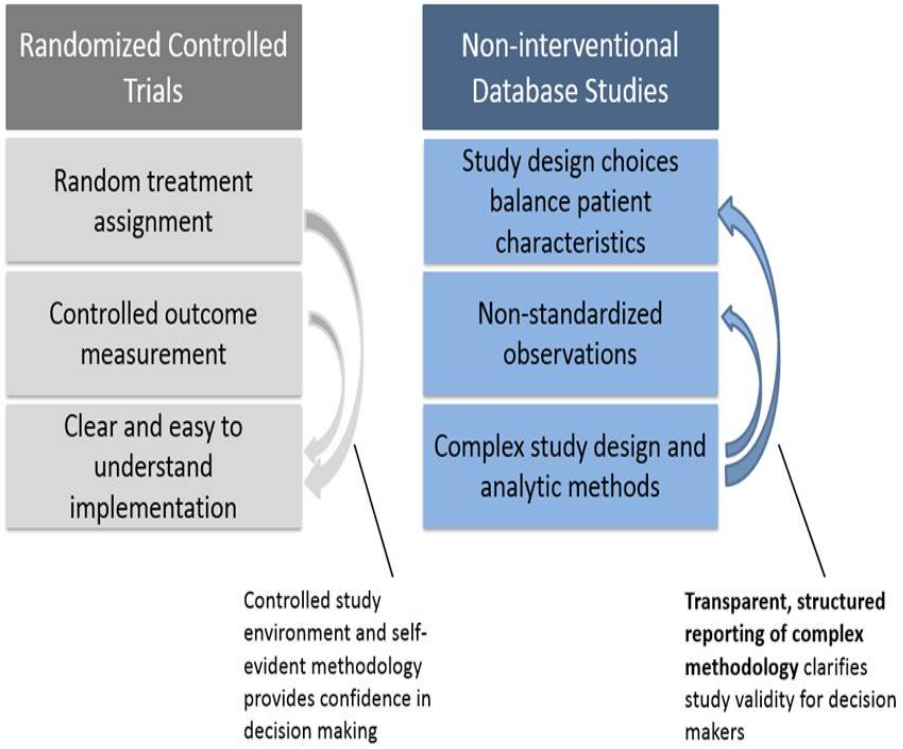


Figure courtesy of S. Schneeweiss

- **Concerns about "p-hacking"**
- **Can propensity scoring and other analytic method control sufficiently for bias such that results are reliable?**
  - **For what endpoints, populations, designs?**
- **What access to source data will there be from RWD sets**
- **Understanding translation of clinical constructs into data specifications and finally into analytic software code**

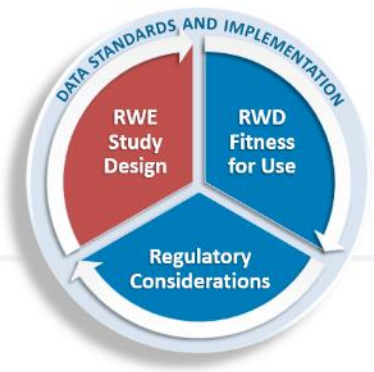
Efforts to Enhance Transparency

Transparency about study design and analysis before 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.



Observational Studies: Initial Questions*

- **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?

*not all-inclusive

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**

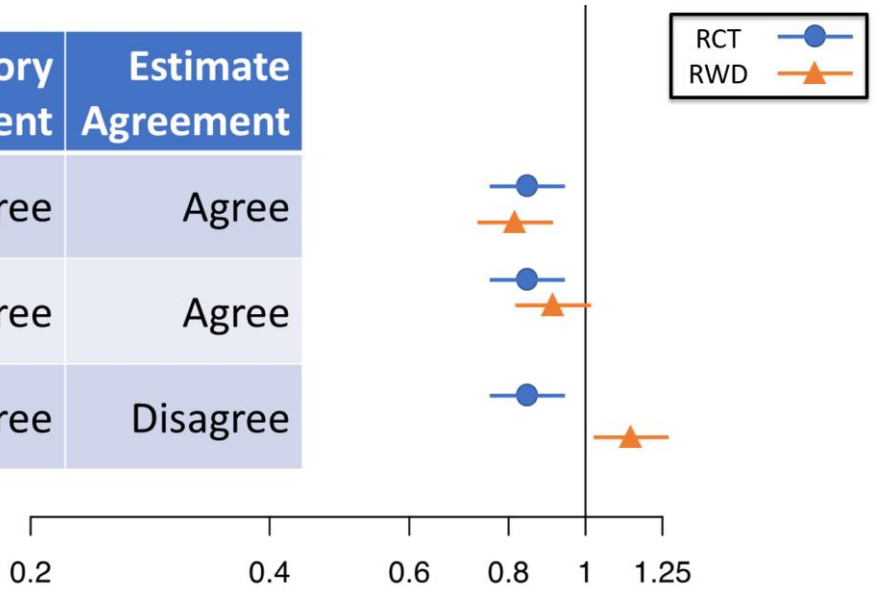
https://www.rctduplicate.org/

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**

JAMA Internal Medicine | Original Investigation

Use of Health Care Databases to Support Supplemental Indications of Approved Medications

Michael Fralick, MD; Aaron S. Kesselheim, MD, JD, MPH; Jerry Avorn, MD; Sebastian Schneeweiss, MD, ScD

- **Comparison of Ramipril to Temisartan that was previously studies in RCT - ONTARGET**
- **Methods**
  - **New user, active comparator**
  - **Propensity score matching after adjusting for 73 patient characteristics**
  - **Sensitivity assay using angioedema outcome comparison**
- **Results: "As seen in ONTARGET, the composite risk of MI, stroke, hospitalization heart failure was similar for the 2 medications"**
- **…But does not include death, which can include out of hospital MI**

FDA

Invited Commentary

Comparison of Observational Data and the ONTARGET Results for Telmisartan Treatment of Hypertension

Bull's-eye or Painting the Target Around the Arrow?

Robert M. Califf, MD

The study by Fralick et al is valuable and technically excellent; however, it examines only 1 drug indication pair of many. Thus, it is open to the criticism that generalizing from positive finding to a vast field of potential treatment comparisons with observational data is analogous to painting the target around the arrow, especially considering the high probability that the telmisartan-ramipril comparison would work.

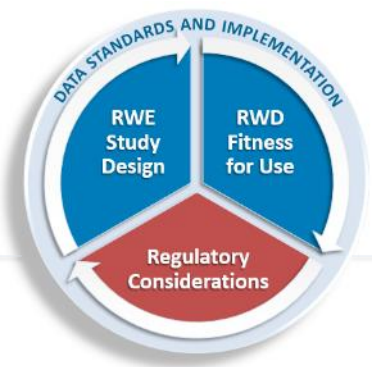
Demonstration Project: Assessment of Non-Interventional Designs (2)

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

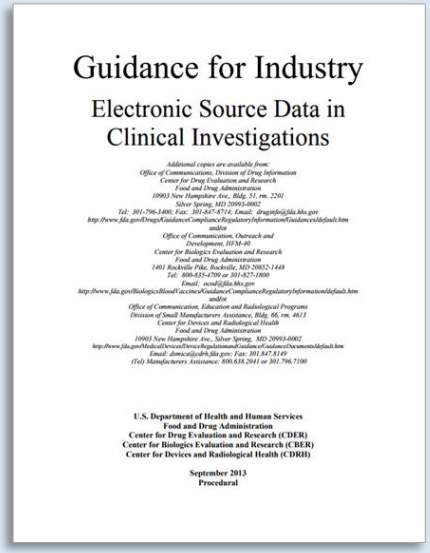
RCT DUPLICATE adds new studies to inform FDA - the first to use real-world evidence to predict treatment safety and efficacy

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

https://www.rctduplicate.org/



Regulatory Considerations

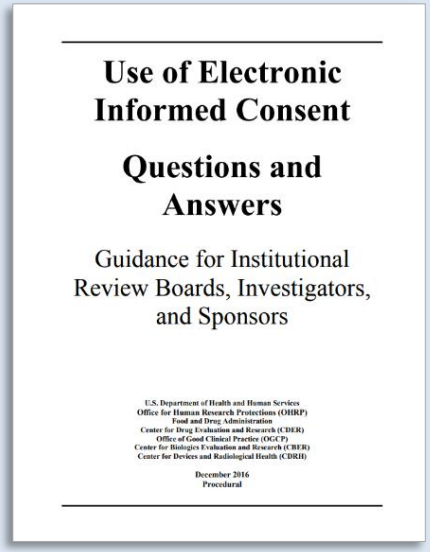


Guidance for Industry

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

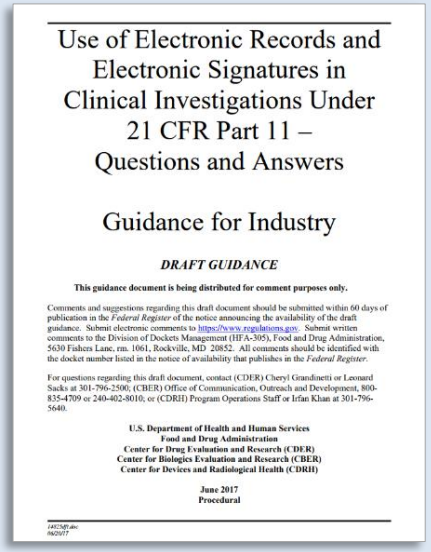


Use of Electronic Informed Consent Questions and Answers

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

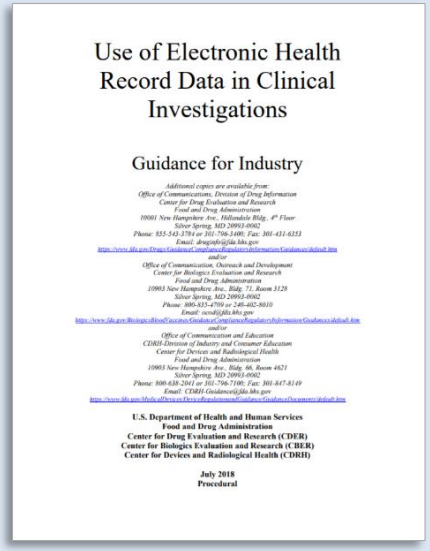
Guidance for Industry

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

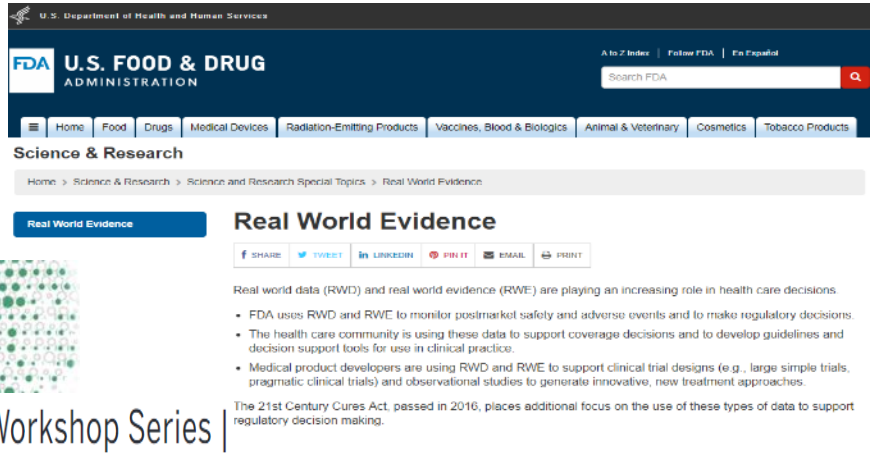
FDA

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

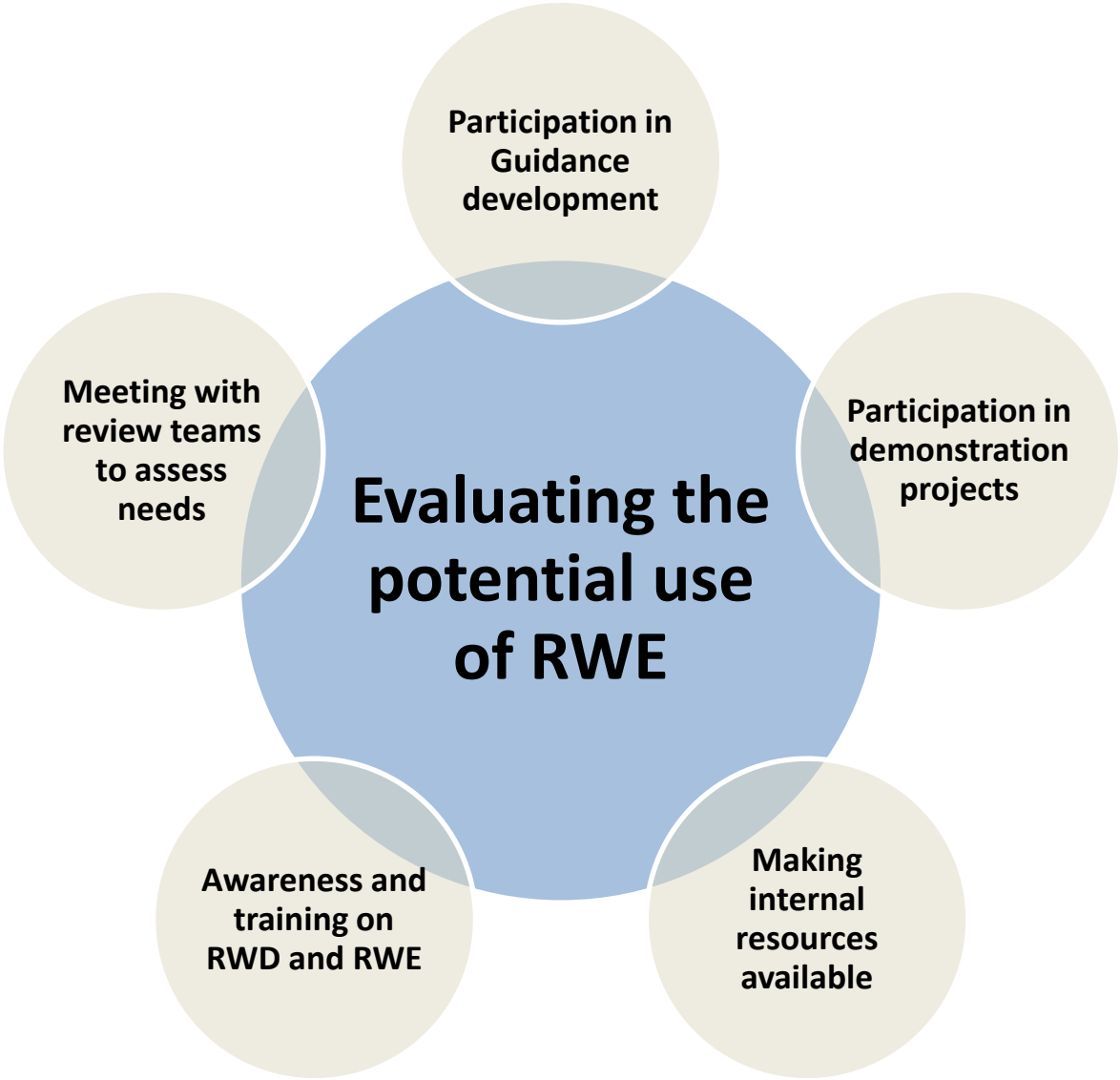
Real world evidence scoping roundtable

DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

The Academy of Medical Sciences

Internal Stakeholder Engagement



Conclusion

- **Framework serves as a roadmap for more fully incorporating RWD and RWE into the regulatory paradigm**
- **RWE remains an FDA priority and it is also relevant to other agencies**
- **FDA is committed to understand its full potential**
- **Multi-stakeholder effort and collaborations will benefit everybody**

Acknowledgements

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION

However…
(reasons RWD/RWE is challenging)

- **Double-blind RCTs "gold standard" – internal validity (does drug work) and safety characterization of *primary importance* in regulatory decision-making**
  - **Broader understanding of treatment effect in indicated population highly desirable – but not as critical to regulatory decision**
  - **In the late phase or post-market setting can pragmatic clinical trials fill the gap**
- **Limitations of observational dataset analyses to draw robust causal inferences**
- **Improvements in analytic and design methodologies *may* overcome limitations of observational analyses**
  - **New user designs**
  - **New methods for matching to balance risks in drug and comparator groups**
  - **Improving database quality (and quantity)**
  - **"Hardening" of EHR, and increasing claims, EHR, and pharmacy database linkages**

Can these solutions now allow us to draw robust causal inferences?