Real World Evidence: What's in a Name?

FDA Small Business Regulatory Education for Industry (REdI)
August 25–28, 2020

John Concato, MD, MS, MPH
Deputy Director
Office of Medical Policy Initiatives
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Soma Kalb, PhD
Director, Division of Clinical Science and Quality
Office of Clinical Evidence and Analysis
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Objectives

Overarching Plenary Objectives

1) Introduce concept of real-world evidence (RWE) and discuss related FDA initiatives

2) Describe examples of RWE used in regulatory decision-making

3) Consider the future direction of RWE involving FDA

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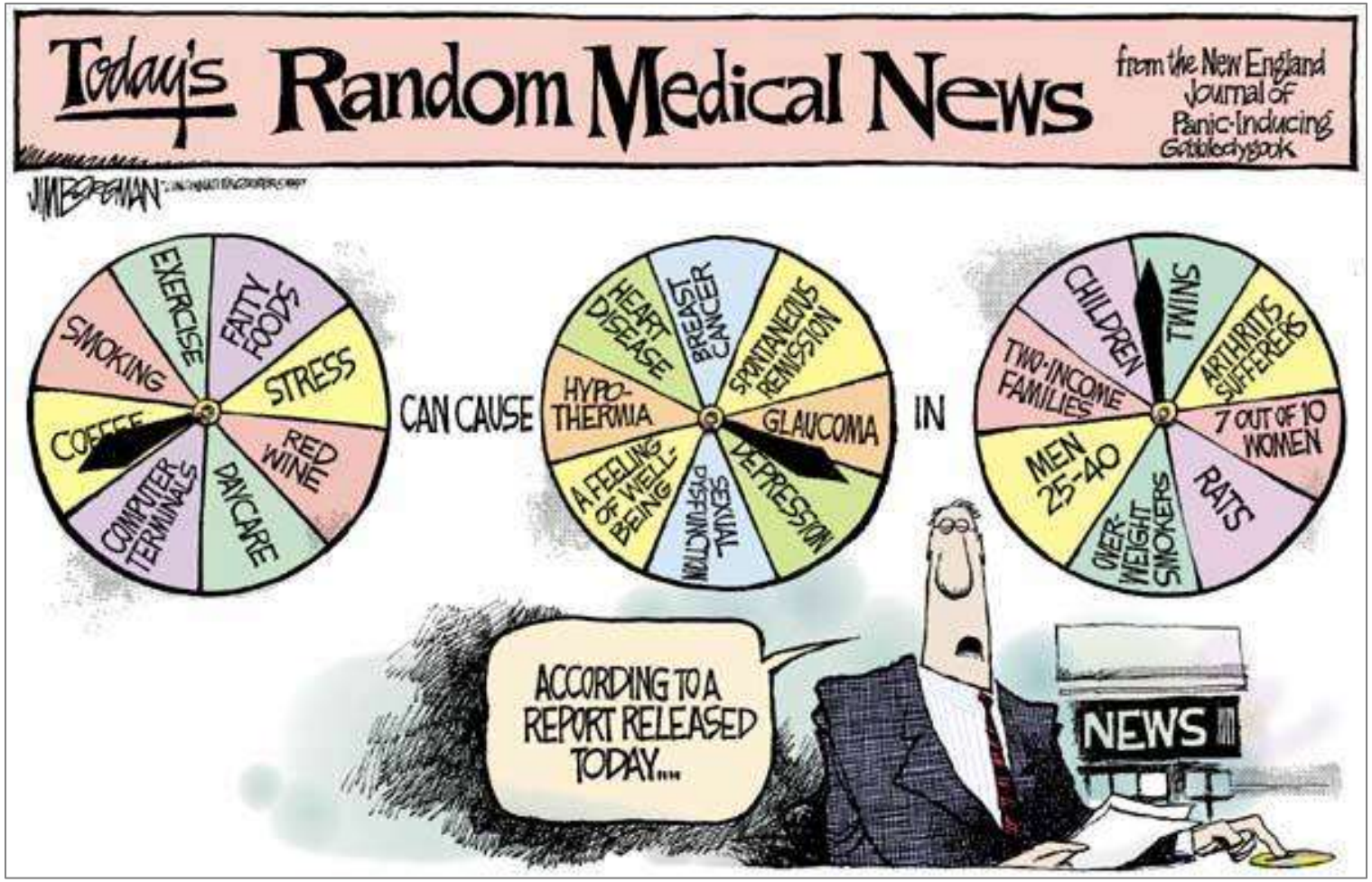
Perception of Medical Evidence



Copyright 2005 Jim Borgman

Topics: Focus on Drugs and Biologics

1) Provide an overview of FDA's Real-World Evidence (RWE) Program

2) Describe the concepts of fit-for-use data and adequate study design

3) Discuss considerations when using RWE in regulatory decision-making

Topic #1

1) Provide an overview of FDA's Real-World Evidence (RWE) Program

Expectations in Law – 21st Century Cures Act (2016)

- **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**
- **Ongoing RWE program is based on 2018 "RWE Framework":**
  - **Describes priority areas, remaining challenges, and potential pilot opportunities that the FDA RWE program will address**
- **Draft Guidance to be issued by 2021**
- **Standard for *substantial evidence* remains unchanged; commitments are aligned with Prescription Drug User Fee Act (PDUFA)**

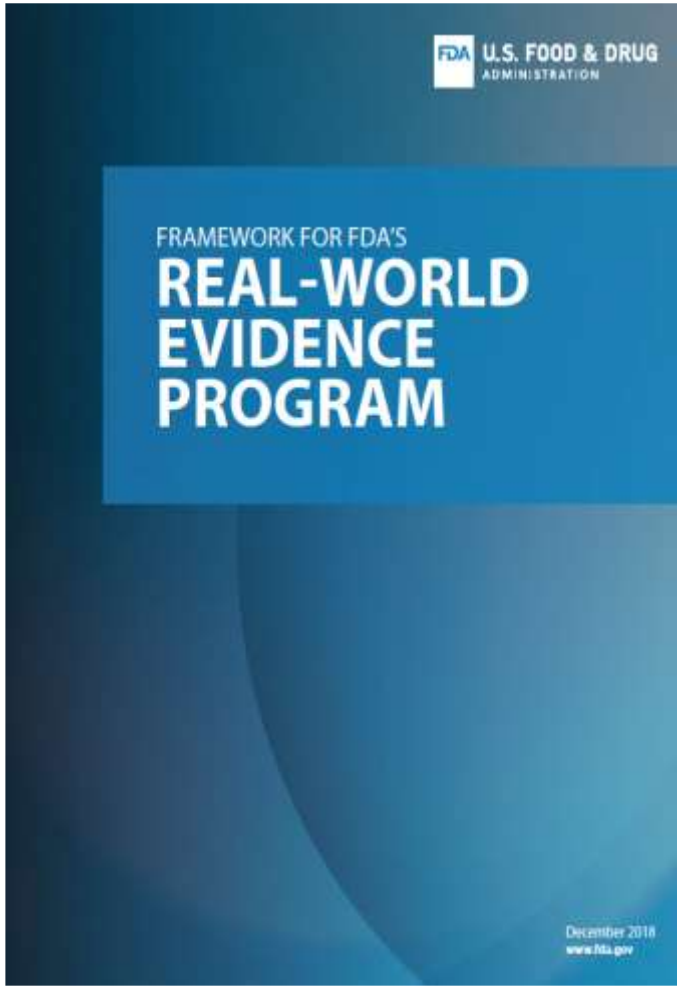
Definitions

FDA definitions from FDA RWE Framework (2018):

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

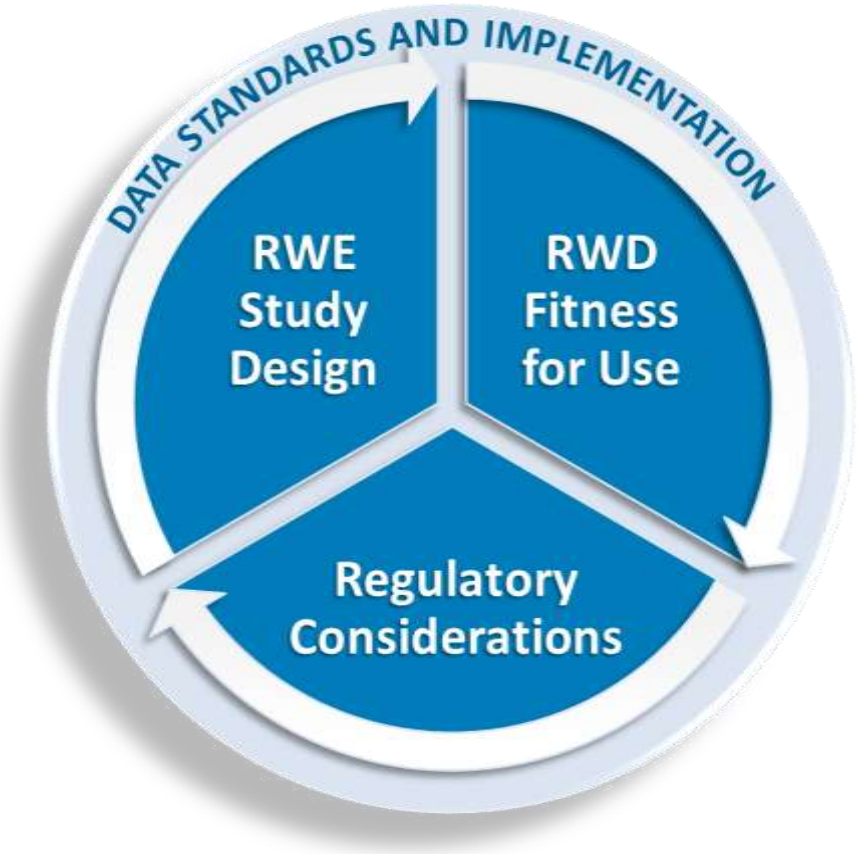
Real-World Evidence (RWE) is clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD

FDA RWE Framework



- **Applies to Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)**
- **Multifaceted program to implement RWE:**
  - **internal processes**
  - **external stakeholder engagement**
  - **demonstration projects**
  - **guidance development**

FDA RWE Framework (cont'd)



Considerations:

- **Whether the RWD are fit for use**
- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question**
- **Whether the study conduct meets FDA regulatory requirements**

RWE Informs Effectiveness When Fit-for-Purpose

DRUG	INDICATION	APPROVED	DATA
Carbaglu *(carglumic acid)*	Treatment of NAGS deficiency	2010	▪ Retrospective, non-random, unblinded **case series of 23 patients compared to historical control group**
Voraxaze *(glucarpidase)*	Treatment of MTX toxicity	2012	▪ Approval based on open-label, **NIH expanded access protocol**
Blincynto *(Blinatumomab)*	Treatment of Acute Lymphoblastic Leukemia	2014	▪ Single-arm trial ▪ Reference group weighted analysis of patient level **data on chart review of 694 patients at EU and US study sites***
Vistogard *(uridine triacetate)*	Overdose of chemotherapy drugs 5-fluorouracil (5-FU)	2015	▪ Two single-arm, open-label expanded access trial of **137 patients compared to case history control**

List not exhaustive

Bold = RWE

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

Blinatumomab vs historical standard therapy of adult relapsed/ refractory acute lymphoblastic leukemia

N Gökbuget[1], M Kelsh[2], V Chia[2], A Advani[3], R Bassan[4], H Dombret[5], M Doubek[6], AK Fielding[7], S Giebel[8], V Haddad[9], D Hoelzer[1], C Holland[10], N Ifrah[11], A Katz[2], T Maniar[12], G Martinelli[13], M Morgades[14], S O'Brien[15], J-M Ribera[14], JM Rowe[16], A Stein[17], M Topp[18], M Wadleigh[19] and H Kantarjian[15]

FDA

- **Blinatumomab = Bispecific T-cell Engager (BiTE) antibody**
- **FDA-approved (Dec 2014) for Philadelphia chromosome-negative, relapsed and refractory B-cell precursor acute lymphoblastic leukemia**
- **Studied in single-arm trial (N=189): primary outcome of complete remission/partial hematological recovery in 43% (95% CI 35–50%)**
- **Results compared to historical data extracted from Europe and United States, with weighted analysis and propensity scoring used to balance compared populations: complete remission 24% (95% CI 20-27%) among n=694 patients in historical arm**

Blood Cancer Journal (2016) 6, e473

RWE Informs Effectiveness When Fit-for-Purpose (cont'd)

DRUG	INDICATION	APPROVED	DATA
Defitelio *(defibrotide sodium)*	Severe hepatic veno-occlusive disorder	2016	▪ Two prospective clinical trials enrolling 179 patients and **an expanded access study with 351 patients**
Lutathera *(lutetium 177 dotate)*	Gastroenteropancreatic neuroendocrine tumours (GEP-NETs)	2017	▪ Open-label clinical trial ▪ **Analysis of a subset of 360 patients who participated in an investigator sponsored, open-label, single-arm, single institution study of 1214 patients that started as an expanded access program**
Zostavax *(Zoster Vaccine Live)*	Prevention of herpes zoster (shingles) in persons 50 years of age and older	2018	▪ **Prospective, observational cohort study using electronic health records in Kaiser Permanente Northern California (KPNC)** to characterize the duration of protection in persons 50 years of age and older
Ibrance *(palbociclib)*	Men with certain types of advanced or metastatic breast cancer	2019	▪ Data from electronic health records and postmarketing reports of the **real-world use of IBRANCE in male patients**

List not exhaustive

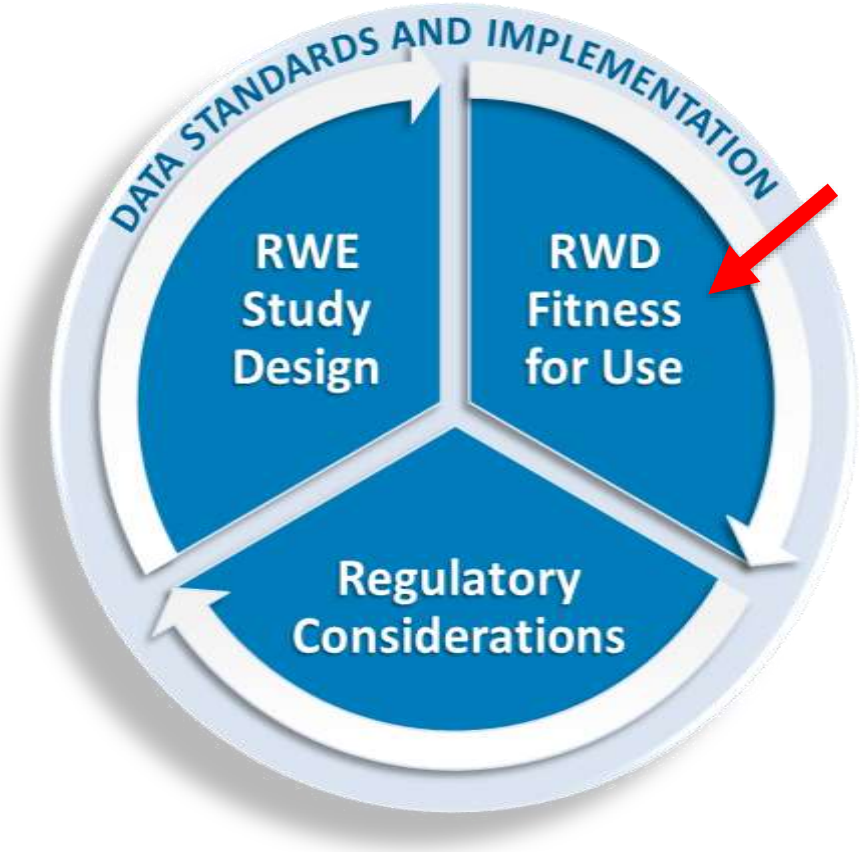
Bold = RWE

Topic #2

1) Provide an overview of FDA's Real-World Evidence (RWE) Program

2) Describe the concepts of fit-for-use data and adequate study design

RWE Framework: Data



Considerations:

- **Whether the RWD are fit for use;**

  with RWD sources including billing claims, electronic health records, registries, device-generated data, patient-generated data

EHR Data – Factors Affecting Reliability and Relevance

- **Selected measurements—including labs, pathology, imaging—are used in both clinical practice and in research (e.g., as endpoints)**
  - **Challenges include curation of unstructured data and inconsistent data format**
- **Timing of assessments in clinical practice may be variable**
  - **Frequency can vary, and patients who show up for follow up are often different than those who don't**
- **Clinical outcome measures for disease progression may not be used, or may not be consistently recorded in practice**
  - **How can gaps and inconsistencies be addressed?**
- **Interoperability will be necessary for studies outside of small populations**
  - **Examples include linkage to claims across healthcare systems for longitudinal data**

Example 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*, Melissa D Curtis, Gregory Smith, James Harnett, & Amy P Abernethy.

Future Oncol 2016;12:1262–74

Fast Healthcare Interoperability Resources (FHIR)

HL7 Publishes FHIR® Release 4

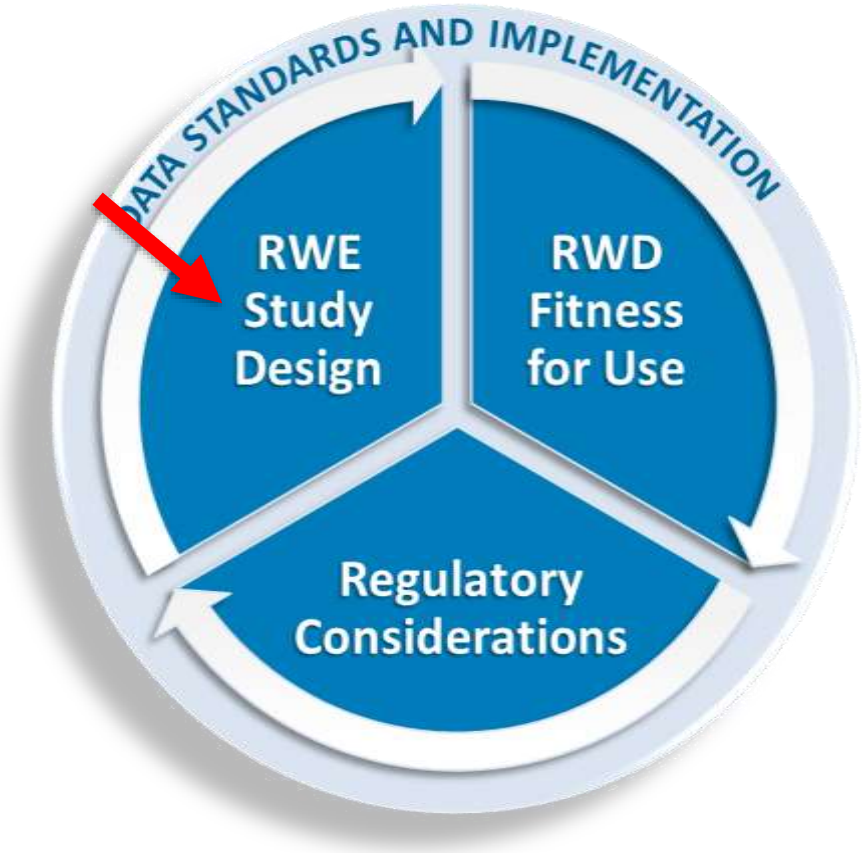
Major new release emphasizes stability and maturity based on broad industry feedback

- Health Level Seven (HL7): international standards organization
- Fast Healthcare Interoperability (FHIR): standards describing data formats and elements as well as application programming interface, to promote data access

<u>Challenges regarding interoperability</u>:

- **How can remaining problems involving standards be solved?**
- **How can remaining technical hurdles be addressed?**
- **What incentives can advance progress?**

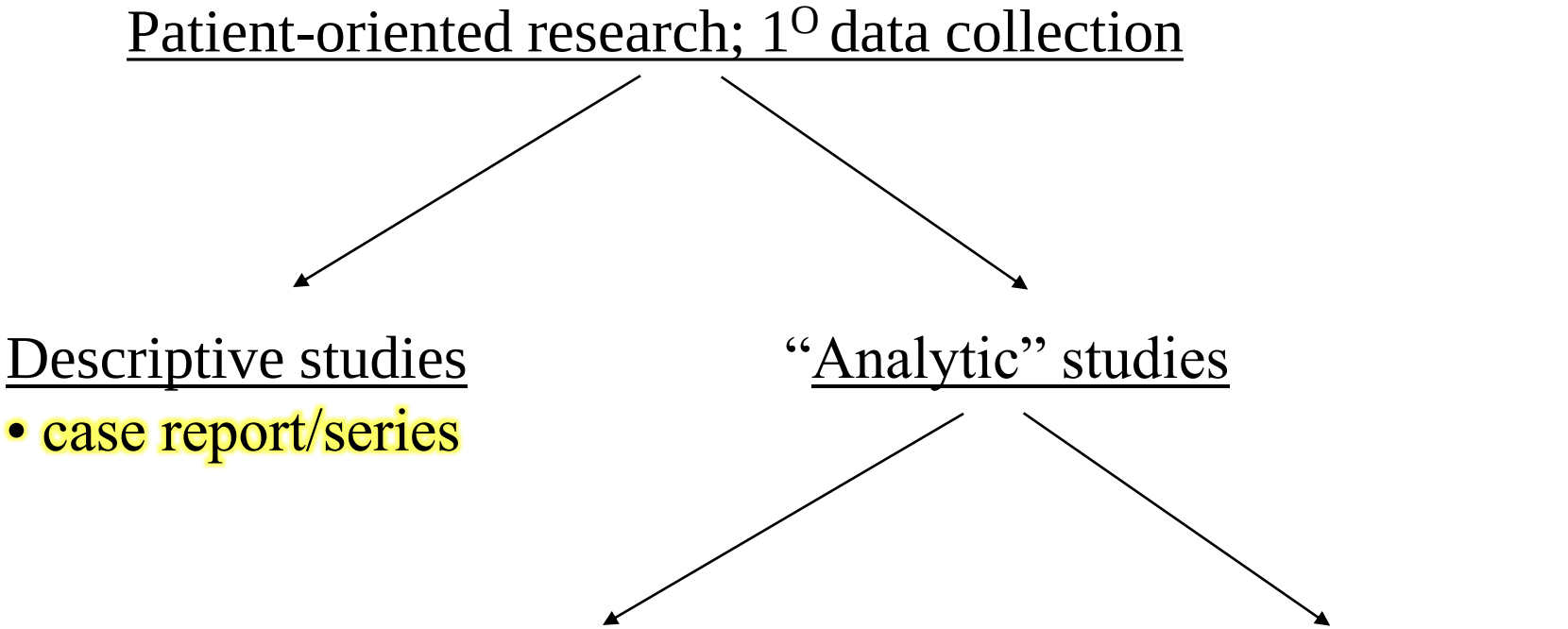
RWE Framework: Design



Considerations:

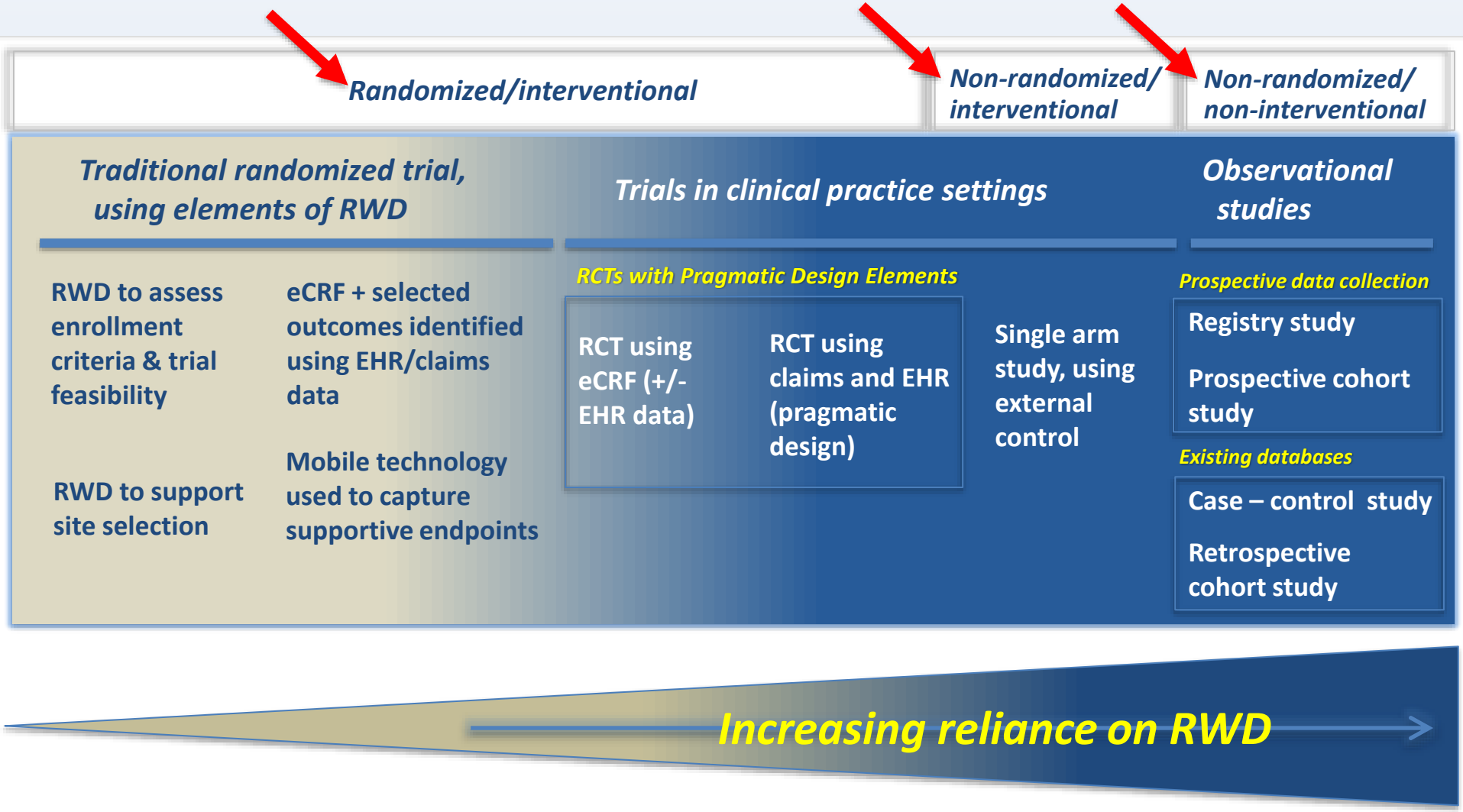
- Whether the RWD are fit for use
- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question**

Overview of Research Architecture

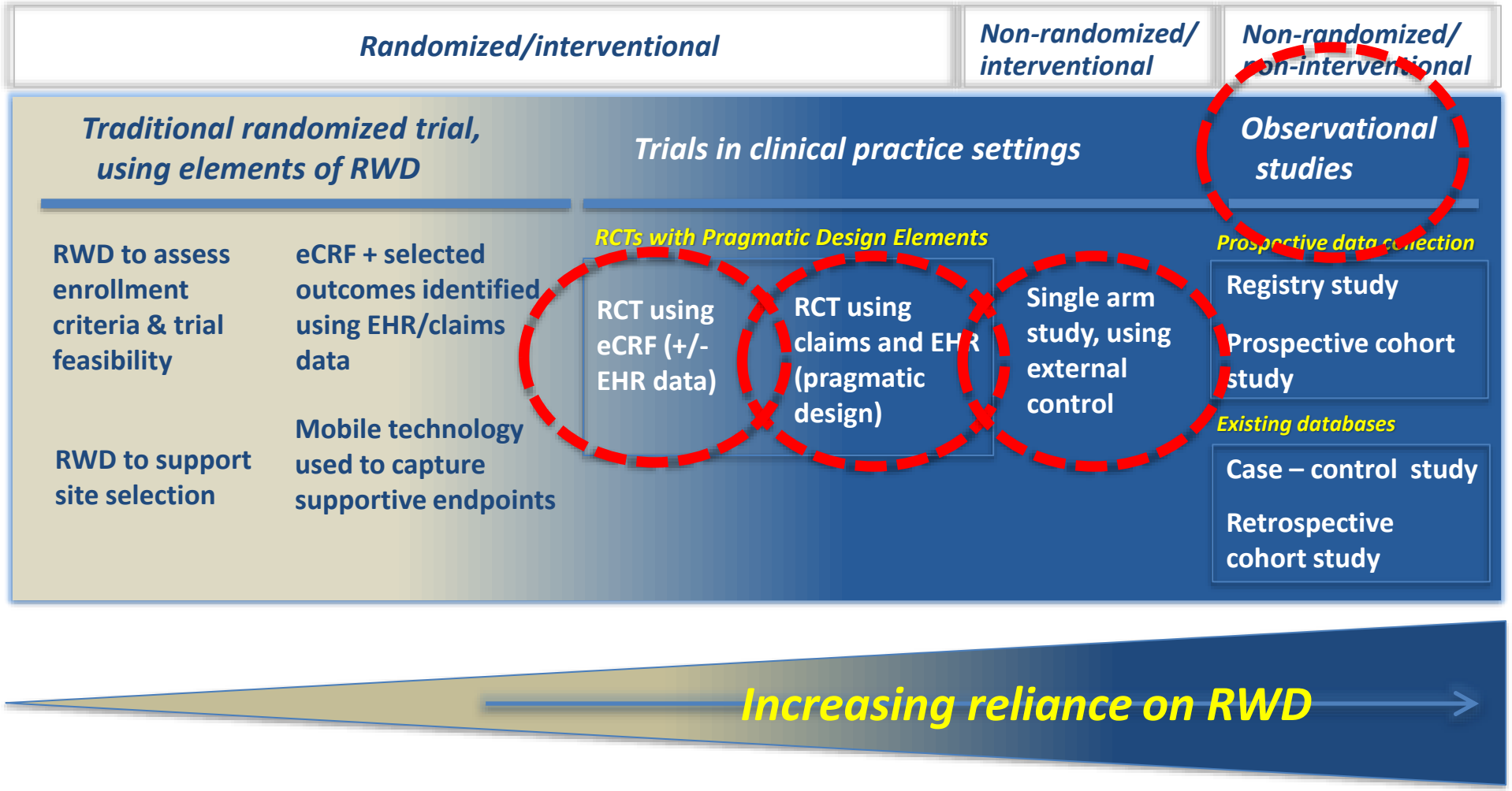


Concato *J Law and Policy* 2004;XII:489-507

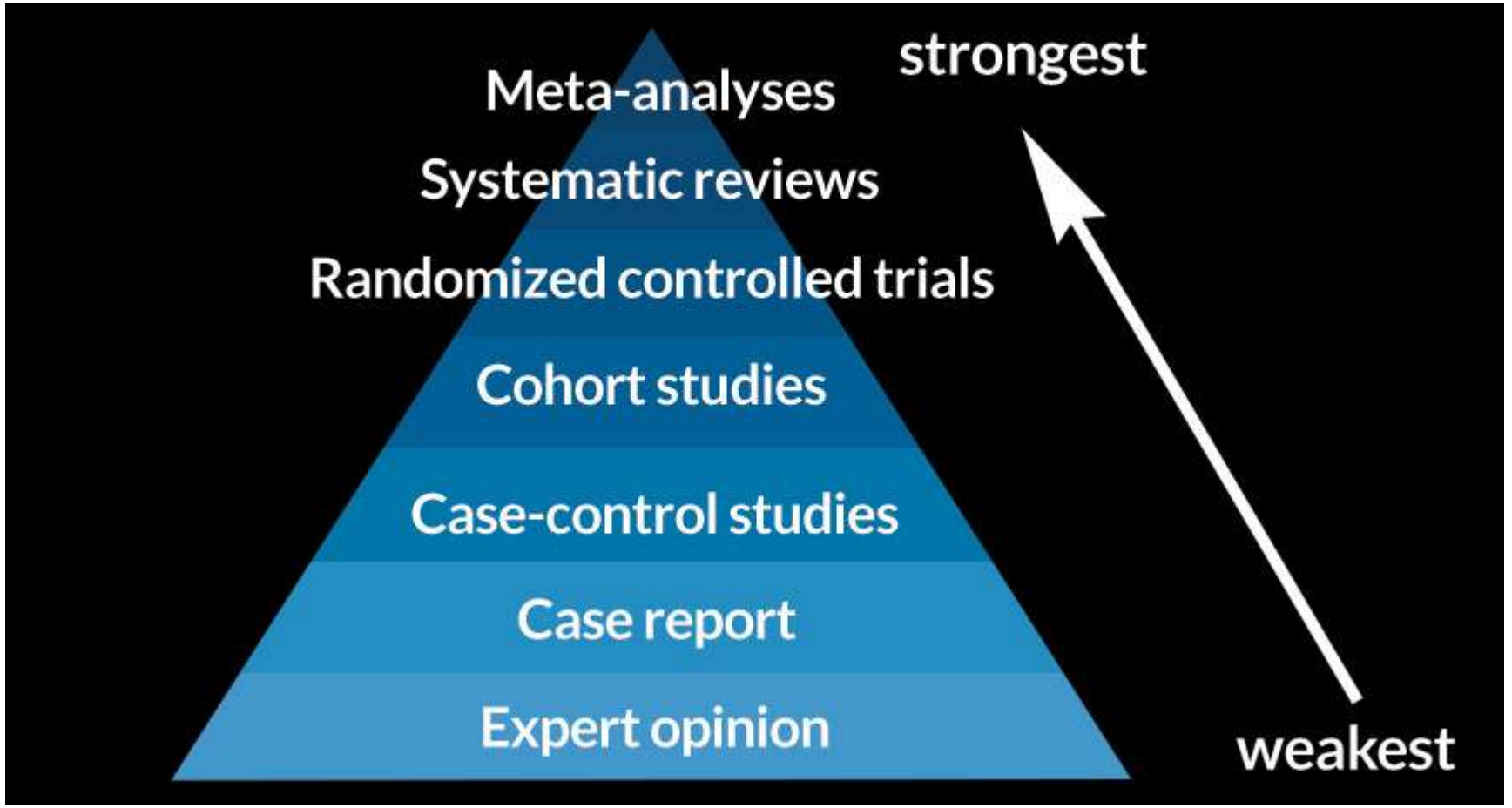
Spectrum of Study Designs



Study Design and Real-World Evidence



Hierarchies of Study Design



https://www.sciencenews.org/blog/context/critique-medical-evidence-hierarchies 6 Aug 2020

Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials

FDA

Cochrane Collaboration – 2014:

- **"[…] on average, there is little evidence for significant effect estimate differences between observational studies and RCTs […]"**
- **"Factors other than study design *per se* need to be considered when exploring reasons for a lack of agreement between results of RCTs and observational studies"**

Citation: Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: MR000034. DOI: 10.1002/14651858.MR000034.pub2.

Observational Studies Analyzed Like Randomized Experiments

An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease

Miguel A. Hernán,[a,b] *Alvaro Alonso,*[c] *Roger Logan,*[a] *Francine Grodstein,*[a,d] *Karin B. Michels,*[a,d,e] *Walter C. Willett,*[a,d,f] *JoAnn E. Manson,*[a,d,g] *and James M. Robins*[a,h]

Conclusions: Our findings suggest that the discrepancies between the Women's Health Initiative and Nurses' Health Study ITT estimates could be largely explained by differences in the distribution of time since menopause and length of follow-up.

(*Epidemiology* 2008;19: 766–779)

Effect Estimates in Randomized Trials and Observational Studies: Comparing Apples With Apples

Sara Lodi*, Andrew Phillips, Jens Lundgren, Roger Logan, Shweta Sharma, Stephen R. Cole, Abdel Babiker, Matthew Law, Haitao Chu, Dana Byrne, Andrzej Horban, Jonathan A. C. Sterne, Kholoud Porter, Caroline Sabin, Dominique Costagliola, Sophie Abgrall, John Gill, Giota Touloumi, Antonio G. Pacheco, Ard van Sighem, Peter Reiss, Heiner C. Bucher, Alexandra Montoliu Giménez, Inmaculada Jarrin, Linda Wittkop, Laurence Meyer, Santiago Perez-Hoyos, Amy Justice, James D. Neaton, and Miguel A. Hernán, on behalf the INSIGHT START Study Group and the HIV-CAUSAL Collaboration

When comparing effect estimates from RCTs and observational studies:

- **harmonize design features, including eligibility criteria, Rx strategies, outcome(s), start/end of follow-up, causal contrast**
- **use similar strategy for data analysis to estimate the causal effect**
- **conduct sensitivity analyses to investigate impact of relevant factors**

Am J Epidemiol. 2019;188(8):1569–1577

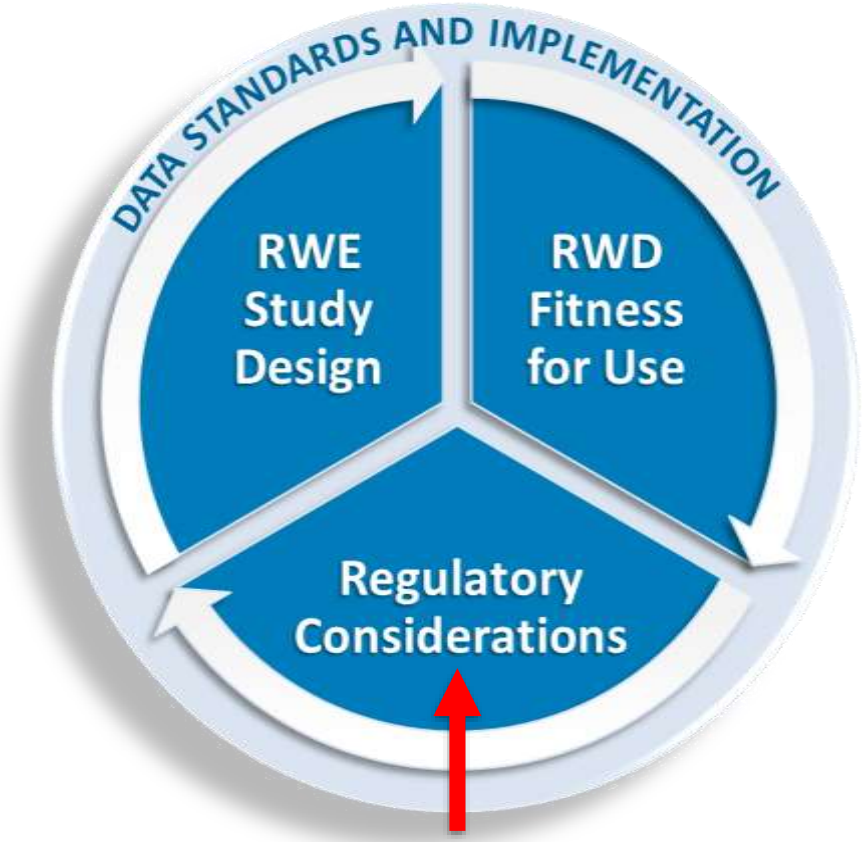
Topic #3

1) Provide an overview of FDA's Real-World Evidence (RWE) Program

2) Describe the concepts of fit-for-use data and adequate study design

3) Discuss considerations when using RWE in regulatory decision-making

RWE Framework: Regulatory



Considerations:

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- 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/RWE: Need for Transparency

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

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

VALUE IN HEALTH 20 (2017) 1003–1008

Transparency about study design and analysis, *before* execution, is critical for ensuring confidence in results

RWE: Demonstration Projects

Selected demonstration projects (*see RWE Framework for citations*):

- **HARMONY-OUTCOMES ancillary study**
  - **whether EHRs are suitable for trial recruitment, baseline assessment, and endpoint ascertainment (>9,000 participants in original trial)**
- **IMPACT-Afib study**
  - **proof of concept for conducting randomized trials using FDA Sentinel infrastructure, involving distributed database and common data model (17 data partners; >300M unique patient IDs; >70M pts accruing data)**
- **RCT DUPLICATE**
  - **longitudinal insurance claims data are being used in observational cohort analyses to emulate randomized controlled trials on the same topic (n > 30 trials)**

RCT DUPLICATE: Agreement Metrics

- **Regulatory Agreement: To what extent would RWE replication have led to same conclusion as RCT regarding statistical significance?**

- **Estimate Agreement: Does RWE treatment effect estimate lie within the confidence interval of "true" effect based on evidence from RCT?**

- ***Note: Even with unbiased RWE replications, we will expect some replications to not match RCTs by chance alone***

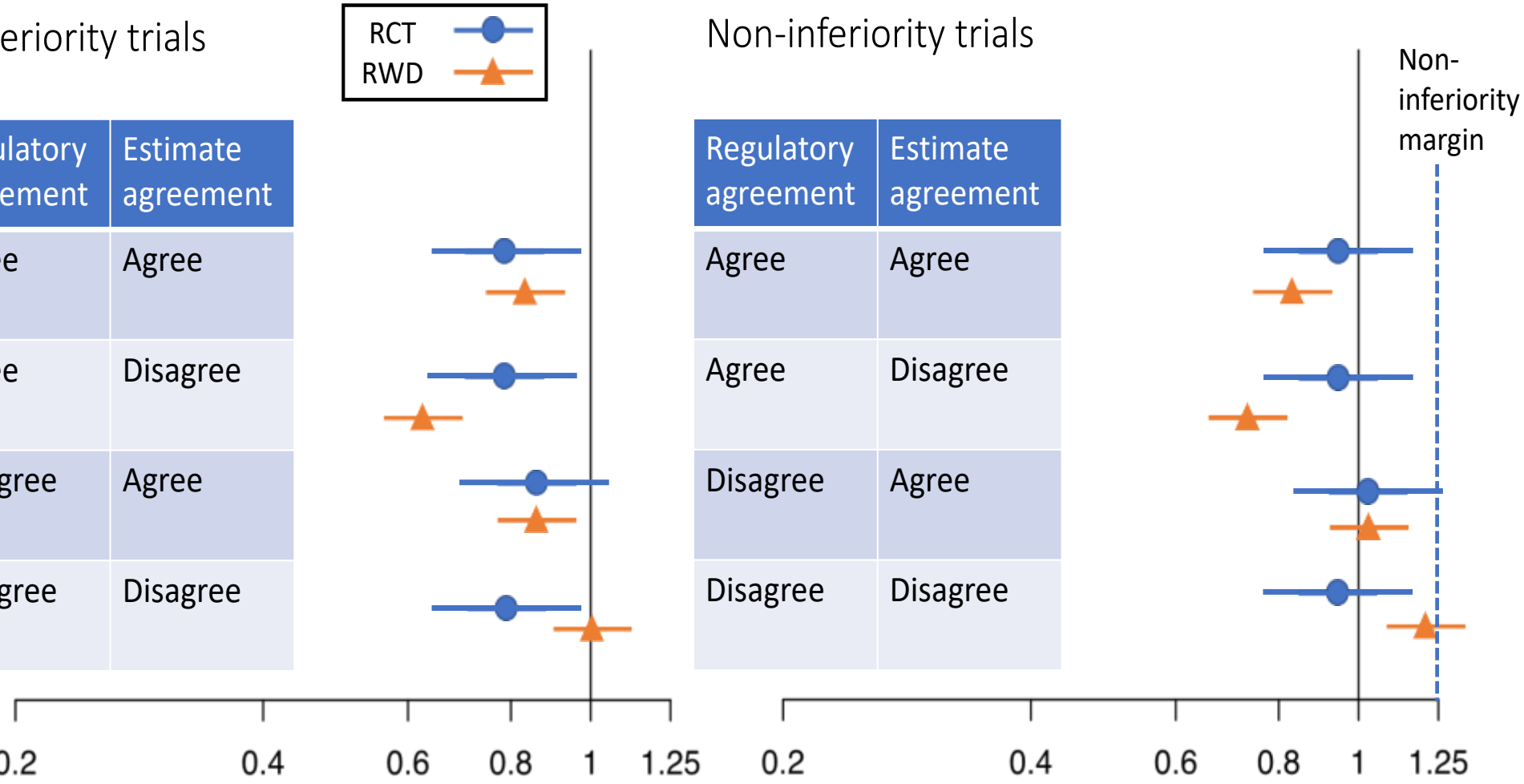
RCT DUPLICATE – Examples of Agreement Metrics

Superiority trials

Regulatory agreement	Estimate agreement
Agree	Agree
Agree	Disagree
Disagree	Agree
Disagree	Disagree

Non-inferiority trials

Regulatory agreement	Estimate agreement
Agree	Agree
Agree	Disagree
Disagree	Agree
Disagree	Disagree



Adequate and Well-Controlled Investigation

Selected Characteristics*

- There is a **clear statement of objectives** of the investigation and **methods of analysis**.
- The study uses a **design** that permits **a valid comparison** with a **control to provide a quantitative assessment of drug effect** […] placebo concurrent control, dose-comparison control, no treatment control, active treatment control, historical control.
- Adequate measures are taken to **minimize bias** on the part of the subjects, observers, and analysts of the data.
- The **methods of assessment** of subjects' response are **well-defined and reliable**.

*From 21 Code of Federal Regulations 314.126

Adequate and Well-Controlled Investigation (cont'd)

Selected Characteristics*

- The **method of selection** of subjects provides adequate assurance that they have the disease/condition being studied […].

- The **method of assigning patients** to treatment and control groups **minimizes bias** and is intended to **assure comparability of the groups** with respect to pertinent variables. Ordinarily, […] assignment is by randomization […].

- There is an **analysis of the results of the study adequate to assess the effects of the drug**.

*From 21 Code of Federal Regulations 314.126

Knowledge Check

Randomized trials are not within the scope of RWD and RWE.

1. True
2. False

Summary (for CBER & CDER)

- **FDA's Real-World Evidence Program is advancing as outlined in the agency's 2018 'RWE Framework'**
- **Ongoing efforts can identify attributes that promote generation of reliable and relevant real-world data as well as valid real-world evidence**
- **Alternative study designs can support and augment—but are not intended to replace—clinical trials for regulatory decision-making**

Acknowledgements

- Jacqueline Corrigan-Curay
- Ken Quinto
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- Peter Stein
- Kayla Holman
- Khair ElZarrad
- Dianne Paraoan
- Juanita Marner
- David Martin
- *many other RWE colleagues*

U.S. FOOD & DRUG ADMINISTRATION

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Topics: Focus on Devices

- **CDRH Strategic Priorities and RWE**
- **RWE for regulatory decision-making**
- **CDRH's engagement in the larger stakeholder community for RWE**

CDRH Vision

Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world

Challenges of Medical Device Development

Use of many devices is highly dependent on clinician knowledge, experience, and skill

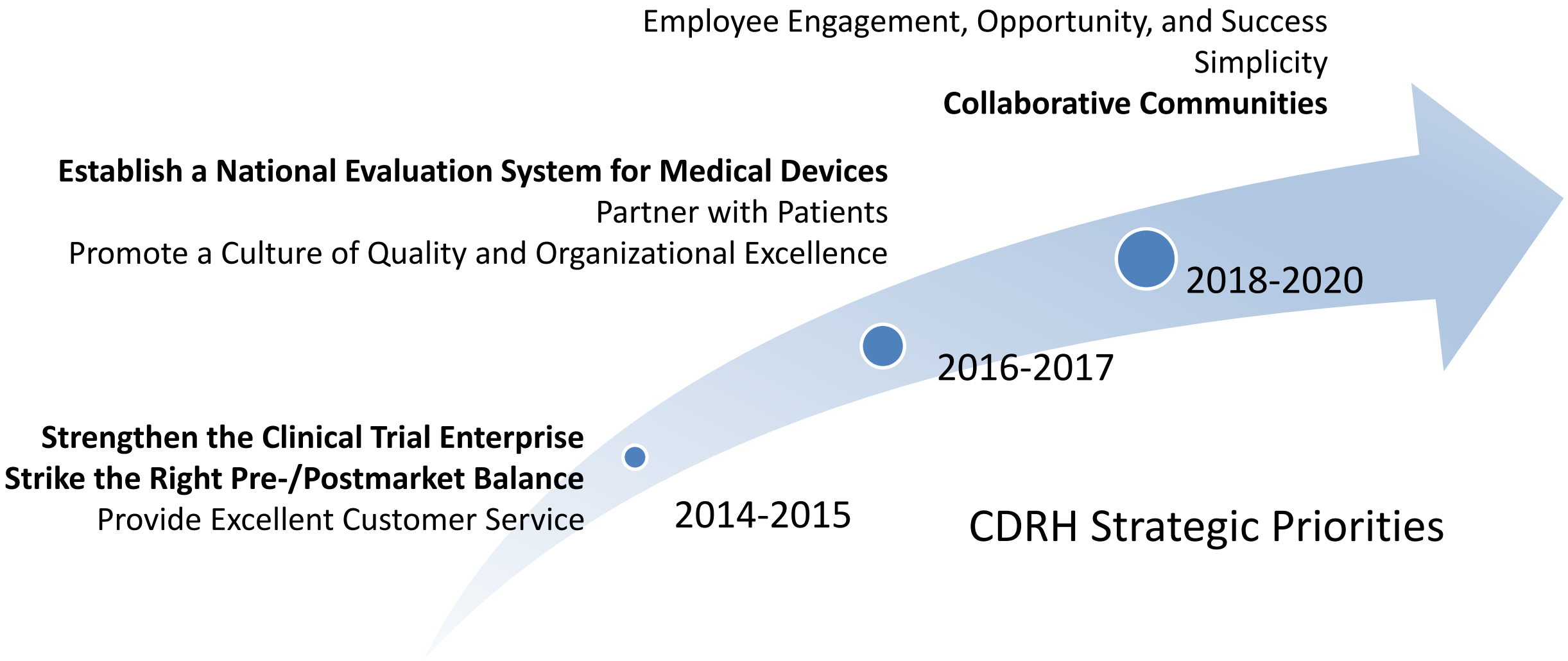
Devices and techniques iteratively and rapidly improve

Gold-standard randomized controlled trial (RCT) often not practical

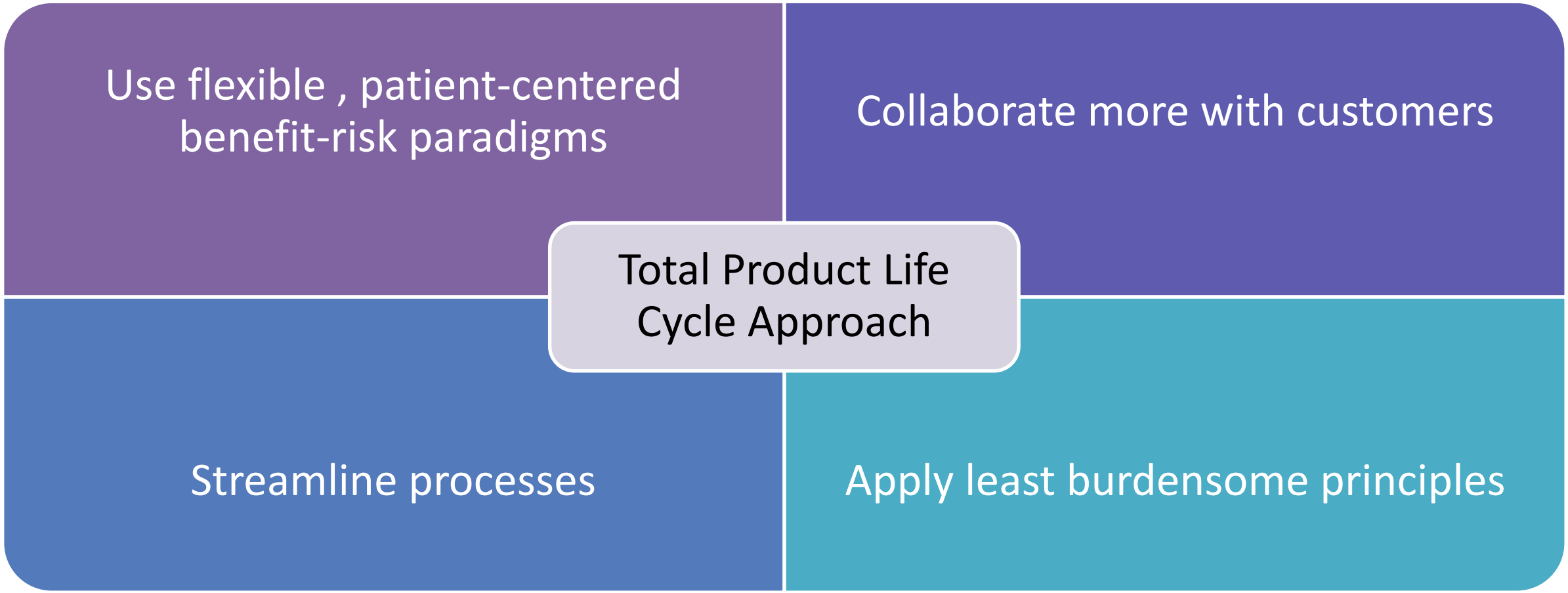
Valid Scientific Evidence – 21 CFR 860.7(c)(2)

"Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use."

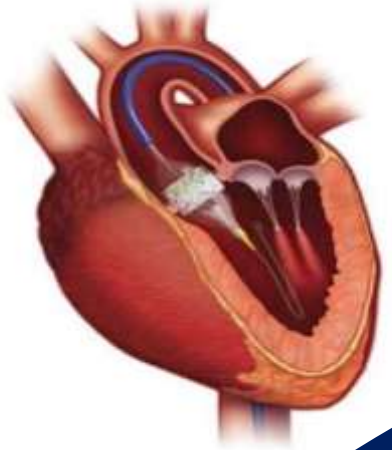
Towards our Vision



CDRH Strategic Priorities:
Reduce Time and Cost of Clinical Evidence Generation



Case Example: Transcatheter Heart Valves
The Road from 42nd



U.S. 42nd Country
to Approve a 1st Generation TAVR Device

TVT Registry
Established at Time of Device Approval

CMS NCD
FDA approval of subsequent indications automatically covered

TVT Registry
Used to Support Approval of Subsequent Indications and Device Generations

Mitral Valve-in-Valve
1st in World

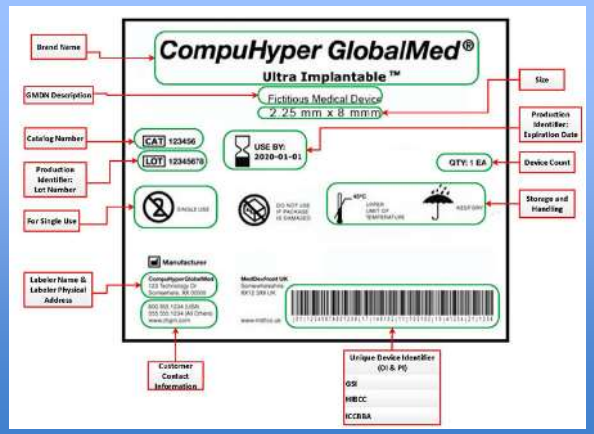
Topics

- **CDRH Strategic Priorities and RWE use**
- **RWE for regulatory decision-making**
- **CDRH's engagement in the larger stakeholder community for RWE**

Real-World Data (RWD) Sources

Diagnostic laboratory and imaging

Device/Patient Registries



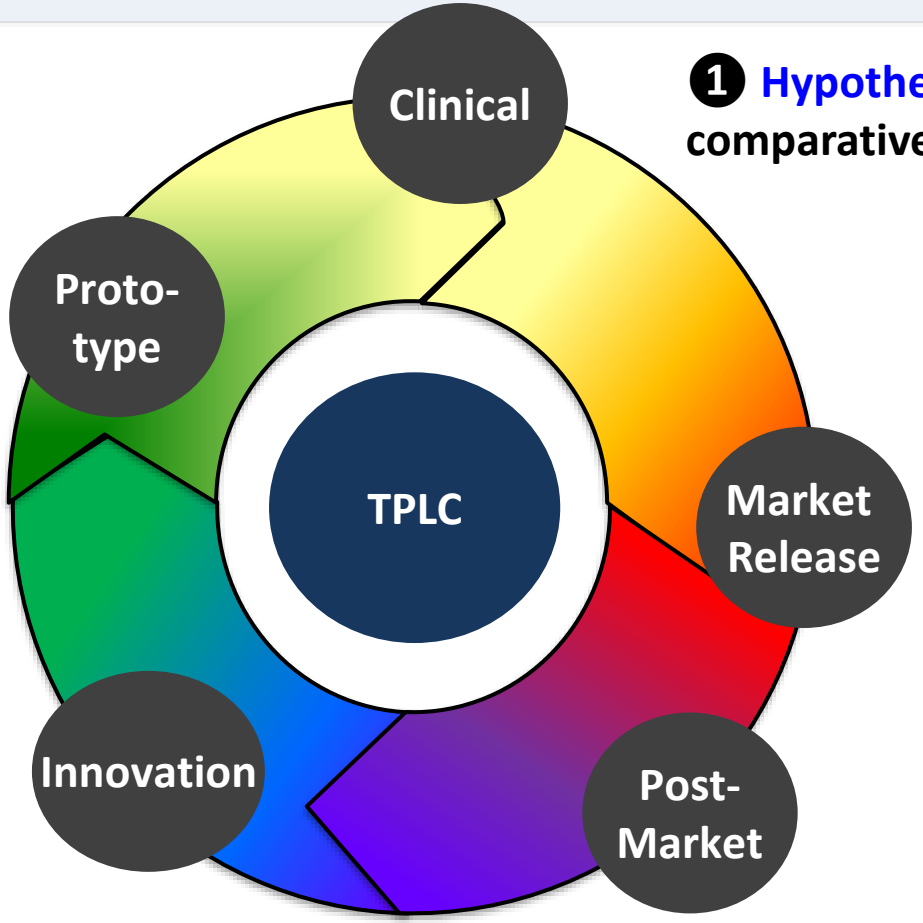
Device Generated Data

Patient Generated Data

Electronic Health Records

Medical Billing Claims

Potential Usages of RWE for Total-Product Life-Cycle Device Evaluation



❶ Hypothesis Generation (e.g. treatment effect estimation for comparative studies)

❷ Inform prospective trial design

❸ RWE as a control arm for a clinical trial

❹ Real-world data source as a platform to support a clinical trial (data collection / randomization)

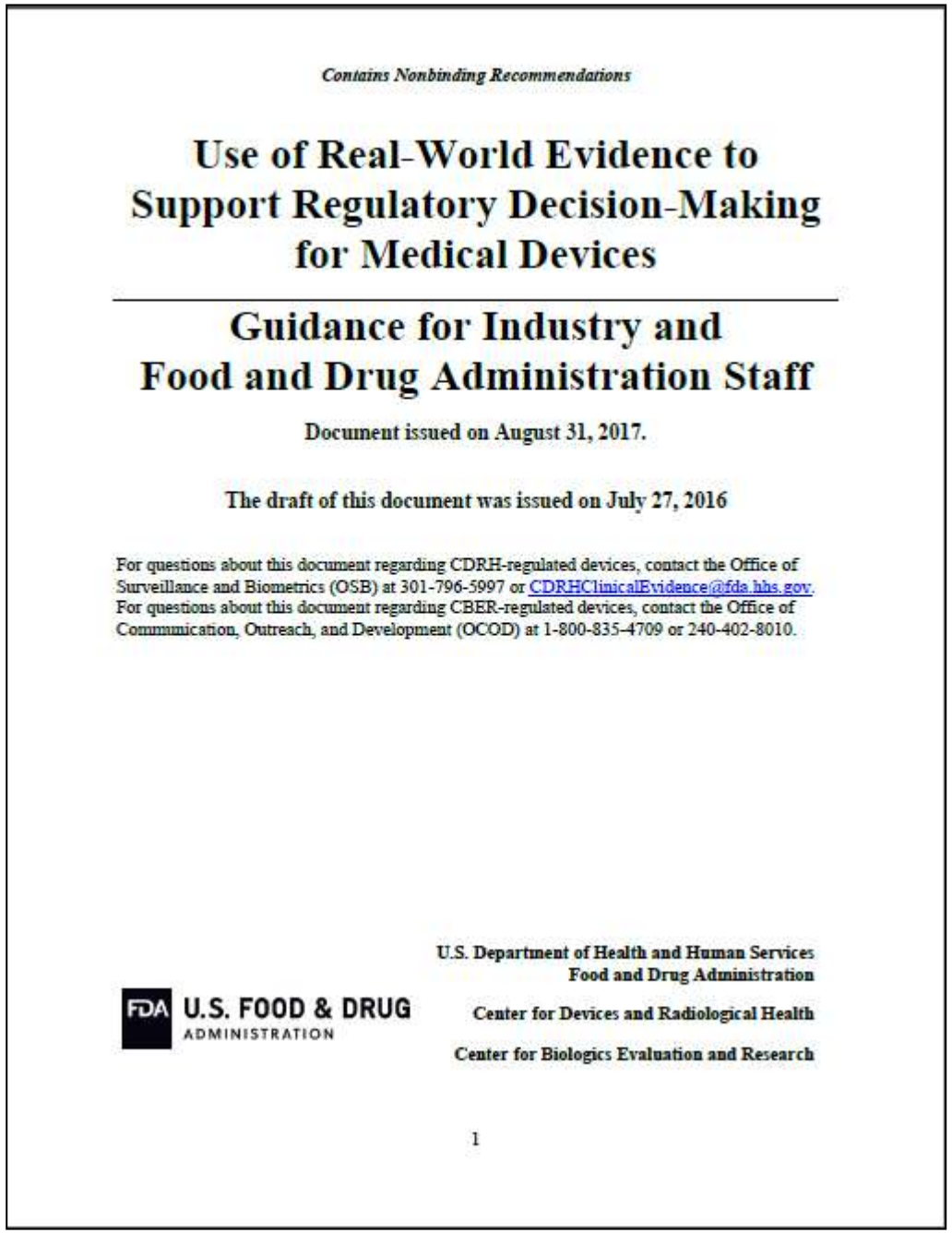
❺ Data collection framework for postmarket evidence generation (e.g. post-approval studies)

❻ Public health surveillance

❼ Generate evidence to support indication expansions and future innovation

Benefits of Real-World Data Sources

- Reduced time/cost to answer important questions
- Understand device performance in real-world environment to inform benefit-risk
- Collect outcomes not always feasible in traditional trials
- Opportunities to partner w/patients in new ways
- Inform future device modifications and new technology development
- Better align evidence generation with innovation cycles



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

1

Key Criteria

- ✓ Relevance
- ✓ Reliability
- ✓ Patient Protections

CDRH Supporting and Advancing RWE

Support Total Product Life Cycle Reviews

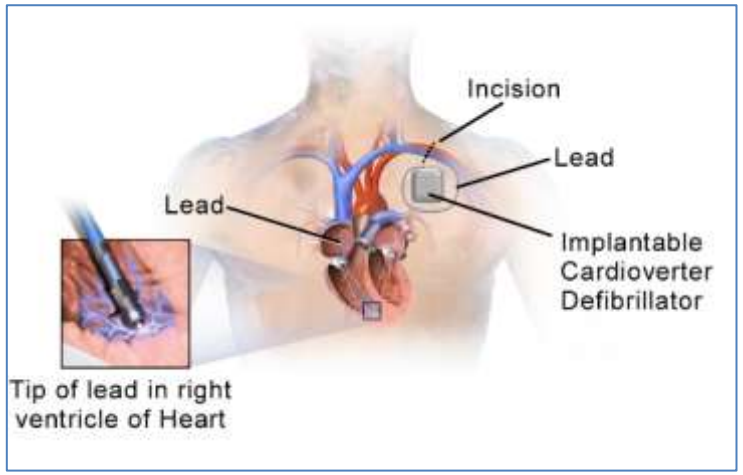
- Since FY15, CDRH has granted marketing authorization for more than 65 new or modified class II and III medical devices using RWE
- Experts within CDRH provide support and training in Good Clinical Practice, Data Quality, Study Design, Analytic Methodology, and knowledge of specific RWD sources
- Leverage high-quality RWD sources to replace traditional post-approval studies and efficiently address postmarket questions
- Advance active surveillance to improve device safety

Case Example: RWE for Postmarket Purposes

"Electrophysiology Predictable and Sustainable Implementation of National Registries (EP PASSION)"

Traditional Post-Approval Study (PAS)

- New enrollment study with direct follow-up of patients
  - 5 year follow up
  - 1500-2000 patients
  - Freedom from complication rate >92.5%



PAS with RWE

- Leverage multiple RWD sources to capture medical device safety performance using data collected in routine care:
  - Manufacturer databases
    - Complaint handling
    - Device Registration
  - Administrative claims (public and private)
  - National death index
  - Remote monitoring / device data

EP PASSION RWE Approach

Multi-stakeholder effort to transition to a sustainable RWE approach to address PAS needs

- **More timely and efficient answers to postmarket questions**
- **The new sustainable paradigm saves ~$9.6M per study**
  - **$390K versus ~$10M**
- **Earlier signal detection**
  - **Larger sample sizes**
  - **More frequent updates**

Knowledge Check

CDRH can not accept Real World Evidence as the primary support for a marketing application.

1. True
2. False

Topics

- **CDRH Strategic Priorities and RWE use**
- **RWE for regulatory decision-making**
- **CDRH's engagement in the larger stakeholder community for RWE**

CDRH Supporting and Advancing RWE

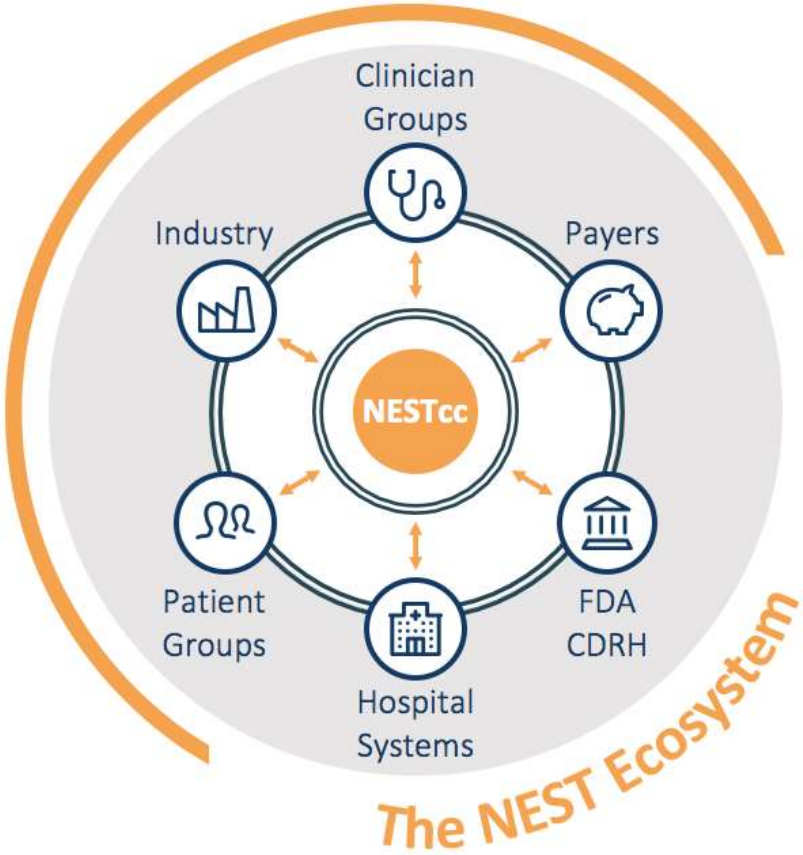
Engagement with Stakeholders

- Infrastructure and network development with professional societies and payers
- Engagement with internal and external groups to develop policies and best practices

National Evaluation System for Health Technologies Coordinating Center (NESTcc) Collaborative Community

- **Comprised of stakeholders in the medical device ecosystem to support development of RWE to enhance regulatory and clinical decision-making**

- **Catalyze timely, reliable, and cost-effective access to and use of real-world evidence to support regulatory decisions**



https://nestcc.org/nestcc-named-one-of-the-first-collaborative-communities-with-fda-participation/

Establishing the NESTcc Research Network

NESTcc has established relationships with Network Collaborators to advance the evaluation and use of high-quality real-world data (RWD)

DukeHealth
HealthCore
INSIGHT Clinical Research Network
Lahey Hospital & Medical Center
MAYO CLINIC
MDEpiNet
Mercy
NWEH NorthWest EHealth
Discover-NOW
PEDSnet A Pediatric Learning Health System
STAR Stakeholders, Technology, and Research CRN
OneFlorida Clinical Research Consortium
VANDERBILT UNIVERSITY MEDICAL CENTER
Weill Cornell Medicine
Yale NewHaven Health

DATA NETWORK BY THE NUMBERS

141M+
Total Population

3,075
Outpatient Practices/Clinics

291
Specialty Clinics

162
Hospitals/Medical Centers

Numbers reflect data as of August 2020

NESTcc Test-Cases Address A Range of Device Questions

NESTcc's Test-Cases span a wide range of devices classes, regulatory pathways, TPLC stages, data sources, and disease areas.

TPLC Alignment	Regulatory Pathway	Device Classes	Disease Area	Data Sources
Pre-Market	510(k)	Class I	Cardiology	Claims
Label Expansion	PMA	Class II	Dermatology	Electronic Health Records (EHR)
Post-Market		Class III	Ear, Nose, & Throat	mHealth
Coverage			Mental Health	Patient-Generated health Data (PGD)
Surveillance (Active)			Oncology	Patient Reported Outcomes (PRO)
			Orthopedics	Registries
			Respiratory	
			Stress Urinary Incontinence	
			Surgery	
			Vascular	

Slides courtesy of NESTcc

NESTcc Activities

NEST 1.0

- Launched on June 30, 2020
- Open for management of sponsor-funded research
- Research network of RWD and expert investigators
- Serving all ecosystem stakeholders

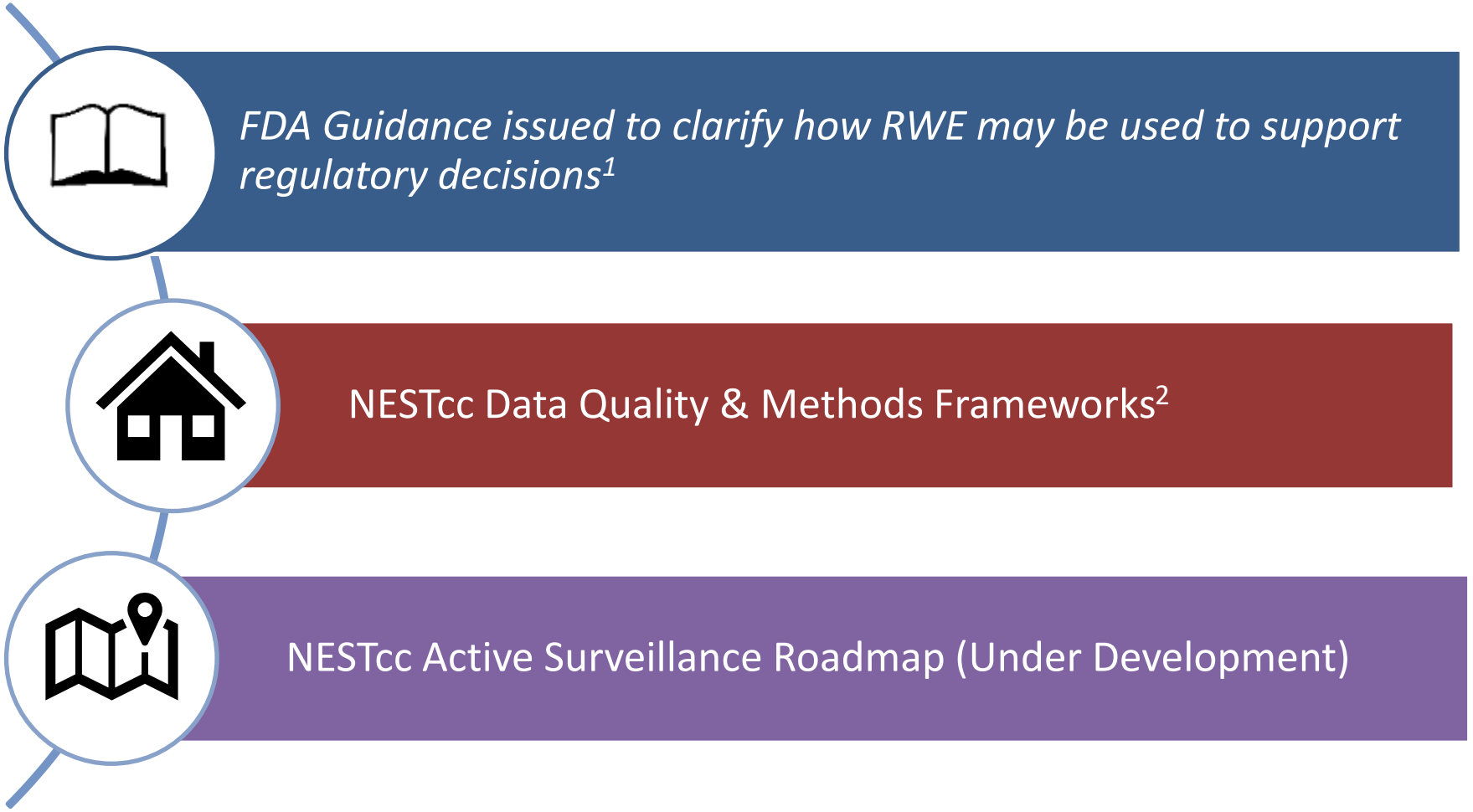
Data Quality and Method Subcommittees

- Data Quality Framework focuses on EHR and covers data governance, characteristics, capture, transformation, and curation
- Methods Framework defines the key components of a study protocol for the evaluation of medical devices

Active Surveillance

- In 2018, FDA awarded $5M to fund NESTcc Active Surveillance work
- Data infrastructure and methods/analytics development ongoing

Pathway to Use of Real-World Evidence



1) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices
2) https://nestcc.org/data-quality-and-methods/

Summary

- Clinical evidence for devices comes in many forms across the total product lifecycle, including RWE
- Supporting evidence generation with relevant and reliable RWE can result in timely access to safe and effective medical devices
- High quality real-world data sources are strategically positioned to further enhance the care of patients and device safety and effectiveness within a collaborative NEST model

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CDRHClinicalEvidence@fda.hhs.gov

Your Call to Action

1. Become familiar with FDA's real-world evidence activities
2. Understand concepts of fit-for-use data and appropriate study design
3. Recognize opportunities for real-world data and real-world evidence to support medical product development


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