FDA U.S. FOOD & DRUG ADMINISTRATION

Opportunities and Challenges of Using Real-World Evidence to Support Regulatory Decisions for Drugs, Biologics, and Devices

Association of Food and Drug Officials (AFDO)
Drug & Medical Products Educational Conference - 2021
13 April 2021

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Chief Medical Officer
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Topics for Focus on Drugs and Biologics

1) Overview of FDA's Real-World Evidence (RWE) Program

2) Concepts of fit-for-use data and adequate study design

3) Considerations when using RWE in regulatory decision-making

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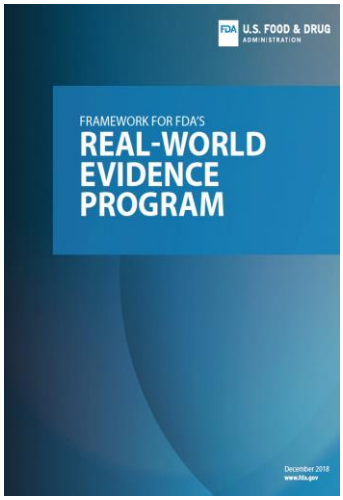
FDA RWE Framework (2018)



- 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

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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 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- **Draft guidance to be issued by December 2021**
- **Standard for *substantial evidence* remains unchanged; commitments are aligned with Prescription Drug User Fee Act (PDUFA)**

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'Real-World' Definitions

<u>from FDA's Framework for Real-World Evidence (2018)</u>:

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 (e.g., *medical claims, electronic health records (EHRs), registries, digital health technologies*)

Real-World Evidence (RWE) is clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD (*involving various study designs, such as randomized or externally controlled trials as well as observational studies)*

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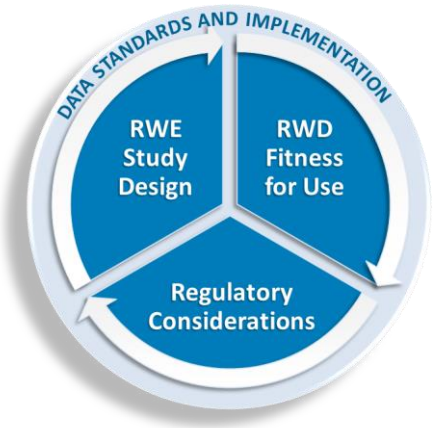
FDA RWE Framework – Key Considerations



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**

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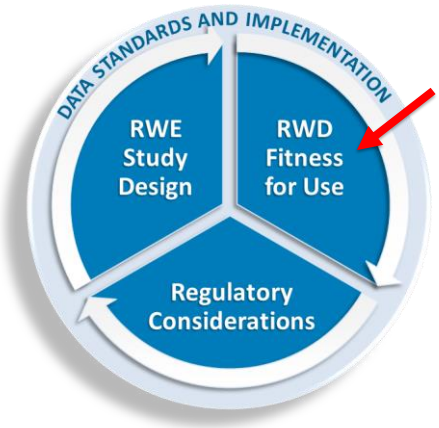
RWE Framework: Data



Considerations:

- **Whether the RWD are fit for use; with RWD sources including billing claims, electronic health records, registries, device-generated data, patient-generated data**

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EHR Data: Factors Affecting Reliability and Relevance

- **Challenges such as "missing" data, capture of unstructured data, consistent reporting, etc.**
- **Timing of assessments in clinical practice can be non-standard and vary based on clinical status**
- **Suitable outcome measures for disease progression might not be used, or might not be recorded consistently in practice**
- **Linkage necessary for studies done across healthcare systems**

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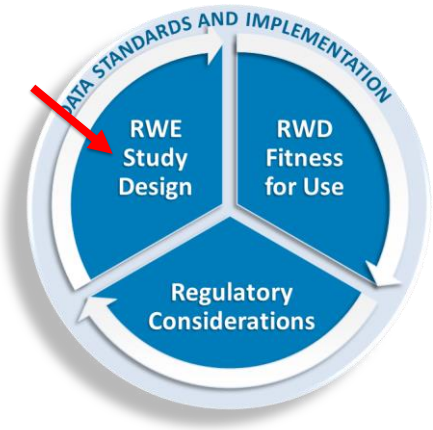
RWE Framework: Design



Considerations:

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Study Design in the Era of Real-World Data

Randomized, observational, interventional, and real-world—What's in a name?

	Interventional	Non-Interventional
Primary data collection for research	• traditional RCTs • decentralized RCTs	• registry-based analyses*
Secondary use of clinical data	• pragmatic RCTs • cluster RCTs	• health records- or claims-based analyses*

*Non-interventional research designs include observational cohort and case-control studies; RCT = randomized, controlled trial.

Pharmacoepidemiol Drug Saf. 2020;29:1514–1517

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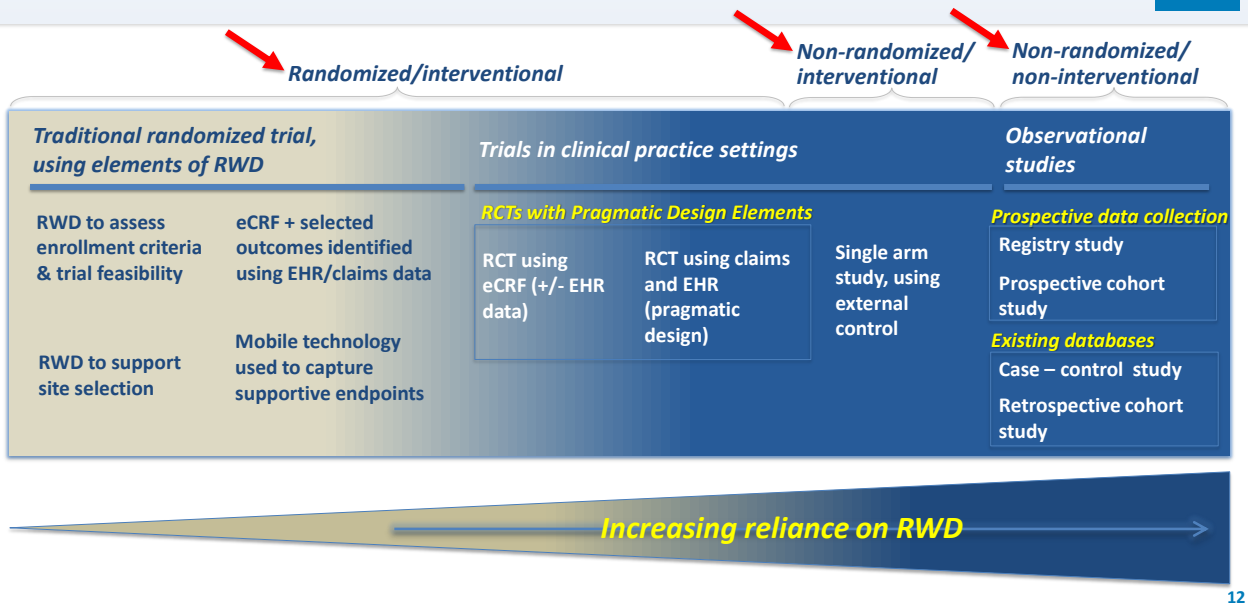
Spectrum of Study Designs



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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

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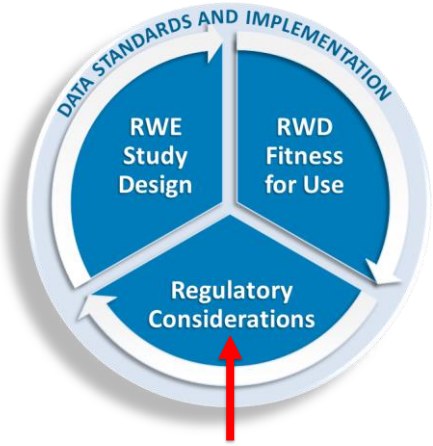
RWE Framework: Regulatory



Considerations:

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- **Whether the study conduct meets FDA regulatory requirements**

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Evidentiary Benchmark

- **FDA standard (21 CFR 314.126) for "substantial evidence" is 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**

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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

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Example of Demonstration Project to Improve RWD

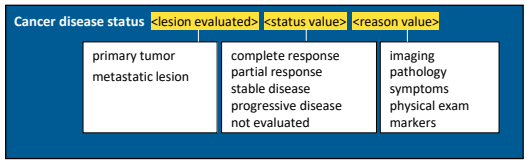
'ICAREdata': Develop and validate EHR-based measures in oncology

Cancer disease status

Clinical Assessment

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

ICAREdata Question Format



Example of Resulting Structured Phrase

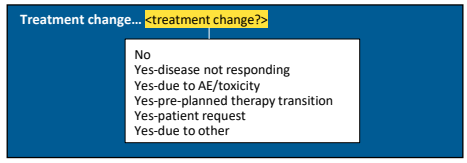
#Cancer disease status observed for #primary tumor was #progressive disease based on #imaging and #symptoms*

Treatment change

Clinical Assessment

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

ICAREdata Question Format



Example of Resulting Structured Phrase

#Treatment change and #yes-disease not responding*

*** Blue font denotes controlled vocabularies**

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RWE Demonstration Projects: Other Examples

- **VESALIUS-EHR: Better understanding of fit-for-use RWD data in clinical trials**
  - **Data available in EHRs are being compared to data collected in the "VESALIUS-CV trial" evaluating evolocumab for the prevention of major cardiovascular events**
  - **Intended to explore the potential for RWD to identify participants, auto-populate baseline characteristics, and capture clinical events of interest in clinical trials**
- **RCT-DUPLICATE: Assess whether observational analyses align with RCTs**
  - **Longitudinal insurance claims data are being used in observational cohort analyses to emulate ≈30 randomized controlled trials (RCTs) on the same topic**
  - **Study objective is to determine if/when RWE can produce similar results and lead to the same regulatory decision as RCTs; public meeting held Feb 2021**
  - **See https://healthpolicy.duke.edu/events/evaluating-rwe-observational-studies-regulatory-decision-making-lessons-learned-trial**

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Demonstration Project Results: RCT-DUPLICATE

Emulating Randomized Clinical Trials with Nonrandomized Real-World Evidence Studies: First Results from the RCT DUPLICATE Initiative

Conclusions: Agreement between RCT and RWE findings varies depending on which agreement metric is used. Interim findings indicate that selection of active comparator therapies with similar indications and use patterns enhances the validity of RWE. Even in the context of active comparators, concordance between RCT and RWE findings is not guaranteed, partially because trials are not emulated exactly. More trial emulations are needed to understand how often and in what contexts RWE findings match RCTs.

Originally published 17 Dec 2020 | https://doi.org/10.1161/CIRCULATIONAHA.120.051718

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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

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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

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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]

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

Blood Cancer Journal (2016) 6, e473

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RWE and COVID-19 – Representative Comments

The pandemic is prompting widespread use–and misuse–of real-world data

www.pnas.org/cgi/doi/10.1073/pnas.2020930117

"The dangers of COVID-19 present an unprecedented opportunity to leverage diverse, real-world data sources to inform medical and regulatory responses. But researchers and clinicians must be careful not to sacrifice methodological rigor."

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Challenge Question

True or False? Real-world evidence for efficacy or comparative safety is held to a lower evidentiary standard than randomized trials

False: RWE submissions are held to the same regulatory standard

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Summary (for CBER & CDER)

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

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U.S. FOOD & DRUG ADMINISTRATION

The Opportunities and Challenges of Using Real World Evidence to Support FDA's Regulatory Decisions in the Area of Drug, Biologics and Devices

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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**

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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

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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

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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."

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Towards our Vision

Employee Engagement, Opportunity, and Success
Simplicity
Collaborative Communities

Establish a National Evaluation System for Medical Devices
Partner with Patients
Promote a Culture of Quality and Organizational Excellence

2018-2020

2016-2017

Strengthen the Clinical Trial Enterprise
Strike the Right Pre-/Postmarket Balance
Provide Excellent Customer Service

2014-2015

CDRH Strategic Priorities

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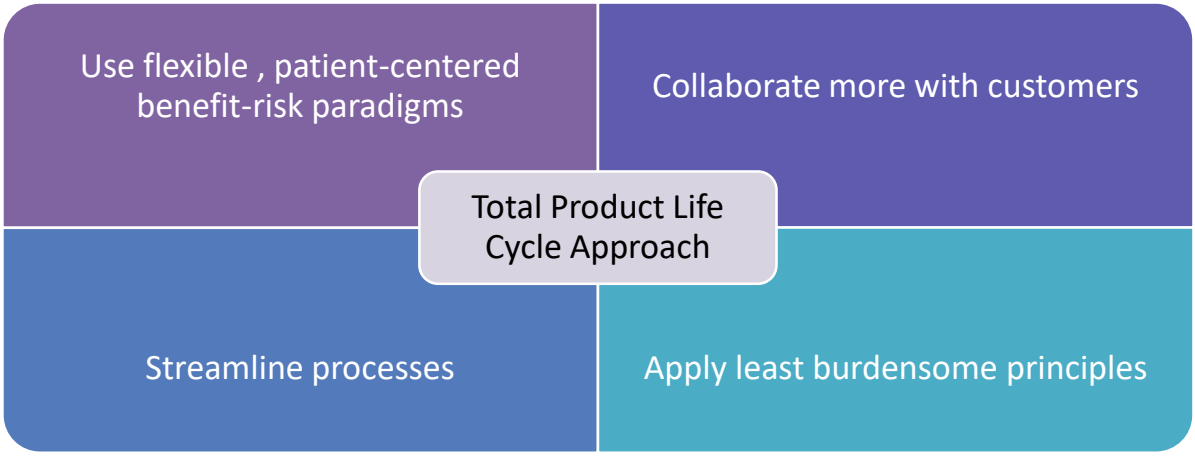
CDRH Strategic Priorities:
Reduce Time and Cost of Clinical Evidence Generation



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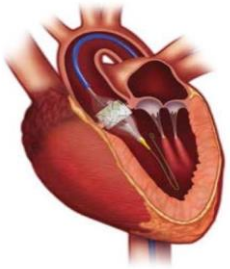
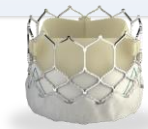
Case Example: Transcatheter Heart Valves The Road from 42nd





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

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Topics

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

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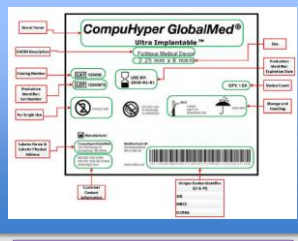
Real-World Data (RWD) Sources

Diagnostic laboratory and imaging

Device/Patient Registries



Device Generated Data

Patient Generated Data

Electronic Health Records

Medical Billing Claims

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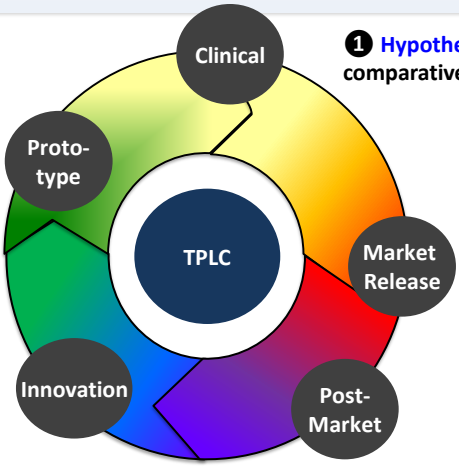
Potential Usages of RWE for Total-Product Life-Cycle Device Evaluation



1. Hypothesis Generation (e.g. treatment effect estimation for comparative studies)
2. Inform prospective trial design
3. RWE as a control arm for a clinical trial
4. Real-world data source as a platform to support a clinical trial (data collection / randomization)

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5. Data collection framework for postmarket evidence generation (e.g. post-approval studies)
6. Public health surveillance
7. Generate evidence to support indication expansions and future innovation

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Benefits of Real-World Data Sources

- 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
- Reduced time/cost to answer important questions
- Inform future device modifications and new technology development
- Better align evidence generation with innovation cycles

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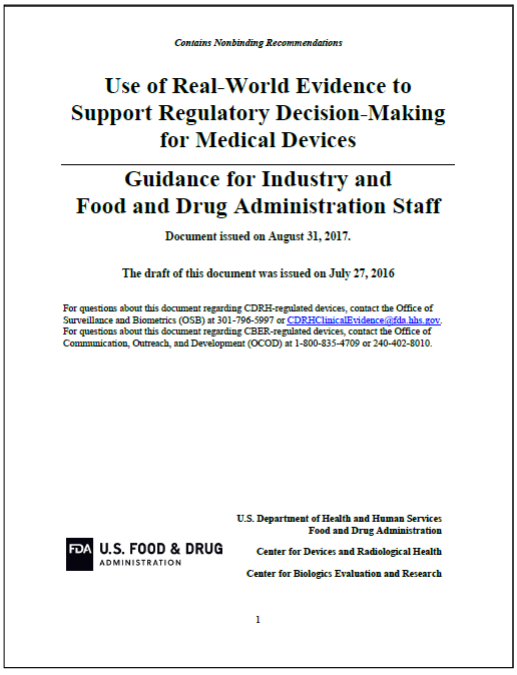

Contains Nonbinding Recommendations

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

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Key Criteria

- ✓ Relevance
- ✓ Reliability
- ✓ Patient Protections

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CDRH Supporting and Advancing RWE

Support Total Product Life Cycle Reviews

- Since FY15, CDRH has granted marketing authorization for more than 90 new or modified class II and III medical devices using RWE
  - ❖ Examples of RWE Used in Medical Device Regulatory Decisions
- 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

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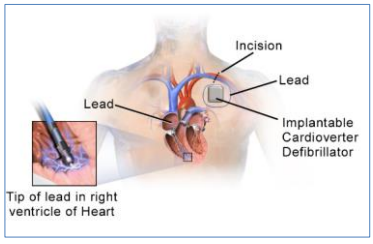
Case Example: RWE for Postmarket Purposes

"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**

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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

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Knowledge Check

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

1. True
2. False

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Topics

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

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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

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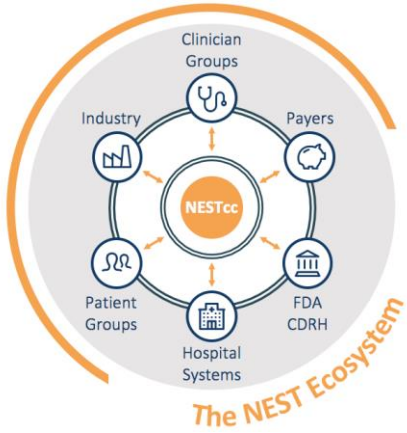
National Evaluation System for Health Technologies Coordinating Center (NESTcc) Collaborative Community

- **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/

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NESTcc Research Network 157 million+

Total Patient Population

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

Data Sources

- Electronic Health Records
- Pharmacies
- Private Claims
- Public Claims
- Registries
- Patient-Generated Data
- Unique Device Identifiers
- Billing, supply chain, genomic data

DukeHealth, HealthCore, INSIGHT Clinical Research Network, Lahey Hospital & Medical Center, Mayo Clinic, MDEpiNet, Mercy, NWEH NorthWest EHealth Discover-NOW, OneFlorida Clinical Research Consortium, PEDSnet A Pediatric Learning Health System, Regenstrief Institute, STAR Stakeholders, Technology, and Research CRN, Vanderbilt University Medical Center, Weill Cornell Medicine, Yale NewHaven Health

Additional Collaborators will be added to the NESTcc Research Network in 2021

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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

NESTcc Data Quality Framework

- Methods Framework defines the key components of a study protocol for the evaluation of medical devices

NESTcc Methods Framework

Active Surveillance

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

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Pathway to Use of Real-World Evidence

FDA Guidance issued to clarify how RWE may be used to support regulatory decisions[1]

NESTcc Data Quality & Methods Frameworks[2]

NESTcc Active Surveillance Roadmap (Under Development)

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/

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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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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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