Duke | MARGOLIS INSTITUTE *for* Health Policy

2024 Duke-Margolis Convening on the State of Real-World Evidence Policy

Virtual Public Meeting
July 25, 2024 | 12:00 p.m. - 4:45 p.m. ET

healthpolicy.duke.edu

Duke | MARGOLIS INSTITUTE *for* Health Policy

Welcome and Keynote
State of RWE Policy 2024

Dr. Mark McClellan
Director and Robert J. Margolis, M.D., Professor of Business, Medicine and Policy at the Duke-Margolis Institute for Health Policy at Duke University

Statement of Independence

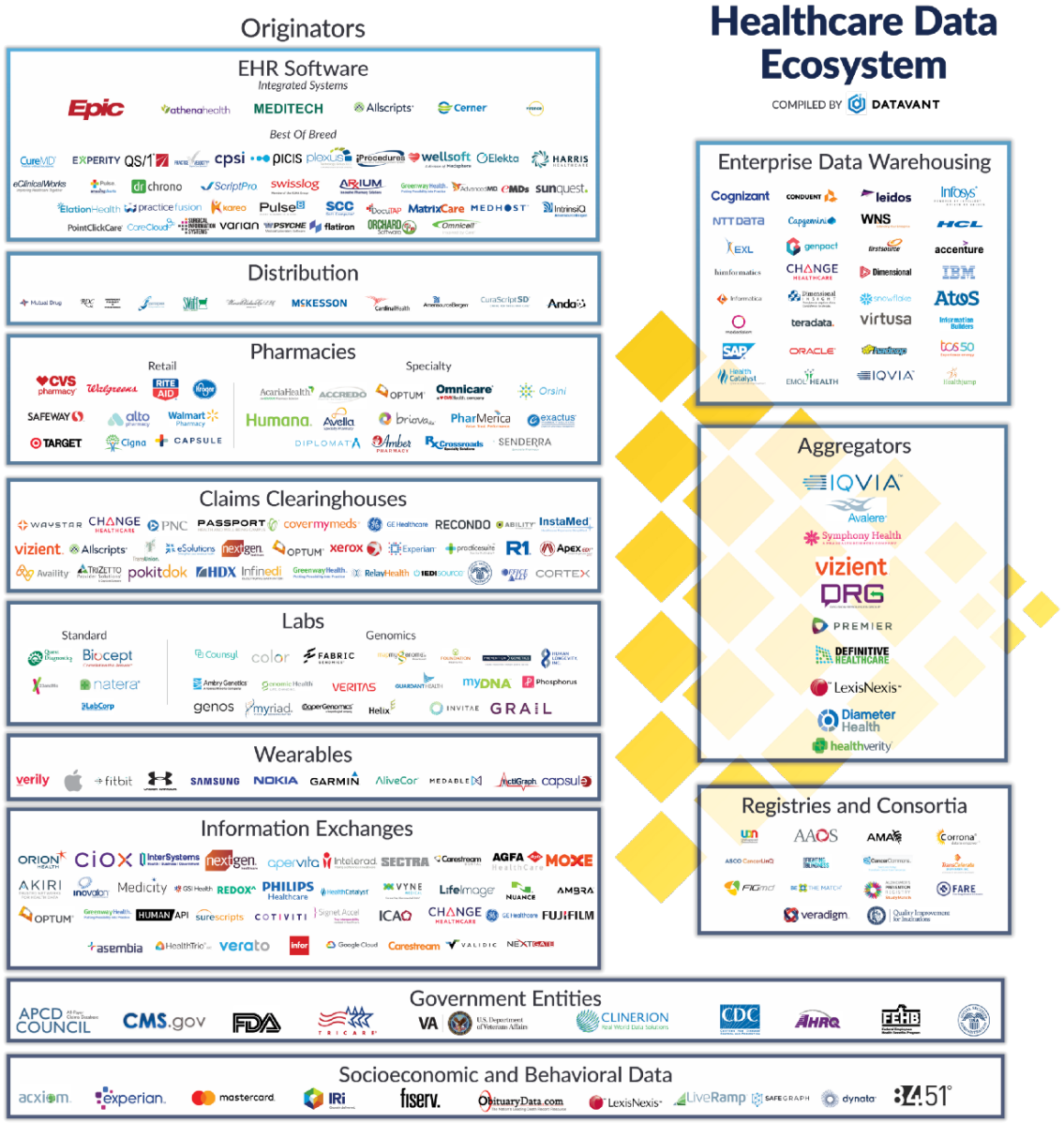
The Robert J. Margolis, MD, Institute for Health Policy is part of Duke University, and as such it honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Center take partisan positions, but the individual members are free to speak their minds and express their opinions regarding important issues.

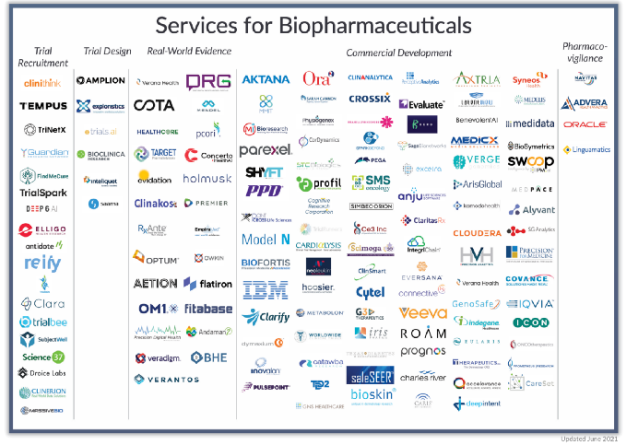
For more details on relevant institutional policies, please refer to the Duke Faculty Handbook, including the Code of Conduct and other policies and procedures. In addition, regarding positions on legislation and advocacy, Duke University policies are available at http://publicaffairs.duke.edu/government.

Meeting Reminders

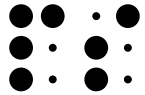
- Attendees are encouraged to contribute throughout the meeting with questions in the Zoom Q&A function.
- This meeting is being recorded, and the recording and slide deck will be posted on the Duke-Margolis event page in the weeks following the meeting.

Vast and Continuously Growing Health Data Landscape



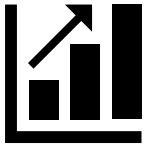


Compiled by Datavant: https://medium.com/datavant/the-fragmentation-of-health-data-8fa708109e13



Real-World Data

Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources (e.g., registries, wearables, EHRs, etc.)



Real-World Evidence

Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Real-World Evidence Uses Continue to Expand

Medical Product Development

- Inform biological understanding of disease
- Identify unmet need
- Therapeutic/device selection
- Trial recruitment efficiency & equity

Regulatory Review

- Inform post-market and pre-market safety effectiveness
- Inform new approvals in rare diseases
- Inform indication and labeling decisions

Care Delivery

- AI-enabled caregiver support
- Support patients' engagement in their own care decisions
- Help drive higher-value care

Value-Driven Payment, Pricing, & Coverage

- Evidentiary alignment between regulators, payers, and HTAs
- "De-risk" or "risk-based" payment for high cost treatments to increase access

RWE Informs All Aspects of the Health System

- Medical product regulatory approval
- Health system policy and clinical practice
- Development and/or use of automated tools like artificial intelligence (AI) in clinical, payment, and/or regulatory settings
- Reasonable and necessary payer coverage

Today's Agenda

- Opening Remarks - Richard Forshee, U.S. Food and Drug Administration
- Session 1: Duke-Margolis RWE Collaborative Updates – Rachele Hendricks-Sturrup, Research Director, Duke-Margolis
- Session 2: Source Data Access for Decision Makers – Trevan Locke, Assistant Research Director, Duke-Margolis
- Session 3: Applications of Artificial Intelligence in RWE Studies – Christina Silcox, Research Director, Duke-Margolis
- Session 4: Leveraging RWD for Pricing, Coverage, and Payment – Nitzan Arad, Assistant Research Director, Duke-Margolis
- Closing Remarks – Rachele Hendricks-Sturrup, Research Director, Duke-Margolis

Session 1: Duke-Margolis RWE Collaborative Updates

- Overview of Duke-Margolis RWE Collaborative Strategic Plan
- International harmonization of RWE standards updates
- Latest RWE developments at the FDA
- Overview of new Duke-Margolis RWE Collaborative white papers
- Fireside chat with panelists from The Evidence Base and AgencyIQ by POLITICO

Session 2: Source Data Access for Decision Makers

- Per recent guidance, the FDA requests access to source records and patient-level data to assess whether RWE is relevant and reliable enough, and of sufficient quality, to infer treatment cause and effect.
- Meeting these FDA expectations presents challenges:
  - Lack of RWD standards
  - Privacy expectations
  - Limited access to source records from aggregated and/or curated datasets
- Technological, regulatory, and other solutions can address these challenges and ensure decision-makers can access data, but it will take a collective community effort to build robust data pipelines.

Session 3: Applications of Artificial Intelligence in RWE Studies

- AI-enabled endpoints and discoveries using RWD
  - New digital monitoring technologies
  - AI tools that identify new correlative or causal relationships between genetics, drug responses, and diseases using clinical data
- AI-enabled site and participant selection
  - AI-enabled diagnostics/screening to more easily identify eligible patients
- Improvement in quality and accessibility of RWD
  - Passive charting, AI decision support, and other clinical and operational AI tools may make clinical data more standardized and complete while reducing the burden on the health care providers
  - AI-privacy preserving technologies like synthetic data may increase RWD availability

Session 4: Leveraging RWD for Pricing, Coverage, and Payment

- CMS continues to implement the IRA Medicare Drug Price Negotiation Program, and most recently published draft guidance for the second round of the program.
- CMS continues to evaluate opportunities to streamline coverage processes for novel technologies by piloting components of the proposed TCET pathway and is expected to finalize a suite of guidance documents on CED, coverage evidence reviews, and evidence thresholds. Additional guidance documents are forthcoming, including Fit-for-Purpose (FFP) Study Guidance.
- CMS, through CMMI, also introduced the Cell and Gene Therapy (CGT) Access Model, which will facilitate access to CMS-designed outcomes-based agreements for CGTs, starting with sickle cell disease gene therapies, requiring the use of RWD to track patient outcomes.
- With sufficient clarity and specificity, further guidance on the relevance, reliability, and quality of RWD for these programs can enhance the predictability and transparency of CMS' evidence use for different technology types.

FDA Remarks

Richard Forshee, PhD
Deputy Director of the Office for Biostatistics and Pharmacovigilance
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

State of Real-World Evidence Policy:

FDA Remarks

Richard Forshee, PhD

Office of Biostatistics and Pharmacovigilance
Center for Biologics Evaluation and Research
US Food and Drug Administration

July 25, 2024

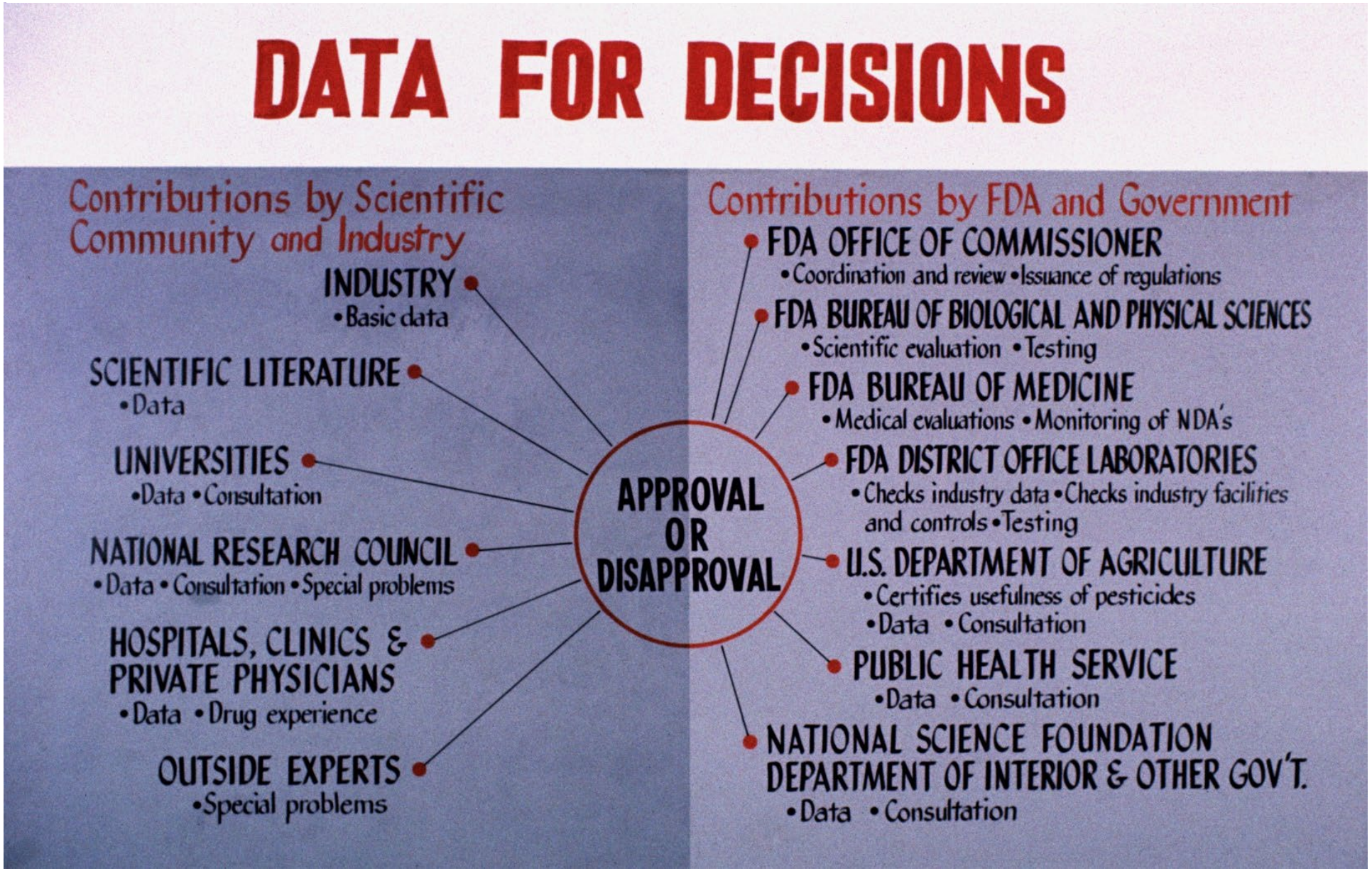
Disclaimer

- This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.
- No conflicts of interest exist related to this presentation.
- Mention of a commercial product should not be construed as actual or implied endorsement.

John Allen Paulos

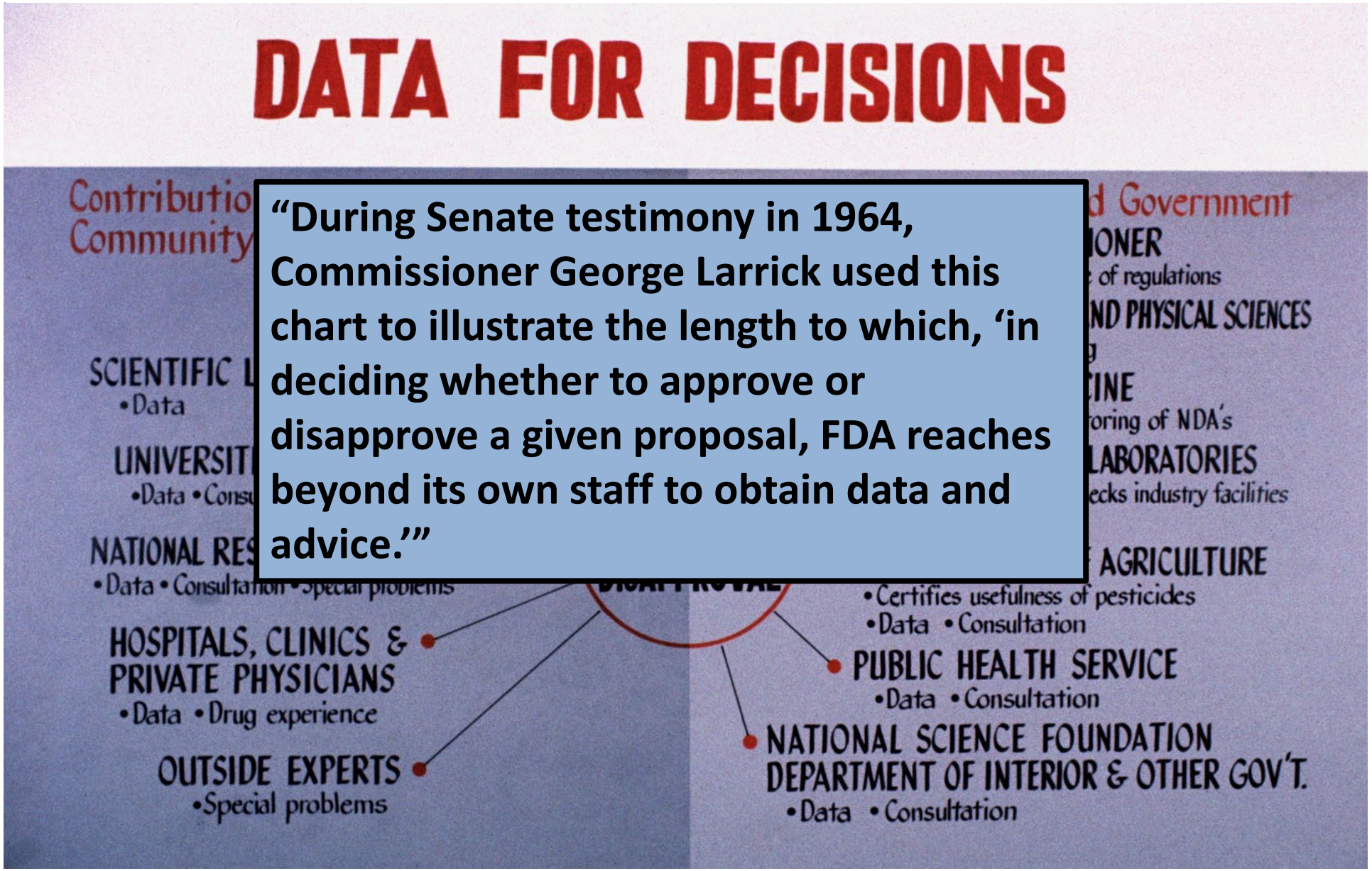
"Uncertainty is the only certainty there is, and knowing how to live with insecurity is the only security."

FDA Must Consider Many Types of Data From Many Sources



https://www.flickr.com/photos/fdaphotos/8205558579/in/album-72157624615595535/

FDA Must Consider Many Types of Data From Many Sources



"During Senate testimony in 1964, Commissioner George Larrick used this chart to illustrate the length to which, 'in deciding whether to approve or disapprove a given proposal, FDA reaches beyond its own staff to obtain data and advice.'"

https://www.flickr.com/photos/fdaphotos/8205558579/in/album-72157624615595535/

Goals of Presentation

- Discuss the value of Real-World Evidence (RWE) and how it complements randomized controlled trials (RCT)
- Share recent RWE activities at FDA
- Provide CBER-specific examples

Real-World Evidence

"The 21st Century Cures Act, passed in 2016, places additional focus on the use of these types of data to support regulatory decision making, including approval of new indications for approved drugs."

https://www.fda.gov/scienceresearch/specialtopics/realworldevidence/default.htm

‘Real-World’ Definitions (from 2018 FDA Framework)

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

- Electronic health records (EHRs)
- Medical claims data
- Product and disease registries
- Digital health technologies in non-research settings
- Other data sources on health status, e.g. questionnaires

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

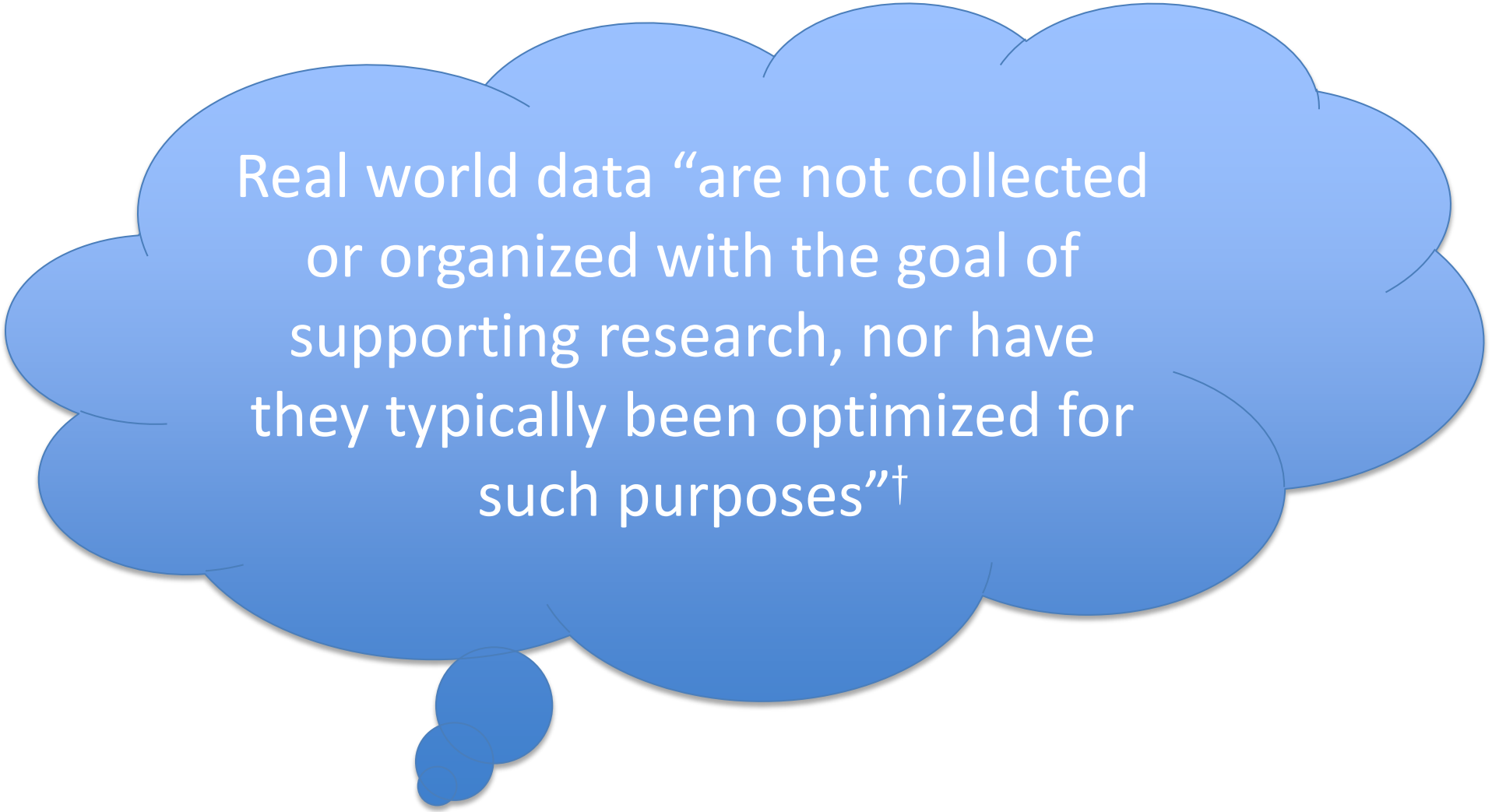
Generated using various study designs—including but not limited to randomized trials (e.g., pragmatic clinical trials), externally controlled trials, and observational studies

https://www.fda.gov/media/120060/download

21st Century Cures of 2016 – Deliverables

- FDA established a program to evaluate the potential use of RWE to:
  - Support a new indication for a drug approved under section 505(c)
  - Satisfy post-approval study requirements
- Draft framework issued in 2018:
  - Describe sources of data, challenges, opportunities, etc.
- Draft guidance for industry issued 2021-2024
- *Note: Standard for substantial evidence to approve drug & biologics unchanged*

Real-World Data (RWD)



†N Engl J Med 2016; 375:2293-2297 DOI: 10.1056/NEJMsb1609216

Slide provided by Yun Lu, FDA/CBER

Analyses of RWD Can Complement RCTs

- Generate hypotheses for prospective trials
- Assess the generalizability of findings from interventional trials (including RCTs)
- Conduct safety surveillance of medical products
- Examine changes in patterns of therapeutic use, and measure and implement quality in health care delivery
- Draw causal inferences about the treatment effects of medical products

Drawn from N Engl J Med 2016; 375:2293-2297 DOI: 10.1056/NEJMsb1609216

Limitations of RWE

- Given the wide range of study designs that could be RWE, it is impossible to provide a comprehensive list of limitations
- Some RWE studies are not randomized
- Many possible sources of bias
- Concerns about data quality
- Publication bias and p-hacking

Current Status of RWE

Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.

Issue being addressed: More than five years after passage of the 21st Century Cures Act, the terms RWD and RWE are being used inconsistently and interchangeably

Content of article:

- Addressed two common misconceptions
- Provided conceptual overview of study design
- Described FDA guidance and demonstration projects
- Highlighted regulatory approvals
- Offered path forward

N ENGL J MED 386;18 NEJM.ORG MAY 5, 2022

Misconceptions Regarding RWD & RWE

Frequent instances of:

- *Misconception #1* – *RWD & RWE are new concepts*:

  "In reality, sources of data and types of study design haven't fundamentally changed, but electronic access to more detailed clinical data is evolving & the data are becoming more relevant and reliable"

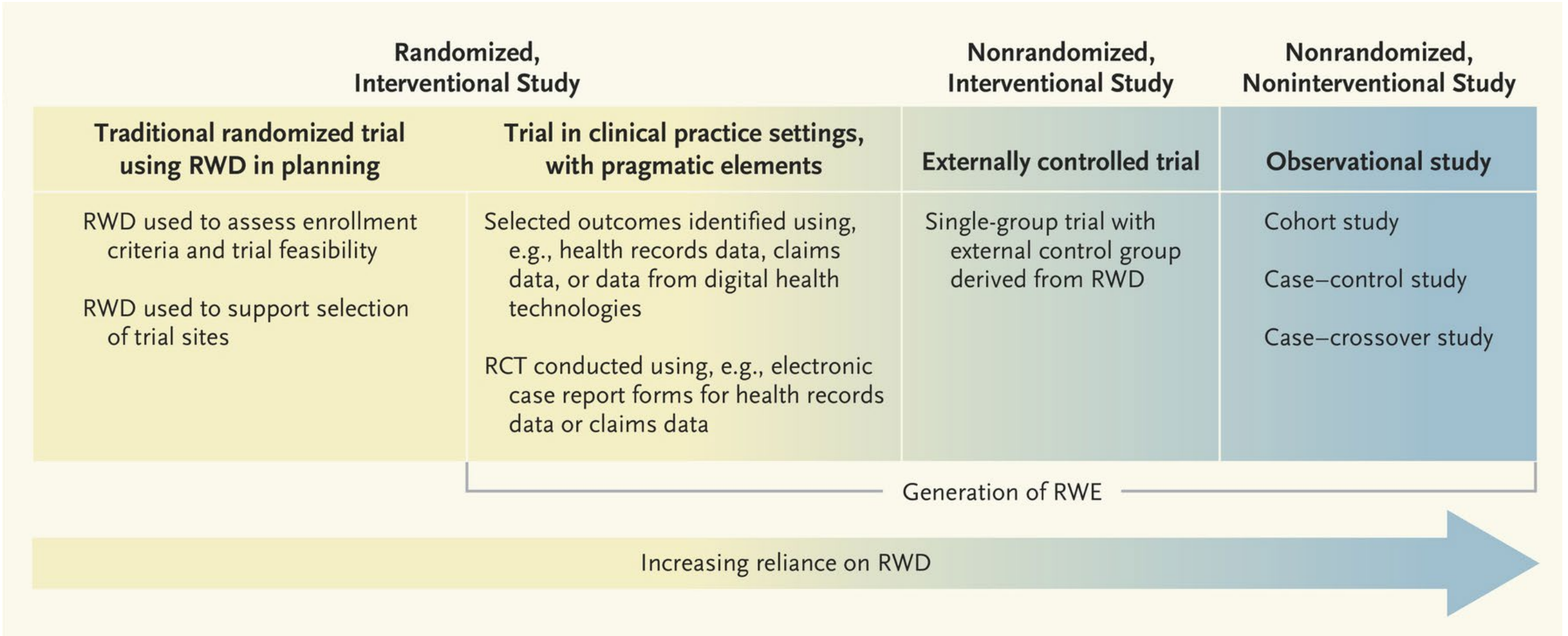
- *Misconception #2* – *A simple dichotomy of randomized trials vs. observational studies exists*:

  "In reality, clinical trials are defined by assignment of treatment according to an investigational protocol, and single-arm trials face challenges similar to those in observational studies in determining whether difference in clinical outcomes (compared to an external control group) represent actual treatment effects"

N ENGL J MED 386;18 NEJM.ORG MAY 5, 2022

Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.



Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

FDA RWE Guidance

Topic	Category	Status
EHRs and claims data	Data considerations	draft issued
Registry data	Data considerations	final issued
Data standards	Submission of data	final issued
Regulatory considerations	Applicability of regulations	final issued
Externally controlled trials	Design considerations	draft issued
Non-interventional studies	Design considerations	draft issued
RCTs in clinical practice settings	*Design considerations*	*in development*
Submitting RWE	Procedural	final issued

https://www.fda.gov/science-research/real-world-evidence/center-biologics-evaluation-and-research-center-drug-evaluation-and-research-real-world-evidence

RWE in PDUFA VII (FY 2023-2027)

***By December 31, 2022**:*

FDA will **establish an Advancing RWE Program** to identify approaches for RWE that meet regulatory requirements; develop agency processes that promote consistent decision-making; and increase awareness of RWE characteristics that support regulatory decisions

By June 30, 2024:

FDA will **report aggregate data on an annual basis** describing submissions to CDER & CBER, including data sources & study designs used, and types of regulatory requests

***By December 31, 2025**:*

FDA will **convene a public workshop or meeting** to discuss case studies, focusing on how to generate RWE that meets regulatory requirements

By December 31, 2026:

FDA will use lessons learned from the Advancing RWE Program to **update existing, or generate new, RWE-related guidance documents**

Advancing RWE Program

- New CDER-CBER-OCE program under PDUFA VII
- Provides up to four meetings with Agency to enable early discussion regarding the potential use of RWE in medical product development; optional pathway, established pathways remain available
- Semi-annual submission deadlines: March 31 and September 30
- One to two requests accepted per cycle in FY23 and 24
- Sponsors notified of status (selected, alternate, denied) within 45 days of deadline

https://www.fda.gov/drugs/development-resources/advancing-real-world-evidence-program

Advancing RWE – Program Goals

- Identify approaches for generating RWE that meet regulatory requirements in support of labeling for effectiveness (e.g., new indications, populations, dosing information) or for meeting post-approval study requirements
- Develop agency processes that promote consistent decision-making and shared learning regarding RWE
- Promote awareness of characteristics of RWE that can support regulatory decisions by allowing FDA to discuss study designs considered in the *Advancing RWE Program* in a public forum

EXAMPLES OF CBER RWE

Clinical Infectious Diseases

MAJOR ARTICLE

Effectiveness and Duration of Protection Provided by the Live-attenuated Herpes Zoster Vaccine in the Medicare Population Ages 65 Years and Older

Hector S. Izurieta,[1,5] Michael Wernecke,[2] Jeff
Christopher Jankosky,[1] Philip Krause,[1] Chris
[1]Center for Biologics Evaluation and Research, Food and D
Washington, DC; [4]National Center for Immunization and R

(See the Editorial Commentary by Bl

Background. Tens of millions of s
vaccine (HZV) reduces that risk, altho
remain. We used Medicare data to inve
Methods. This retrospective cohor
adjustments to account for potential l

Clinical Infectious Diseases

EDITORIAL COMMENTARY

Herpes Zoster Vaccine and the Medicare Population

Steven Black
Center for Global Health, Cincinnati Children's Hospital, Ohio

(See Major Article by Izurieta et al on pages 785-93.)

Keywords. herpes; vaccines; Medicare; aging populations.

The incidence of herpes zoster rises dramatically after 50 years of age, and reactivation of latent virus is associated with a vesicular rash and at times debilitating patients receiving the vaccine, because of the information it provides to public health policy makers to facilitate decisions regarding this and other vaccines effectiveness in seniors in the United States overall.

The primary analysis in this study a demonstrated a 33% (95% CI, 32%–35%)

The accompanying editorial states: "..this study demonstrates the utility of large-linked databases in the evaluation of vaccine effectiveness..
...such studies should be considered for all newly introduced vaccines"

Our 2012-13 season High dose vs Standard dose influenza comparative effectiveness study (Lancet Infect Dis 2015) was accompanied by a very positive editorial that highlighted our methods, results were strikingly similar to a randomized study (Diaz-Granados et al)

Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis

Hector S Izurieta*, Nicole Thadani*, David K Shay, Yun Lu, Aaron Maurer, Ivo M Foppa, Riley Franks, Douglas Pratt, Richard A Forshee, Thomas MaCurdy, Chris Worrall, Andrew E Howery, Jeffrey Kelman

Summary

Background A high-dose trivalent inactivated influenza vaccine was licensed in 2009 by the US Food and Drug Administration (FDA) on the basis of serological criteria. We sought to establish whether high-dose inactivated influenza vacc
beneficiaries

Methods In
received high
vaccines duri
primary outc
dispensing o
department
comparing o
multivariate

Findings Betw
recipients of
presence of u
(95% CI 15–2
of probable i
more effectiv
dose cohort v

Interpretation
older, high-d
prevention of
show, for the
standard-dose

Our findings were discussed at the March, 2015 CDC ACIP Influenza Working Group, and in other scientific and regulatory meetings

Novel observational study designs with new influenza vaccines

In *The Lancet Infectious Diseases*, Hector Izurieta and colleagues[1] presented results of a cohort study in 929 730 older people (65 years and older) who received a high-dose influenza vaccine (high-dose Fluzone, Sanofi Pasteur, PA, USA, 60 µg per strain) and compared rates of influenza-related visits and hospital admissions with 1 615 545 older people who received a standard dose of the same vaccine (15 µg per strain). The high-dose vaccine

symptoms of laboratory-confirmed influenza in the Netherlands.[3] Randomised placebo-controlled influenza vaccine trials in older people and other high-risk groups are usually thought to be unethical because many studies supporting the vaccine's benefit have already been done and immunisation is recommended worldwide.

Non-randomised (variations of) case-control or cohort vaccine effectiveness studies are suitable alter-

This is the first RWE study showing that the cell-cultured flu vaccine has higher effectiveness than comparable vaccines produced in eggs

The Journal of Infectious Diseases

MAJOR ARTICLE

Relative Effectiveness of Cell-Cultured and Egg-Based Influenza Vaccines Among Elderly Persons in the United States, 2017–2018

Hector S. Izurieta,[1,4] Yoganand Chillarige,[2] Jeffrey Kelman,[3] Yuqin Wei,[2] Yun Lu,[1] Wenjie Xu,[2] Michael Lu,[2] Douglas Pratt,[1] Steve Chu,[3] Michael Wernecke,[2] Thomas MacCurdy,[2] and Richard Forshee[1]

[1]Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, [2]Acumen, Burlingame, California, and [3]Centers for Medicare & Medicaid Services, Washington DC; [4]Department of Epidemiology, Universidad Rey Juan Carlos, Spain

Background. The low infl
be due to vaccine virus adaptat
Medicare beneficiaries.

Methods. Retrospective c
tured, egg-based quadrivalent;
Poisson regression to evaluate

Results. Of >13 million be
confidence interval [CI], 7%–
comparison, cell-cultured (RV
egg-based quadrivalent vaccin

Conclusions. The modest

Our results were presented at the June, 2018 ACIP

The Journal of Infectious Diseases

EDITORIAL COMMENTARY

Comparing Influenza Vaccine Types: The Path Toward Improved Influenza Vaccine Strategies

Brendan Flannery and Alicia M. Fry

Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia

The 2017–2018 influenza season was a reminder that seasonal influenza can be associated with a large burden of severe s aged ≥65 years affected; 660 000 000 deaths were iated with influ- n this age group [1]. Older adults are a priority group A(H3N2)-predominant seasons, such as 2017–2018.

In this issue of *the Journal of Infectious Diseases*, Izurieta et al used data from Medicare beneficiaries aged ≥65 years to compare *International Classification of Diseases, 10th Revision* (ICD-10)–coded influenza-associated hospital visits among recipients of different influenza higher relative effectiveness of high-dose as compared to standard-dose egg-based vaccines, although results from observational studies vary. An MF59-adjuvanted egg-based vaccine is also licensed for use in older adults [8]. One observational study reported a higher relative effectiveness of adjuvanted as compared to nonadjuvanted vaccines in this age group

Looking Forward

Closing paragraph from 2022 NEJM article:

- "The FDA remains committed to robust policy development aligned with the 21st Century Cures Act while maintaining evidentiary standards in honoring our obligation to protect and promote public health. Focusing on the distinction between interventional studies and noninterventional studies can help researchers, sponsors, and regulators better understand and describe relevant methodologic issues. Gaining more experience, including conduct of rigorous noninterventional studies, will help to advance drug development."

N ENGL J MED 386;18 NEJM.ORG MAY 5, 2022

Thank you!

Richard Forshee, Ph.D.
FDA/CBER

Richard.Forshee@fda.hhs.gov

39

Thank You!

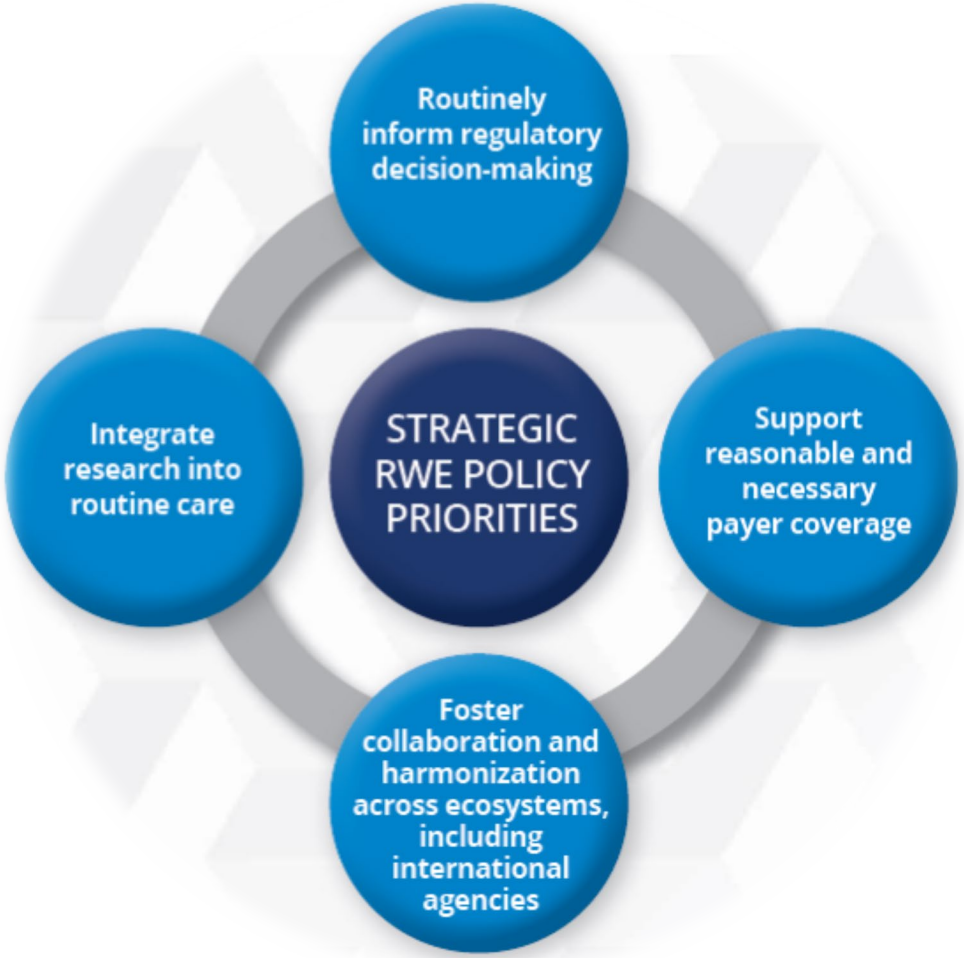
Duke | MARGOLIS INSTITUTE *for* Health Policy

Duke-Margolis RWE Collaborative Updates

State of RWE Policy 2024

Rachele Hendricks-Sturrup, DHSc, MSc, MA
Research Director, Real-World Evidence

Duke-Margolis RWE Collaborative Strategic Plan



- Engage an Advisory Group and other members of the RWE Collaborative with key stakeholders **to directly inform national and international regulatory agencies engaged in advancing the state of RWE policy**.
- Develop strategies to **ensure real-world data is capable of generating high-quality and compelling evidence** that meets the reasonable and necessary coverage needs of patients, health systems, payers, and regulators.
- Monitor the growing global RWE policy landscape and contribute thought leadership to challenging topics and questions posed by medical product regulators and policymakers globally concerning RWD/E implementation to **support timely patient access to innovative treatments and treatment approaches**.
- Explore the prospective and systematic collection of RWD to drive randomized clinical trial conduct at the point-of-care, particularly to **improve post-market evidence that may offer meaningful insights for regulatory agencies, policymakers, payers, and providers**.

June 2022 – International Coalition of Medicines Regulatory Authorities (ICMRA) Statement

Areas for Collaboration	Description
Harmonization of RWD and RWE terminologies	•Generating standardized definitions of RWD and RWE •Leveraging existing ICH activities
Convergence on RWD and RWE guidance and best practice	•Using common principles for RWD quality •Using metadata to characterize and discover RWD •Creating templates for study protocols and reports that can be used in several regulatory jurisdictions
Readiness	•Enabling the rapid creation of international expert groups on specific topics of interest •Fostering collaboration on governance and processes to allow for the efficient conduct of studies based on RWD from different countries
Transparency	•Promoting the publication of study results in open-source, peer reviewed journals •Defining common practices for systematic registration of pre-specified study protocols and results in public registries

International Harmonization of RWE Dashboard

Number of RWE Guidance Documents and Frameworks Across Regulatory Agencies

Based on our observations, 3 regulatory agencies (EMA, FDA and TFDA) globally have defined all of the following terms: quality, reliability, relevance, real world data/evidence.

Source: https://healthpolicy.duke.edu/projects/international-harmonization-real-world-evidence-standards-dashboard

Key Definitions Across Regulatory Agencies

	Reliability	Relevance	Fit for purpose	Quality	Real World Data/Evid..
European Medicines Agency (EMA)	Quality."The dimension that covers how closely the data reflect what they are ..	Quality. "For the purpose of Data Quality assessment, relevance is defined ..	characteristics needed to address a specific goal. The emphasis of data quality is ensuri..	purpose for users' needs in relation to health research, policymaking, and re..	data relating to patient health status or the delivery of health care from a va..
Food and Drug Administration (FDA)	"The term reliability includes data accuracy, completeness, provenance, and traceability." (page 3)	"The term relevance includes the availability of key data elements (exposure, outcomes, covariates) and sufficient numbe..	"If sponsors include RWE in support of regulatory submissions, they should include their fit-for purpose asses..	The evaluation of RWD data quality is made based on: - "the quality of data element population (e.g., whether abstra..	"Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources." (..
Health Canada/Canada's Drug and Health Technology Agency (CADTH)	Undetermined.	Undetermined.	Undetermined.	Not formally defined but stated as having characteristics including "data	"Real-world evidence (RWE) is evidence about the use, safety, and effectiveness of a

View on Tableau Public Share

Source: https://healthpolicy.duke.edu/projects/international-harmonization-real-world-evidence-standards-dashboard

Latest International Harmonization Guidance

- Prepared under the auspices of the **International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)**.
- Outlines general principles **on planning, designing, and analyzing observational (noninterventional) pharmacoepidemiological studies** that utilize **fit-for-purpose data** for safety assessment of medicines (drugs, vaccines, and other biological products).
- Includes **recommendations and high-level best practices** for the conduct of these studies, and is intended to **streamline the development and regulatory assessment of postmarketing pharmacoepidemiological safety studies that include RWD**.
- Seeks to improve the ability of the **study protocol and/or results to be accepted across health authorities** and support decision making in response to study results.

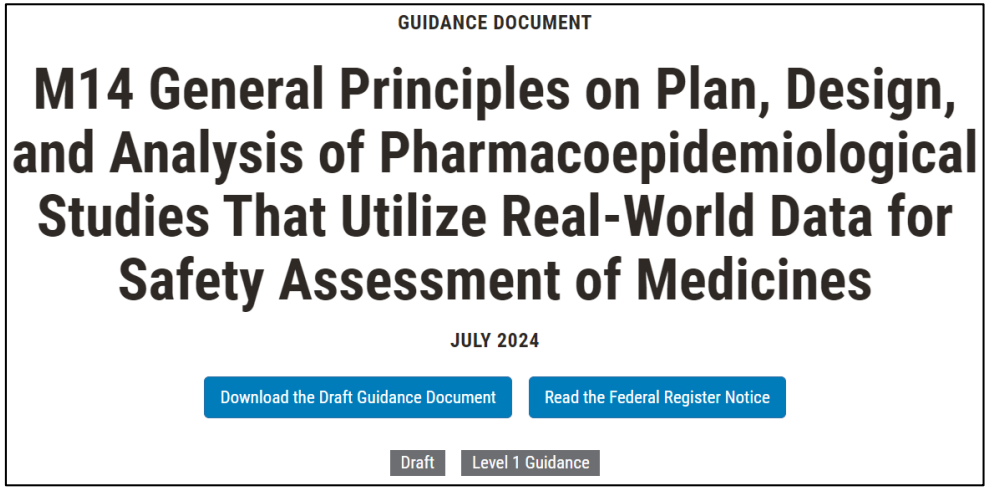
ICH M14 draft Guideline reaches Step 2 of the ICH process

24 May 2024

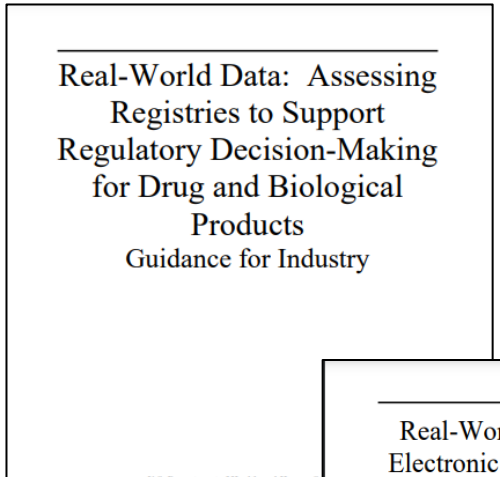
The ICH M14 draft Guideline on "General Principles on Plan, Design and Analysis of Pharmacoepidemiological Studies That Utilize Real-World Data for Safety Assessment of Medicines" has reached *Step 2* of the ICH process on 21 May 2024.

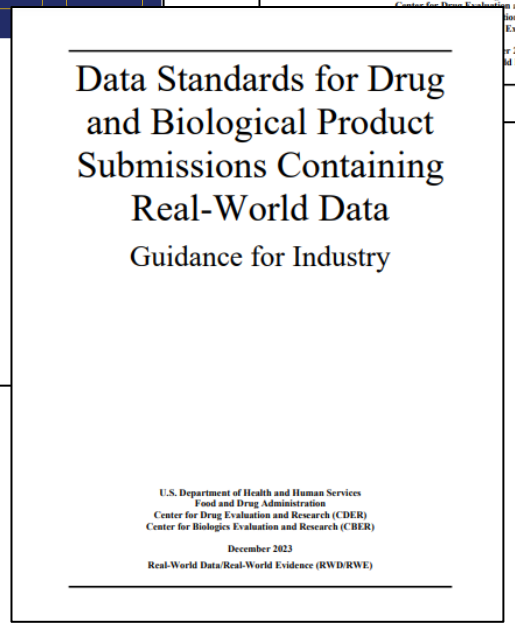
The M14 draft Guideline is available for download on the M14 Page.

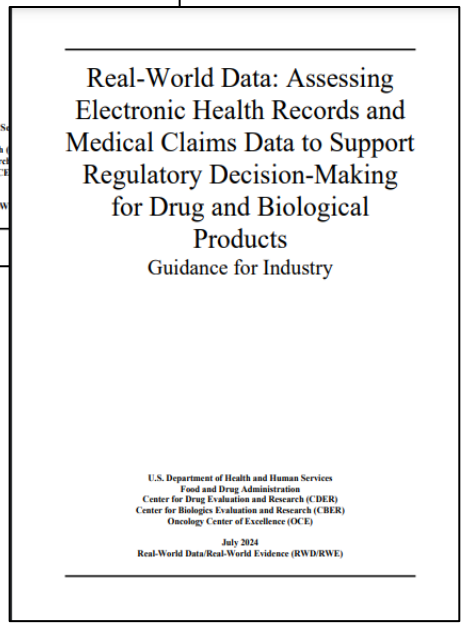
This draft Guideline outlines recommendations and high-level best practices for the conduct of these studies, to streamline the development and regulatory assessment of study protocols and reports. These recommendations and practices also seek to improve the ability of the study protocol and/or results to be accepted across health authorities and support decision-making in response to study results.



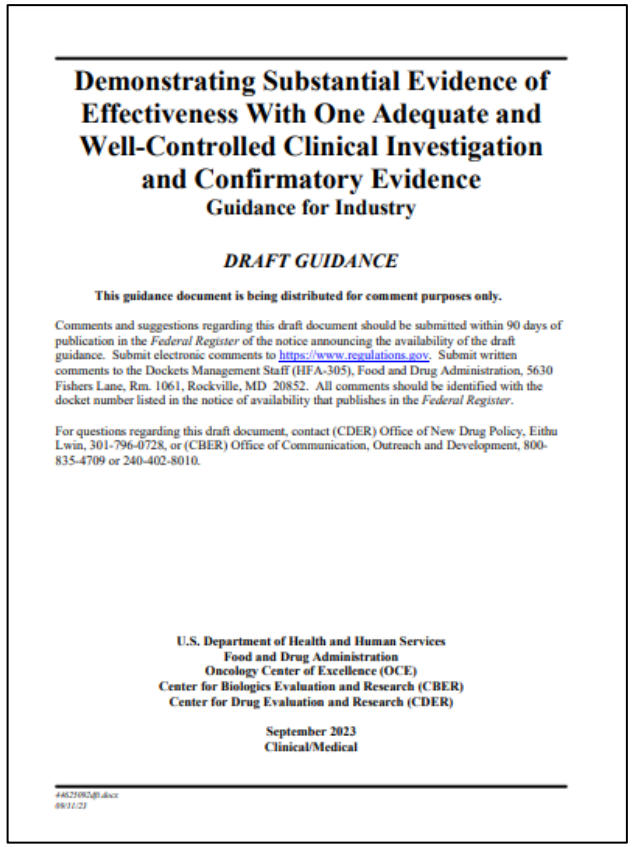
Latest FDA Guidance & Developments







Latest FDA Draft Guidance



Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

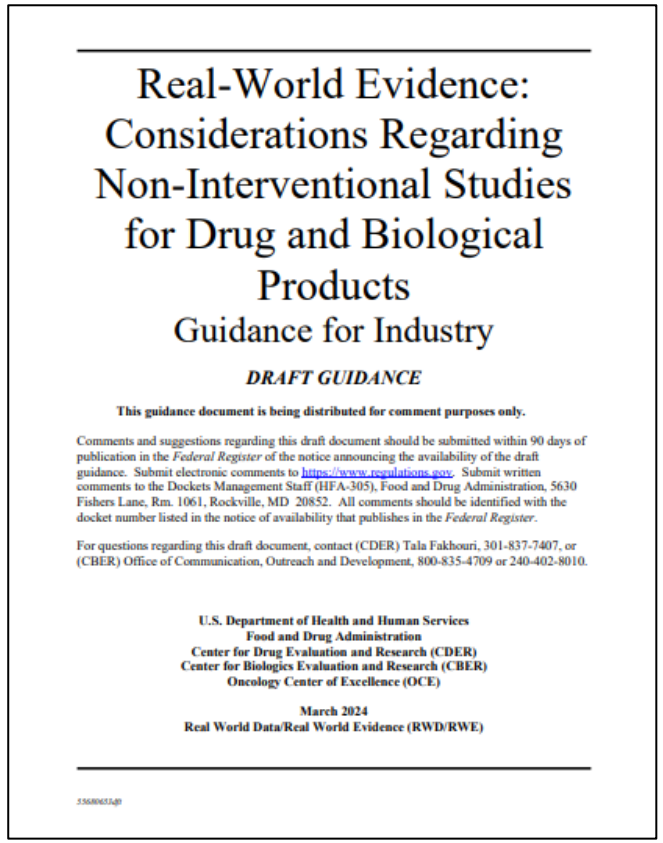
Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of New Drug Policy, Eithu Lwin, 301-796-0728, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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

September 2023
Clinical/Medical

#46259820.docx
09/11/23



Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

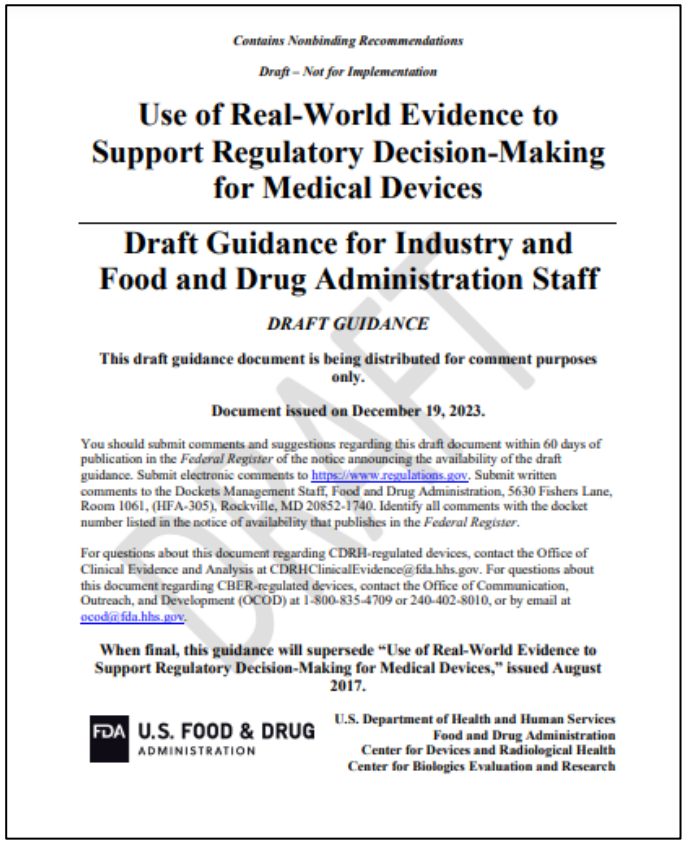
Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Tala Fakhouri, 301-837-7407, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)
Oncology Center of Excellence (OCE)

March 2024
Real World Data/Real World Evidence (RWD/RWE)

5568065Ldt0



Contains Nonbinding Recommendations

Draft – Not for Implementation

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

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on December 19, 2023.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852-1740. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document regarding CDRH-regulated devices, contact the Office of Clinical Evidence and Analysis at 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, or by email at ocod@fda.hhs.gov.

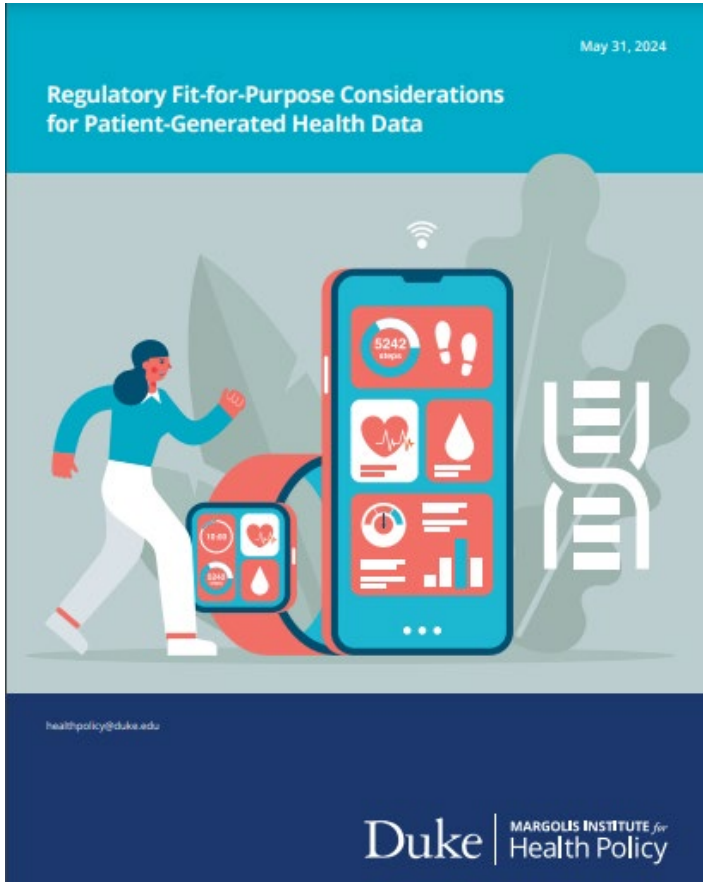
When final, this guidance will supersede "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," issued August 2017.

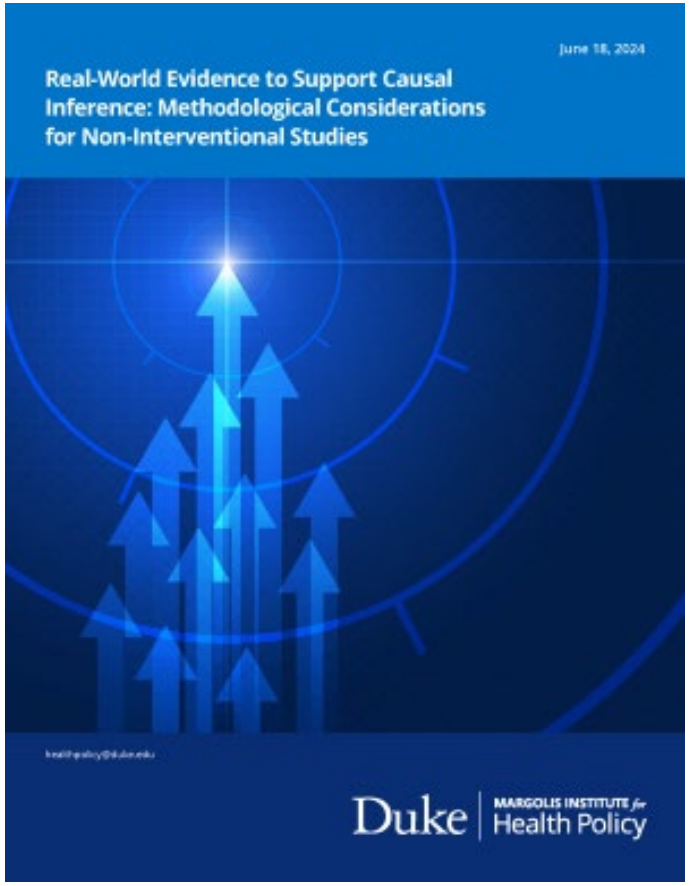
FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

DRAFT

New Duke-Margolis White Paper Publications





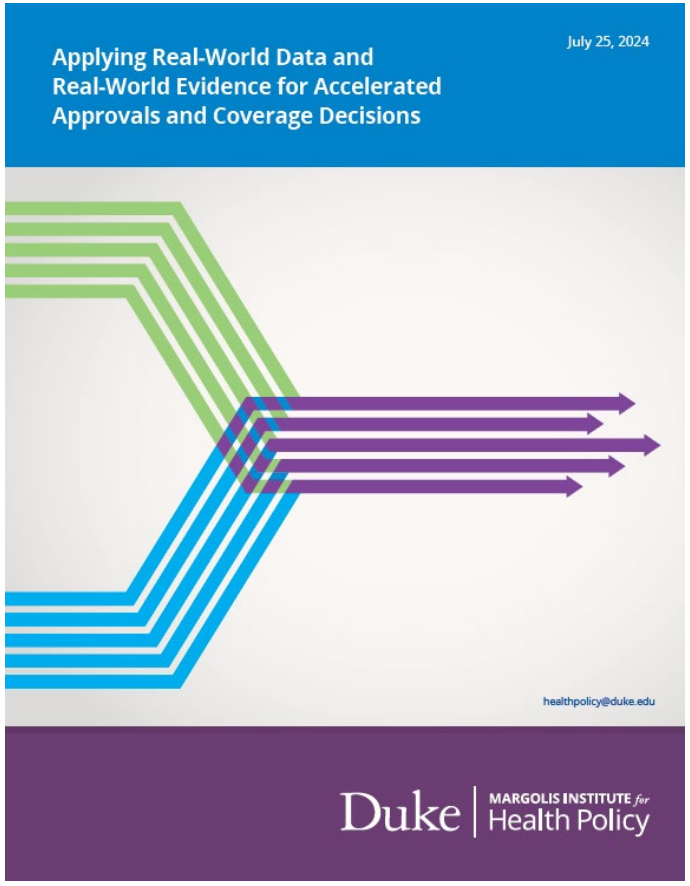


Table 1 | Operational Considerations for Regulatory Fit-for-Purpose PGHD

PGHD Source	Operationalizing Fit-for-Purpose PGHD		
	Relevance *Data availability, timeliness, generalizability, and linkages*	**Reliability** *Data accrual, quality, and integrity*	**Quality** *Accuracy, completeness, and transparency*
Wearables and Mobile App Data	Sponsors should consider data linkages across different wearable and mobile devices that collect the same forms of biometric data, and attempt to standardize related measures.	Developers should ensure that collection methods are accurate, consistent, and systematically processed across users and technological models.	Developers should continuously monitor and improve upon the collection and processing of biometric data, and be transparent about how various pieces of health data are measured, either in discrete or ongoing settings, via wearable devices and mobile apps.
Direct-to-Consumer Genetic Testing Data	Sponsors should provide any relevant and linked supplemental data, such as preexisting conditions, labs, and demographic information to regulatory agencies.	Sponsors and/or the FDA need to discern the clinical validity, a component of reliability of direct-to consumer tests identified by the FDA, before the tests are used in regulatory decision making. Companies should implement verifiable methods to ensure that genetic data are collected in the most reliable and accurate way possible.	Sponsors must consider the logical plausibility of the direct-to-consumer data (whether a data point corresponds to/with a specific genetic variant). Sponsors should evaluate direct-to-consumer tests in accordance with specified data quality assurance plans and procedures.
Patient-Powered Registry Data	Sponsors should identify and confirm preexisting data linkages between a patient-powered registry and other RWD sources, apply a predefined and scientifically valid linkage methodology where needed, describe system interoperability features where they exist, and account for differences in coding and reporting across sources. Sponsors and registry owners should describe measures taken to ensure individual-level privacy in the presence of data linkages.	Sponsors may find value in educating patients who input their data into registries to ensure uniform data collection. Registry owners should establish data dictionaries to provide common definitional frameworks for both researchers and patients who will input their data into the registry.	Sponsors should be transparent about the provenance of data within patient-powered registries, as well as algorithmic transformations to the data.
Patient-Reported Outcomes (PROs) Data	Patient advocates should ensure PRO data are generalizable and inclusive to the target population and/or subpopulation of interest.	Sponsors should confirm PRO data are collected and processed in a consistent and methodologically sound manner.	To ensure data accuracy and completeness, sponsors should ensure data is collected in a thorough and clear manner. Sponsors and patient advocates should provide patients with education and other support needed to accurately capture and report their PRO data. Sponsors should balance the need for data transparency with patient privacy and discretion.

Framework for Causal Inference Studies Using Observational RWD	Key Features & Considerations*
Estimand Framework**	• Structured approach to clarify study objectives and address uncertainties, particularly in the presence of deviations—including intercurrent events like treatment discontinuation or emergency medication use. • Consists of five key attributes: treatment, population, outcome variable, population-level summary, and handling intercurrent events.
Target Trial Framework**	• Grounded in counterfactual theory and offers a structured process for evaluating observational RWD. • Involves specifying a hypothetical RCT's protocol (defining eligibility, treatment/treatment regimen, follow-up periods, outcomes, etc.) and mimicking these components using observational data.
Causal Roadmap Framework	• Explicit, itemized, and iterative process that guides investigators to prespecify study design and analysis plans and addresses a wide range of guidance within a single framework. • Involves seven steps to help investigators prespecify design and analysis plans for studies that utilize RWD.

***While the FDA has mentioned that they do not endorse the use of one causal framework over another, they encourage sponsors to describe their proposed approach to support causal inference and mitigate bias and confounding.**

****Target trial and estimand framework can be combined to help facilitate choices around the best estimand.**

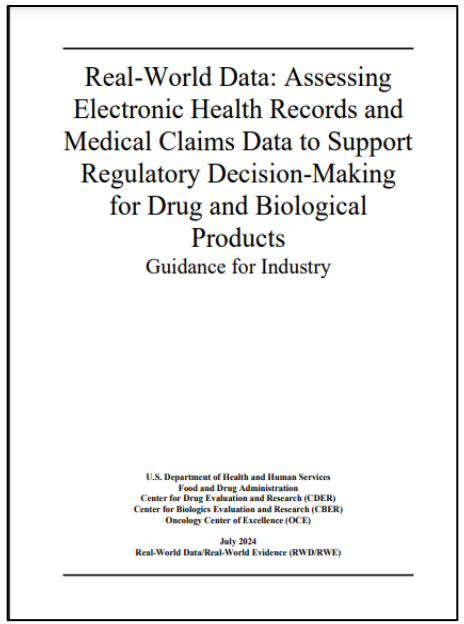
Highlights	Evidentiary Alignment Considerations for Regulators and Payers
Real-World Context in Endpoint Selection	Accelerated approval and payment decisions are context dependent - endpoint and measurement selection must consider reliability, validity, sensitivity to treatment effects, and align with data quality specifications to reflect real-world outcomes to ensure that endpoints are relevant for decision-makers.
Generalizability and Representativeness	Important factors to consider when assessing clinical benefit and value. RWD can provide larger data sources to strengthen the totality of evidence for products granted accelerated approval.
Data Repositories and Registries	Registries can provide information needed to determine sample size, selection criteria, and study endpoints needed to power both initial and confirmatory evidence generation. Using or building registries for the purpose of sourcing or storing fit-for-purpose RWE that is complete, reflective of the patient journey, and available when an appropriate external comparison group could be beneficial.
External Controls	Developing methods to support using historical or concurrent external control data from RWD sources, even where assessment timelines might not align, or uses of hybrid external control arms, where a small control arm of the trial is supplemented by external data to lessen the need for a larger sample size in the control arm.
Postmarket Point-of-care Trials	Under favorable conditions (e.g. products with well understood safety profiles, endpoints that are collectable in routine care), RWE-based approaches, such as point-of-care, may be appropriate to address the limitations of more traditional, confirmatory trial approaches.
Considerations for Private Payers	As concerns about the affordability of new and expensive products continue to rise, payer involvement in evidence generation in postmarket settings will be critical.

Duke | MARGOLIS INSTITUTE for Health Policy

Health Policy in Action

Operationalizing EHR-Sourced Data for Quality, Relevance, and Reliability

Generate actionable recommendations for stakeholders to improve the quality, relevance, and reliability of data found in EHRs.

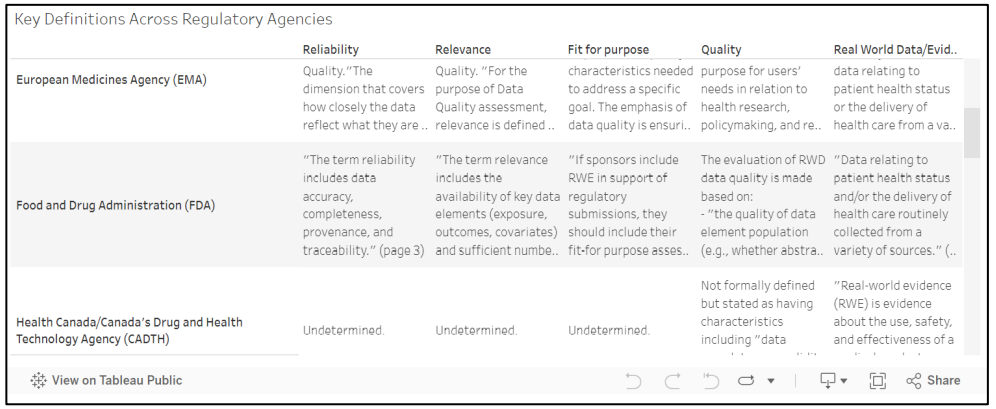


Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products

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)
Oncology Center of Excellence (OCE)

July 2024
Real-World Data/Real-World Evidence (RWD/RWE)



Key Definitions Across Regulatory Agencies

	Reliability	Relevance	Fit for purpose	Quality	Real World Data/Evid..
European Medicines Agency (EMA)	Quality. "The dimension that covers how closely the data reflect what they are ..	Quality. "For the purpose of Data Quality assessment, relevance is defined ..	characteristics needed to address a specific goal. The emphasis of data quality is ensuri..	purpose for users' needs in relation to health research, policymaking, and re..	data relating to patient health status or the delivery of health care from a va..
Food and Drug Administration (FDA)	"The term reliability includes data accuracy, completeness, provenance, and traceability." (page 3)	"The term relevance includes the availability of key data elements (exposure, outcomes, covariates) and sufficient numbe..	"If sponsors include RWE in support of regulatory submissions, they should include their fit-for purpose asses..	The evaluation of RWD data quality is made based on: - "the quality of data element population (e.g., whether abstra..	"Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources." (..
Health Canada/Canada's Drug and Health Technology Agency (CADTH)	Undetermined.	Undetermined.	Undetermined.	Not formally defined but stated as having characteristics including "data	"Real-world evidence (RWE) is evidence about the use, safety, and effectiveness of a

View on Tableau Public Share

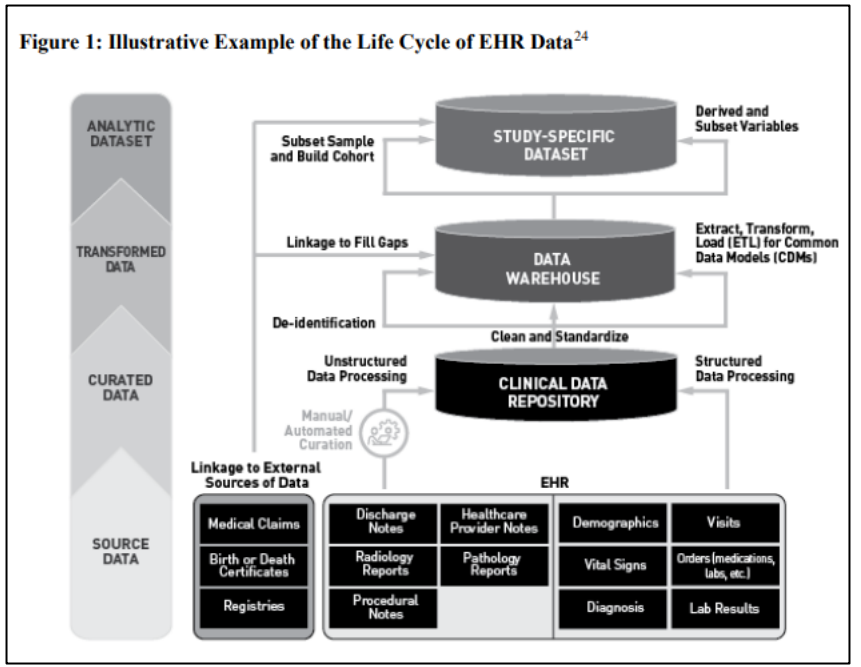


Figure 1: Illustrative Example of the Life Cycle of EHR Data[24]

Duke | MARGOLIS INSTITUTE for Health Policy

Health Policy in Action

When can real-world data generate real-world evidence?

Motiur Rahman, Gerald Dal Pan, Peter Stein, Mark Levenson, Stefanie Kraus, Aloka Chakravarty, Donna R. Rivera, Richard Forshee, John Concato

First published: 19 October 2023 | https://doi.org/10.1002/pds.5715 | Citations: 1

Viewpoint | Integrating Clinical Trials and Practice

June 3, 2024

Why Should the FDA Focus on Pragmatic Clinical Research?

Ali B. Abbasi, MD[1]; Lesley H. Curtis, PhD[1]; Robert M. Califf, MD[1]

Author Affiliations | Article Information

JAMA. 2024;332(2):103-104. doi:10.1001/jama.2024.6227

Comparison of two assessments of real-world data and real-world evidence for regulatory decision-making

Lily Yuan, Motiur Rahman, John Concato

First published: 13 December 2023 | https://doi.org/10.1111/cts.13702 | Citations: 1

Special Communication | Integrating Clinical Trials and Practice

July 1, 2024

Why Evidence Generation Should Matter to Payers and How They Can Help

Ali B. Abbasi, MD[1]; Lesley H. Curtis, PhD[1]; Lee A. Fleisher, MD[2]; et al

Author Affiliations | Article Information

JAMA. Published online July 1, 2024. doi:10.1001/jama.2024.7616

Fireside Chat Introduction & Discussion

Joanne Walker
Co-Founder & Publishing Director
At Becaris Publishing

Laura DiAngelo
Director, Life Sciences Regulatory Policy and Intelligence Division
at Agency IQ By POLITICO

Thank You!

Contact Us

healthpolicy.duke.edu

Subscribe to our monthly newsletter at dukemargolis@duke.edu

1201 Pennsylvania Avenue, NW,
Suite 500 • Washington, DC 20004

DC office: 202-621-2800
Durham office: 919-419-2504

Follow Us

DukeMargolis

@dukemargolis

@DukeMargolis

Duke Margolis

Duke-Margolis Institute For Health Policy

Real-world data/evidence

Policy landscape in 2024

AGENCYIQ
BY POLITICO

July 2024

U.S. FDA: Guidance

The U.S. regulator's current and ongoing work on RWD/E policy in the last few years

Policy	Summary	Status
RWD: Assessing EHR/Medical Claims Data to Support Regulatory Decision-Making for Drugs and Biological Products	Recommendations on the selection, justification of "electronic health data" RWD sources	Draft issued 2021; Finalized July 2024.
RWD: Assessing Registries to Support Regulatory Decision-Making for Drugs and Biological Products	Recommendations on the selection, justification of registry-based sources of RWD	Draft issued 2021; Finalized December 2023.
Data Standards for Drug and Biological Product Submissions Containing RWD	Recommendations on submitting RWD to FDA using existing data standard catalog	Draft issued 2021; Finalized December 2023.
Considerations for the Use of RWD/E to Support Regulatory Decision-Making for Drugs and Biological Products	Recommendations on how the Investigational New Drug (IND) regulations ("part 312") apply for studies leveraging RWD	Draft issued 2021; Finalized August 2023.
Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products	Recommendations on the use of RWD sources for external control arms in clinical trials	Draft issued February 2023.
Submitting Documents Utilizing RWD/E to FDA for Drugs and Biologics	Recommends practice for flagging RWD/E in submission cover letters	Draft issued 2019; Finalized September 2022.

U.S. FDA: Pilots and Projects

The current Prescription Drug User Fee program (PDUFA VII) commitments include several RWD/E related projects for FDA

Advancing RWE Program

- Launched October 2022;
- Will run 2023-2027, with expectations for future policy development.
- Open to drug/biological product sponsors with an IND/pre-IND proposing to use RWE in support of labeling, effectiveness, or post-approval studies.

Sentinel Demonstrations

- In addition to operational improvements to Sentinel, the commitments call for projects:
  - Negative control identification;
  - Double negative control adjustments in vaccine efficacy studies;
  - Pregnancy safety studies.

Workshops and Policy work

- Report on RWE submissions to CBER/CDER so far (June 2024);
- Public workshop or meeting on RWE case studies and regulatory approach for effectiveness decisions (December 2025);
- Guidance updates to CDER/CBER RWE program (December 2026).

E.U. EMA: Policy, projects and reports

The E.U. life sciences regulatory body has several workstreams underway on the use of RWD/E in regulatory contexts.

EMA REFLECTION PAPER

Draft issued May 2024. Focused on RWD in non-interventional studies; public consultation currently open through **August 2024.**

EMA REGISTRY STUDY GUIDELINE

Drafted in 2020, guideline adopted October 2021. Focused on the use of registry-based studies in regulatory decision-making.

RWE GUIDANCE "ROADMAP"

EMA MWP & CHMP workplans call for the development of "a roadmap of RWE guidance" – including (MWP) a landscape analysis, "identify and prioritise" areas of future guidance.

REGULATOR REPORT

Published June 2023, report from EMA on its experience with regulator-led RWE studies from 2021-2023; describes RWE approaches across different regulatory use-cases.

DARWIN EU

EMA's RWD coordination centre, the **Data Analysis and Real World Interrogation Network** (DARWIN). The goal for 2024 is onboarding of 10 additional data partners.

HMA-EMA CATALOGUES

Two online catalogues: RWD sources and RWD studies.
Draft Good Practice Guide for the use of the RWD sources catalogue issued September 2022.

International collaborations: Terminology, pharmacoepidemilogy, etc.

The International Council on Harmonisation

ICH Terminology Paper

- June 2023 Reflection Paper from the International Council on Harmonisation (ICH) called for “a common understanding of the types and scope of RWD and RWE” – citing divergence in definitions across international regulators.
- Co-sponsored by EMA, FDA, Health Canada.

ICH M14 Guideline

- Long-awaited draft guideline issued May 2024
- M14 provides general principles on the plan, design, and analysis of pharmacoepidemiological studies that use RWD for safety assessments.
- Currently under consultation.

ICMRA Collaboration

- ICMRA forum work on RWE policy harmonization;
- 2022 workshop identified four areas:

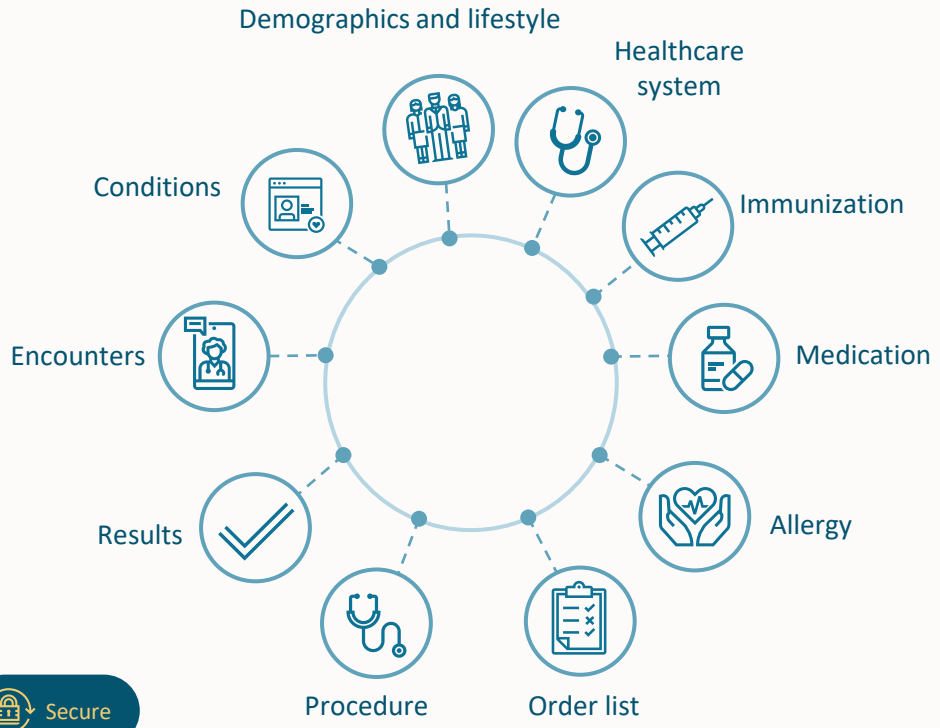
1. Harmonization in terminology (ICH paper);
2. Convergence on RWD/E guidance;
3. Readiness;
4. Transparency.

Session 2: Source Data Access for Decision-Makers

Moderator: **Trevan Locke**, Assistant Research Director, Duke Margolis Institute for Health Policy

Panelists:
Dena Jaffe, Oracle Life Sciences
Stella Chang, OMNY Health
Katy Sadowski, Boehringer Ingelheim
Nicholaas Honig, Aetion, Inc.

Healthcare system direct patient care



Secure

Healthcare system population management

Person Matching & De-duplication Longitudinal data

Data Standardization

Concept normalization

Secure

Data curation for research

Patient & Health System Filtering

Tokenization

De-identification HIPAA Expert Determination methodology

Masking & Generalizations

Secure

De-identified data available to researchers

Real-World Data access

Relevant

Reliable

High Quality

Secure

The materials in this presentation pertain to Oracle Health, Oracle, Oracle Cerner, and Cerner Enviza which are all wholly owned subsidiaries of Oracle Corporation. Nothing in this presentation should be taken as indicating that any decisions regarding the integration of any EMEA Cerner and/or Enviza entities have been made where an integration has not already occurred.

Figure 1: Illustrative Example of the Life Cycle of EHR Data[16]

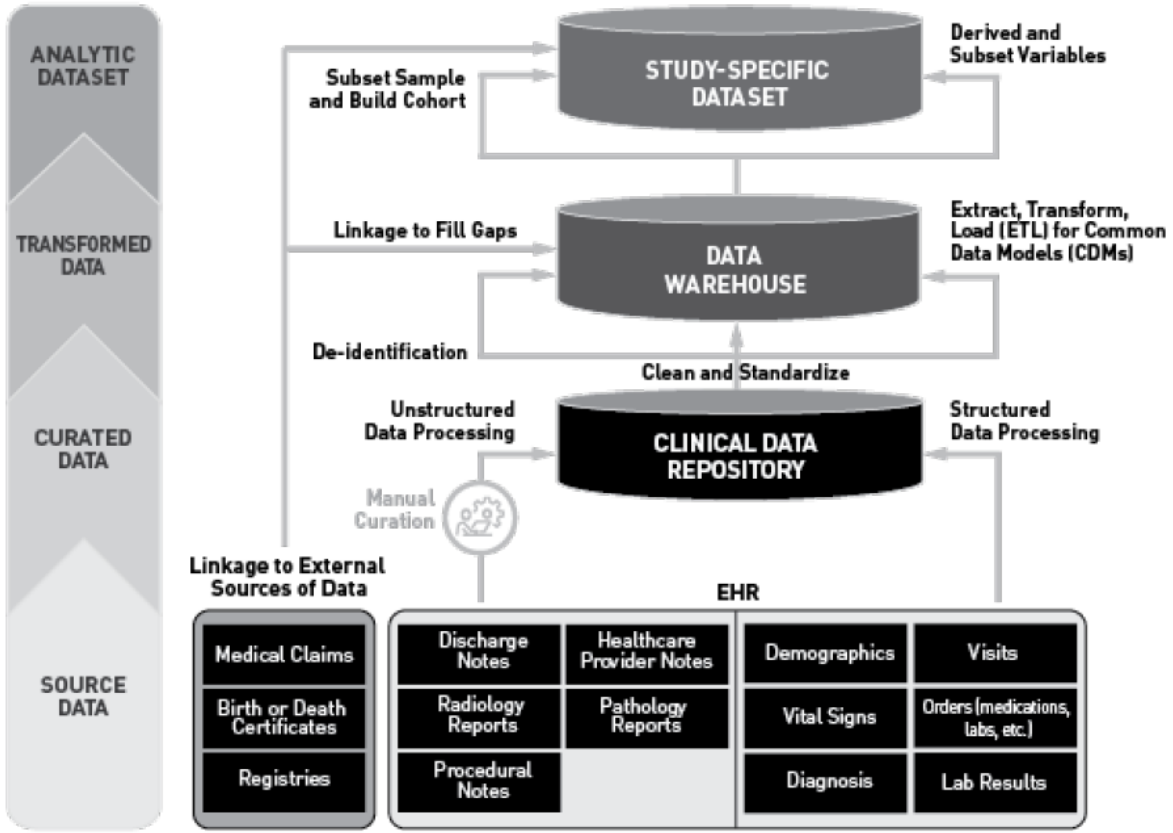


Image from FDA draft guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drugs and Biological Products* (September 2021)

Break

Workshop will resume at **2:30pm ET**

Session 3: Applications of Artificial Intelligence in RWD studies

Moderator: **Christina Silcox**, Research Director, Duke Margolis Institute for Health Policy

Panelists:
David Rhew, Microsoft
Jaime Smith, Parexel
Joe Franklin, Verily Life Sciences
Hussein Ezzeldin, U.S Food and Drug Administration

Session 4: Leveraging RWD for Pricing, Coverage and Payment

Moderator: **Nitzan Arad**, Assistant Research Director, Duke Margolis Institute for Health Policy

Panelists:

Lee Fleisher, Rubrum Advising, LLC

Inmaculada Hernandez, University of California, Skaggs School of Pharmacy and Pharmaceutical Sciences

Rodrigo Refoios Camejo, GlaxoSmithKline (GSK)

Annette James, American Academy of Actuaries

Closing Remarks

Rachele Hendricks-Sturrup, **DHSc, MSc, MA** Research Director of Real World Evidence, Duke-Margolis Institute for Health Policy

Thank You!

Contact Us

healthpolicy.duke.edu

Subscribe to our monthly newsletter at dukemargolis@duke.edu

1201 Pennsylvania Avenue, NW,
Suite 500 • Washington, DC 20004

DC office: 202-621-2800
Durham office: 919-419-2504

Follow Us

DukeMargolis

@dukemargolis

@DukeMargolis

Duke Margolis

Duke-Margolis Institute For Health Policy