The 2024 CRDSA Summit

The Patient Data Revolution: From Promise to Realization

Keynote: Mark McClellan

Director, Duke-Margolis Institute for Health Policy
Former Commissioner, U.S. Food and Drug Administration

Host: Virginia Nido

Global Head, Realization Office and
Industry Collaborations, Roche
CRDSA Co-founder, Past Board Chair

Sessions:

- The (Regulatory) Data Future
- Standards for Secondary Use Research and Data Contribution
- Data Governance and Privacy Methodology: Moving from Confusion to Clarity
- Board Roundtable: The Future of the Data Reuse Ecosystem

CRDSA
Clinical Research Data Sharing Alliance

www.crdsalliance.org

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The Patient Data Revolution
CRDSA Virtual Summit

Mark McClellan MD PhD
February 29, 2024

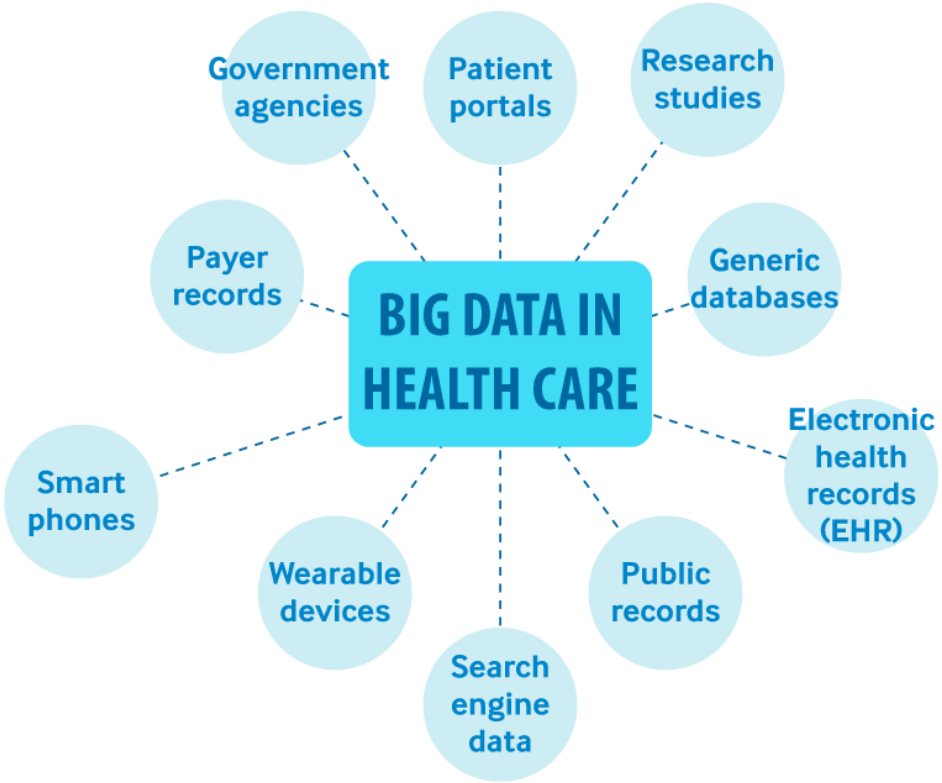
The Duke-Margolis Institute

Launched in 2016, the Institute focuses on:

- Transforming health care
- Driving biomedical innovation
- Educating the next generation

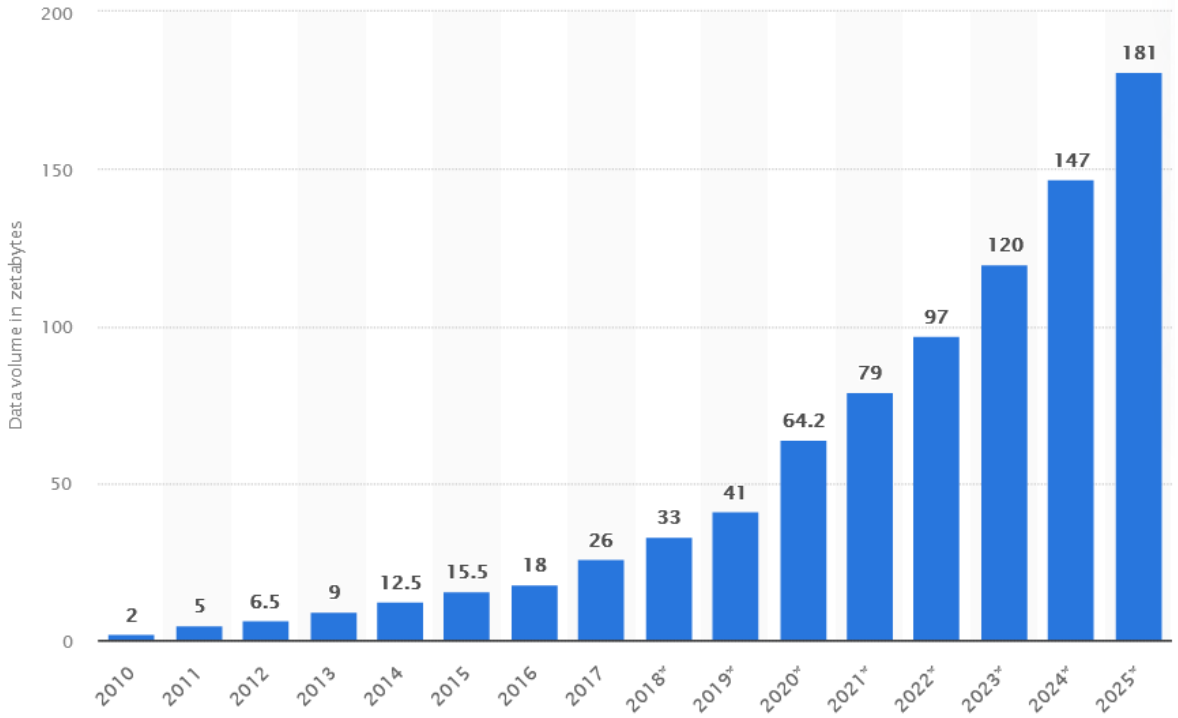
“Brilliant” Future of Big Data: Are We There Yet?

Sources of Big Data in Health Care



NEJM Catalyst (catalyst.nejm.org) © Massachusetts Medical Society

Volume of data/information created, captured, copied, and consumed worldwide from 2010 to 2025



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Additional Information

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https://www.statista.com/statistics/871513/worldwide-data-created/

Real-World Data and Evidence Uses Are Expanding

Lifecycle Approach for Real-World Data and Evidence

1. Medical Product Development

- Inform biological understanding of disease
- Identify unmet need
- Drug selection
- Improve RCT recruitment efficiency

2. Regulatory Review

- Inform PM safety
- Inform new approvals in rare diseases
- Inform indication and labeling decisions

3. Care Delivery

- AI-enabled CDS to personalize dx and tx decisions
- Support patients' engagement in their own care decisions
- Help drive higher-value care

4. Value-Based Payment and Coverage

- Increase stakeholder understanding of value of technology by incorporating RWE
- "De-risk" payment for high cost treatments to increase access

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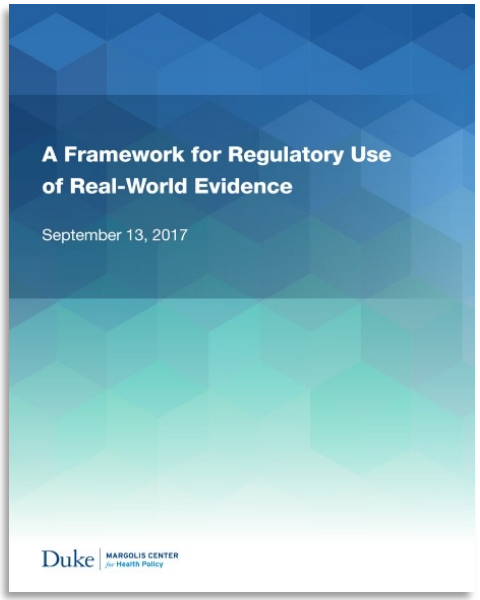

Generating RWE Fit for Regulatory Purposes

Regulatory Context

What specific decision is FDA considering?

- New indication
- Labeling revision
- Safety revision
- Benefit-risk profile

Clinical Context

Can the clinical question be reliably addressed with RWE?

- Prevalence of the disease
- Clinical equipoise
- Expected treatment effect size
- Relevant prior evidence

Data Considerations

Is the real-world dataset fit for regulatory purpose?

1. **Is the data relevant?**
   - Representative of the population of interest
   - Contains key variables and covariates
2. **Is the data of adequate quality?**
   - Minimal missing data
   - Data reliability and validity is satisfactory for study purpose
   - Known provenance and transparency of data processing

Methods Considerations

Are the methodological approaches of sufficient rigor?

1. **Are the methods credible?**
   - Appropriate analytic approach
2. **Can the approach produce actionable evidence?**
   - Interplay of body of clinical evidence and tolerance for uncertainty

Fit-for-purpose RWE

Matching data sources and methods to answer specific clinical and regulatory questions determines applicability of RWE for different regulatory uses

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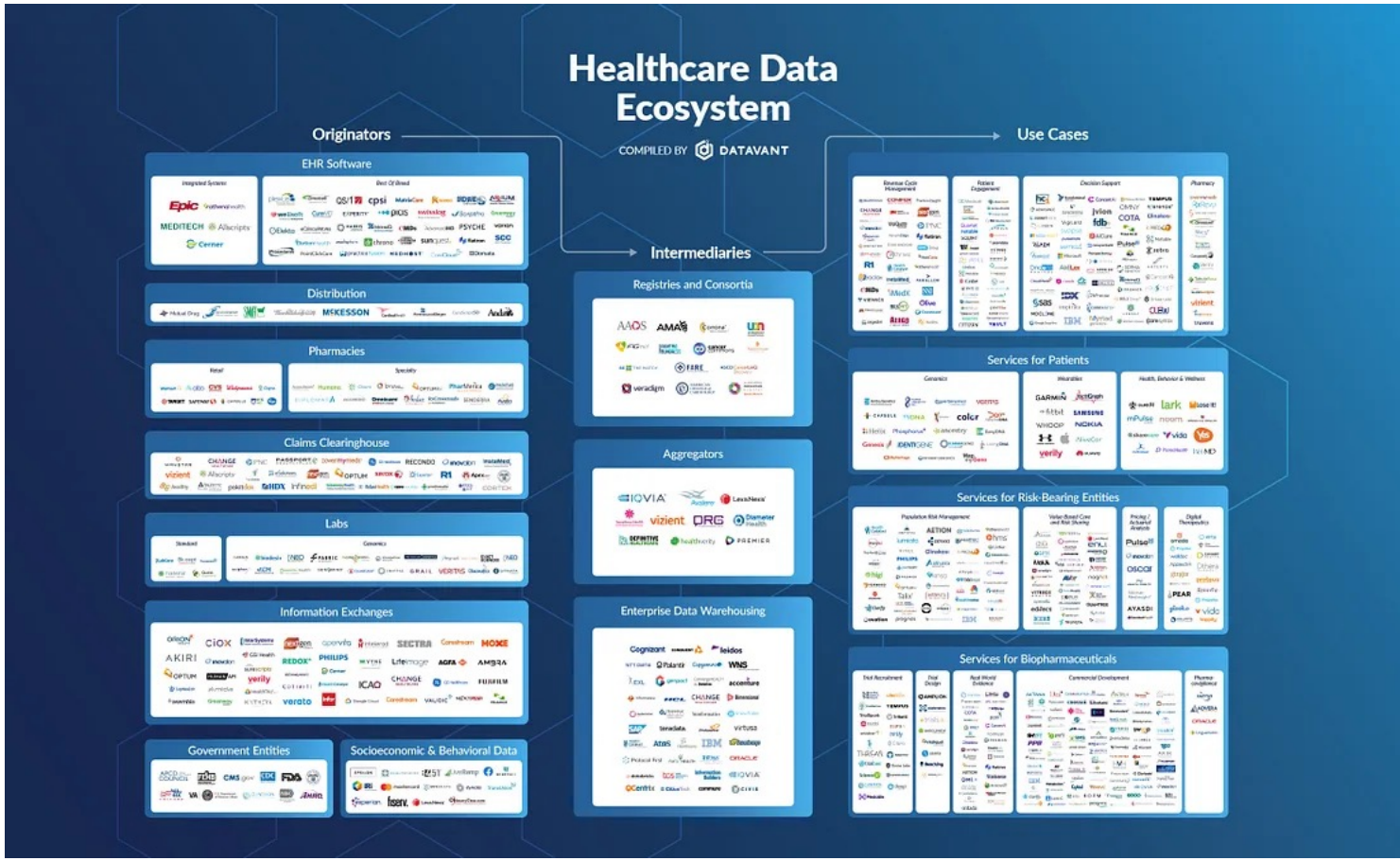
Regulatory Grade RWD/E

OPINIONS+ STAT+

The need for regulatory grade evidence: Are you in the stadium or the sandbox?

By Meg Richards Oct. 28, 2022 Reprints

"One of the most pressing concerns involves what constitutes 'regulatory grade' real-world data and real-world evidence, and when sponsors need to ensure that research conducted using data other than those generated via clinical trials meets the definition of regulatory grade."



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

RWD Audit Readiness Initiative: Landscape Assessment Insights Framework

2020-2021 Literature Review Findings*

DRAFT

Data Relevance

Data Reliability

	RELEVANCE	ACCRUAL	PROVENANCE	COMPLETENESS	ACCURACY
Definition	Robust and representative of the population of interest, and the data elements available for analysis address scientific/ regulatory questions when valid and appropriate analytic methods are applied (PICOTS)	Process by which data are collected/aggregated and patients are included in a study (including record prompts for entry/exit from dataset, operational definitions, and inclusion/exclusion criteria)	Origin(s) of data, sometimes including a chronological record of data custodians and transformations (sometimes referred to as 'data lineage' or 'data traceability').	Presence of all needed and expected elements for a given percentage of data points of an individual variable	Whether data values stored for an object are correct values and stored in consistent and unambiguous form
Documentation	Protocol; Final study report (FSR)	Protocol; Statistical analysis plan (SAP); Data mgmt. plan (DMP); Standard Operating Procedures (SOPs)	Protocol; SAP; DMP; SOPs	Customized report for key variables; DMP; SOPs; FSR	Customized report for key variables; DMP; SOPs; FSR
Gaps	No widely accepted approach for validation	No widely accepted approach (level of detail) or most appropriate place to document	No widely accepted approach (level of detail, structured vs. unstructured) or most appropriate place to document	None evident	Unclear: Validation or verification

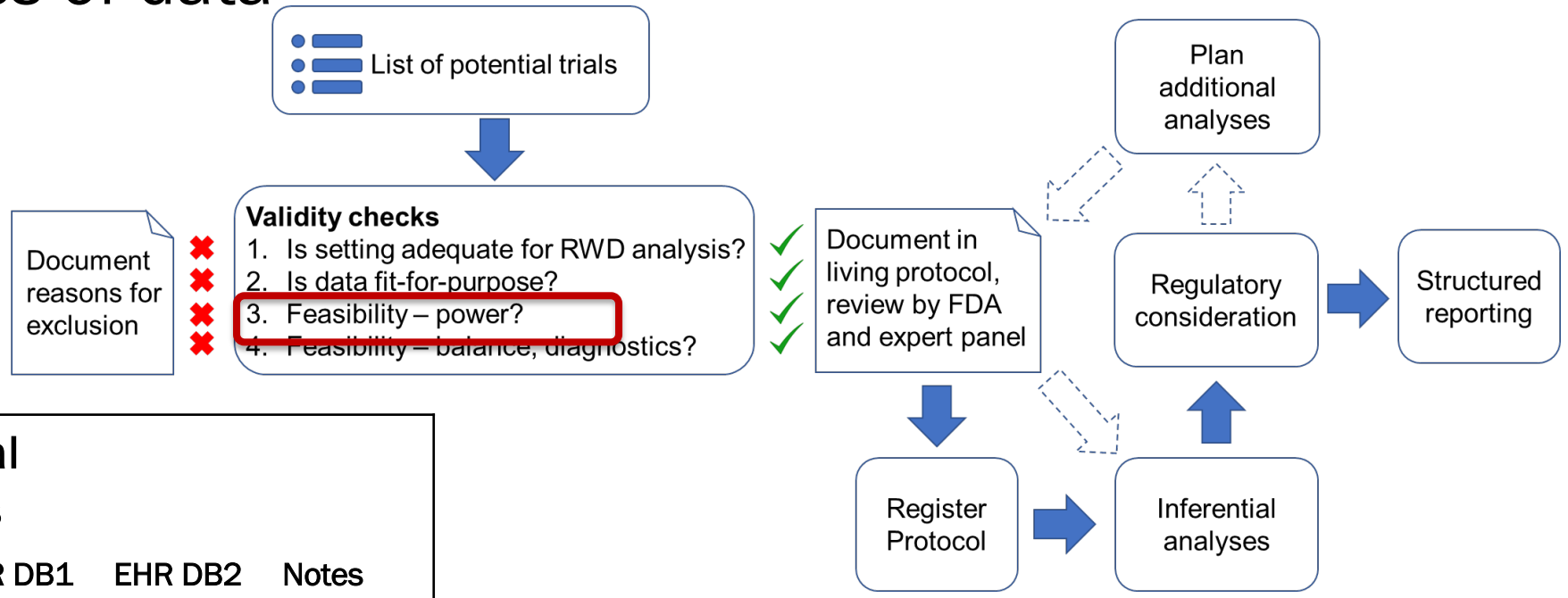
Validation Process

* Insights gathered from targeted literature review, including the following sources: Daniel et al. Characterizing RWD Quality and Relevancy for Regulatory Purposes. Oct 2018; Franklin et al. Evaluating the use of nonrandomized real-world data analyses for regulatory decision making. Clin Pharmacol Ther 2019;105:867; Kahn et al. A Harmonized Data Quality Assessment Terminology and Framework for the Secondary Use of Electronic Health Record Data. Egems 2016;4:1244; Mahendraratnam et al. Determining Real-World Data's Fitness for Use and the Role of Reliability. Sep 2019; US FDA. Framework for FDA's Real-World Evidence Program. Dec 2018

Slide presented by Dr. Cathy Critchlow, DIA, 2022

DIA

Assessing fitness of data



	Operational Definitions			
	RCT	EHR DB1	EHR DB2	Notes
Time 0				
Exposure				
Comparator				
Outcome				
Follow up start				
Follow up end				
Inclusion criteria				
Exclusion criteria				
Effect estimation				
Causal estimand				

Operational definitions

- Where do the algorithms come from?
- What are the performance characteristics?
- Relevance, reliability of data for key study parameters?
- Color code to summarize and help make decisions, fit-for-purpose?

Gatto et al 2022, CPT, SPIFD
Wang et al 2022, PDS & ViH, HARPER

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	•Enable the rapid creation of international expert groups on specific topics of interest •Foster 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

The United States FDA is the only regulatory agency that has released a Real World Evidence Framework.

Key Definitions Across Regulatory Agencies

	Real World D..	Data Quality	Reliability	Relevance	Fit for purpose
Danish Medicines Authority (DKMA)	Undetermine..	Undetermine..	Undetermine..	Undetermine..	Undetermine..
European Medicines Agency (EMA)	"Routinely collected data relating to patient health	"Data quality is defined as fitness for purpose for	EMA defines reliability as it relates to Data Quality."The	EMA defines relevance as it relates to Data Quality. "For	"Possessing all required data quality

+ableau

Lead Topics:
"RWD"
"Reliability"
"Relevance"

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FDA Advancing Real-World Evidence (RWE) Program

- Provides sponsors who are selected into the Program the opportunity to meet with Agency staff—before protocol development or study initiation—to discuss the use of RWE in medical product development.
- Fulfills an FDA commitment under PDUFA VII, incorporated as part of the FDA User Fee Reauthorization Act of 2022

FDA Advancing Real-World Evidence (RWE) Program

- Per FDA, the Advancing RWE Program is designed to:
  - 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; and
  - 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.

Further coordination and collaboration

- **Areas for coordination:**
  - **Infrastructure**
    - Registries
    - Point-of-Care Clinical Trial Platforms
    - Electronic Health Record (EHR) interoperability
  - **Protocols and templates for consistent use of real-world data**
  - **Innovative scientific methods to improve causal inferences**
    - Trial Emulations
    - Subgroup Analyses

- **Keys for coordination**:
  - Harmonizing data standards for ecosystem stakeholders (e.g., regulator and payer)
  - Harmonizing shared stakeholder goals and initiatives in a pre-competitive space
  - Advancing policies to support learning health systems
- **Keys for motivation and momentum for collaboration:**
  - Engaging “use cases” to highlight how initiatives address key evidentiary gaps to motivate collaboration and practical focus
  - Plan for resources to support appropriate and reliable data re-use

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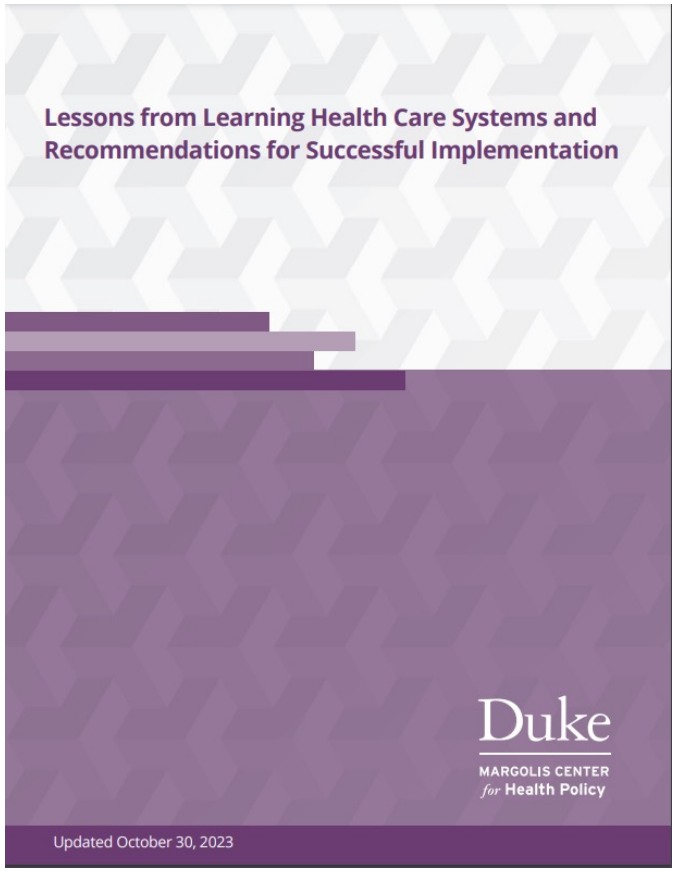
Learning Health Systems and RWD

- Learning health concepts are well known, and could enable reuse of data for regulatory purposes, but implementation varies.
- We explored how RWD is currently used in a cross section of health systems to identify recommendations and considerations for further leveraging RWD to advance learning health care.



Adoption Challenges and Solutions for Building a Learning Health Culture

Current Health System Challenge	Potential Strategy
Administrative and time burden on providers for entering complete data into EHRs.	• Support sustainable uses of infrastructure and digital tools, including wearable devices, to enable easier collection of patient data. • Hire support staff or incorporate new digital tools to manage provider burnout while still collecting complete data.
Lack of staff with data informatics expertise to make use of the RWD collected.	• Partner with data curating firms, academic systems, and consortia that inform and train new and veteran staff in new principles and have participating staff educate their health system colleagues in turn. • Incorporate LHS principles and data analytics into curricula to educate students who will become care providers and health care administrators.
Low patient buy-in and participation in evidence generation.	• Incorporate patient voices and perspectives from the beginning of LHS development. • Ensure patients understand which of their data is being collected, for which purposes, and what is the governance/ownership structure.
Low provider engagement in efforts to leverage RWE to support health system decision-making.	• Collect comprehensive patient-reported outcomes for departments that may lack either internal or external data linkages to show impact. • Foster competition by rewarding better patient outcomes with increased shared savings bonuses.
Siloed data within health systems and lack of interoperability between internal health system data platforms.	• Begin with the EHR(s). Evaluate each EHR's individual interoperability and customization capabilities and look to maturity models such as EMRAM to guide interoperability development. • Revise and/or create system-wide methods and standards for collecting and storing data.

Learning Health Systems: Foundation for Reusable RWD/RWE Platforms

ACT@POC
Coalition for Advancing Clinical Trials at the Point of Care

- The Coalition for Advancing Clinical Trials at the Point of Care (ACT@POC) engages health care systems and their frontline clinicians to integrate clinical research to routine care
- Effort originated from concerns of health system leaders of failure to generate timely needed evidence in COVID-19 through existing clinical trial infrastructure
- Focus extended to address critical gaps in clinically relevant evidence to guide use of new and existing treatments to reduce risks and complications from common chronic diseases
- Three major areas of work:
    - Platform pilot projects
    - Policy updates: regulatory, payment, health system culture
    - Digital tools

actpoc.org

Randomized Trial Approach Continuum: Fit-for-Purpose Clinical Trial Design

Explanatory Trials

Pragmatic Trials

Traditional Trials

Usually in specialized **centers; locations m**ay limit diverse patient participations

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Trial and routine care visits are separate; data from visits may not be shared (e.g. via EHRs)

Accommodates more **complex endpoints** and **detailed data collection**

Hybrid Decentralized Trials*

Study visits may occur outside of specialized centers through telehealth, routine care, or remote site visit, but **often do not fully integrate workflows**

Potential to reach patients and providers who might not engage in traditional research

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Typically feature **centralized administration**

Ability to **leverage virtual components** (e.g. wearables and web portals)

Partially Embedded Trials

May take place where patients receive routine care

Integrates some elements of research into health care delivery

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Potential to reach patients and providers closer to the point of care

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Aligns more closely with clinical workflows

Additional patient follow-up, (e.g., lab visits) may be needed

Point-of-Care Trials

Occurs where patients receive routine care

Integrates with EHR systems for enrollment, randomization, and data collection

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Reaches patients at the point-of-care, providing **virtually indistinguishable** patient experience between research and care

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Fully integrated care and research workflows focused on **streamlined data collection**

ACT@POC

Coalition for Advancing Clinical Trials at the Point of Care

More Complex Protocols, Less Integrated Into Care → **Simplified Protocols, More Integrated Into Care**

**Adapted from* CTTI Recommendations to Sponsors for Planning Decentralized Trials

Improving External Control Arms for Rare Diseases

- External control arms are a promising means of leveraging RWD to inform the development of therapies for rare diseases
- However, as noted in recent FDA draft guidance and ensuing stakeholder responses, there is significant uncertainty about how best to leverage these approaches
- A major challenge is appropriately aligning assessment timing and frequency and differences in care approaches between real world and trial settings.
- Policies that encourage more routine use of health system data to assess care and outcomes for rare diseases, and that better characterize how previously collected external control data (e.g., from clinical trials) matches data from current practice, could help advance rare disease research

Patient-Generated Health Data

- Duke-Margolis white paper to be published March 2024
- Focuses on PGHD relevance, reliability, and quality, highlighting implications for rare disease populations
    - Wearable and mobile app data hold promise to evaluate disease progress and/or interventions. One study explored the use of wearable devices for pediatric rare disease patients, evaluating ambulation of children with Niemann-Pick C (NP-C), Juvenile Idiopathic Arthritis (JIA), Duchenne Muscular Dystrophy (DMD).
    - All three conditions are neuromuscular illnesses, and patients downloaded disease-specific smartphone apps Bluetooth-paired with a wearable device. They then provided PGHD in the form of 30-min epochs that measured average daily maximum steps, average daily steps, and average daily steps per 30-min epoch. This evaluation demonstrates opportunities for child-friendly rare disease progress monitoring solutions through the use of PGHD. The study's findings support PGHD utility in describing sleep impairment as wrist actigraphy was able to monitor both sleep and motor impairment in children with DMD.
- Recommendations a pathway for FDA collaboration with holders of PGHD to develop potentially resusable registries, or databases or platforms that can be the basis for RWE generation, through guidance on key elements of relevance, reliability, and quality

McErlane F, Davies EH, Ollivier C, Mayhew A, Anyanwu O, Harbottle V, Donald A. Wearable Technologies for Children with Chronic Illnesses: An Exploratory Approach. Ther Innov Regul Sci. 2021 Jul;55(4):799-806. doi: 10.1007/s43441-021-00278-9. Epub 2021 Apr 12. PMID: 33844190.

Summary

- Lack of interoperability, expertise, and buy-in has hindered the use of real-world data for regulatory uses, but growing experience and applications for RWD and RWE is changing that
- Supported by stakeholder interests, collaborations, and insights, regulatory and other government agencies are advancing standards and guidance for fit-for-purpose data use for RWE, including reusable data platforms from learning health systems.
- Further work to harmonize standards and advance regulatory guidance for fir-for-purpose data can enable easier reuse of data for secondary research purposes and support more robust observational studies – as well as practical RWD-based randomzised studies
- This includes guidance and incentives to enable reusable RWD platforms that learning health care systems can use to conduct observational and randomized studies, inform clinical guidelines, improve care delivery pathways – and substantially expand regulatory-grade RWD and RWE

Thank You!

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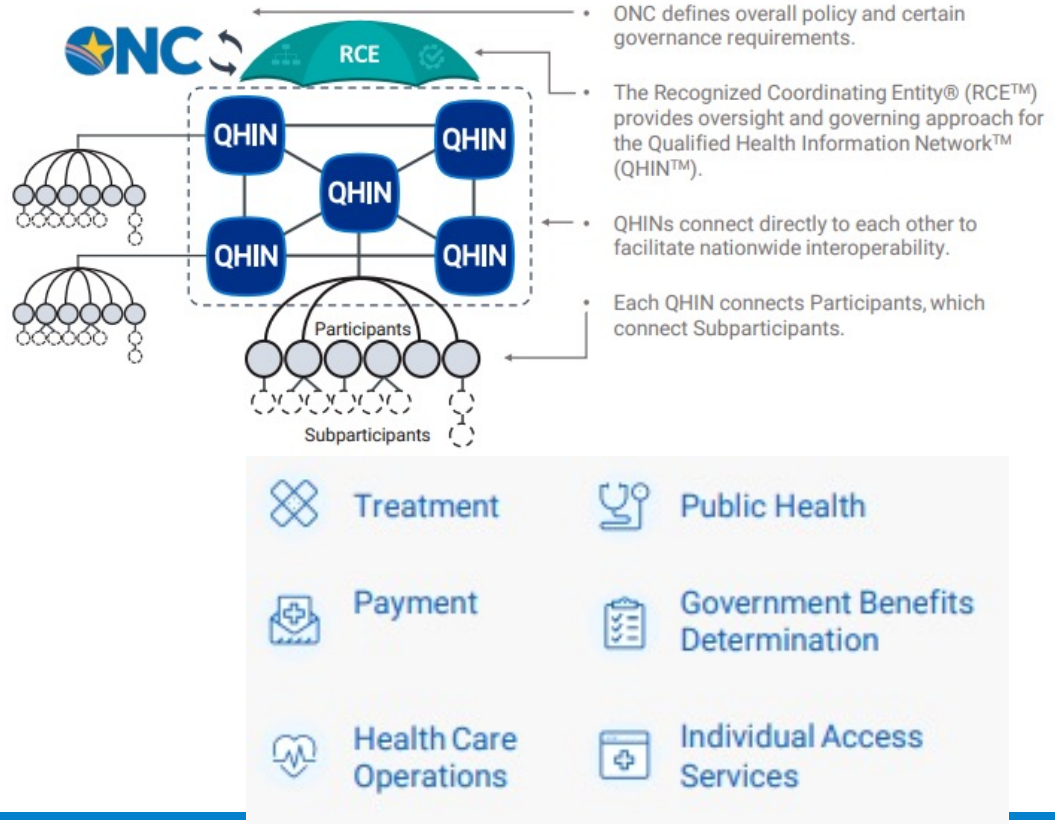
Trusted Exchange Framework and Common Agreement (TEFCA)

Becoming operational in late 2023, TEFCA is intended to establish a nationwide technical floor for interoperability and enable organizations to securely exchange data to drive better patient care and access to data

Currently seven Qualified Health Information Network™ (QHIN™) are part of the agreement and directly connected to facilitate interoperability



https://www.healthit.gov/topic/interoperability/policy/trusted-exchange-framework-and-common-agreement-tefca

USCDI/USCDI+

The United States Core Data for Interoperability and its extensions in USCDI+ are intended to establish a standardized set of data elements to enable nationwide interoperable health data exchange

USCDI+ domains currently include public health, quality, cancer, behavioral health, and maternal health

https://www.healthit.gov/isa/united-states-core-data-interoperability-uscdi

The 2024 CRDSA Summit

The Patient Data Revolution: From Promise to Realization

Session 1:
The (Regulatory) Data Future

Dramatic advances in the data landscape bring both tremendous opportunities and unique challenges. This panel will explore what's on the regulatory horizon, from the use of alternative data sources to novel trial designs to AI-generated evidence.

Gracy Crane
Regulatory Chapter Lead & Regulatory Science Lead (RWD), Global Regulatory Science Team
Roche

Karin Hoelzer
Director of Policy and Regulatory Affairs
National Organization for Rare Diseases (NORD)

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Parexel International

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Thank you!

For additional resources and information, please visit:

https://crdsalliance.org/resources