2022 Duke-Margolis Convening on the State of Real-World Evidence Policy

May 12, 2022

12:00 pm – 5:00pm ET

Duke | MARGOLIS CENTER *for* Health Policy

Welcome & Overview

Mark McClellan, MD, PhD

Director, Duke-Margolis Center for Health Policy

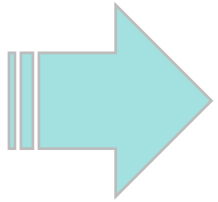
Statement of Independence

The Robert J. Margolis, MD, Center 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.

Key Terms

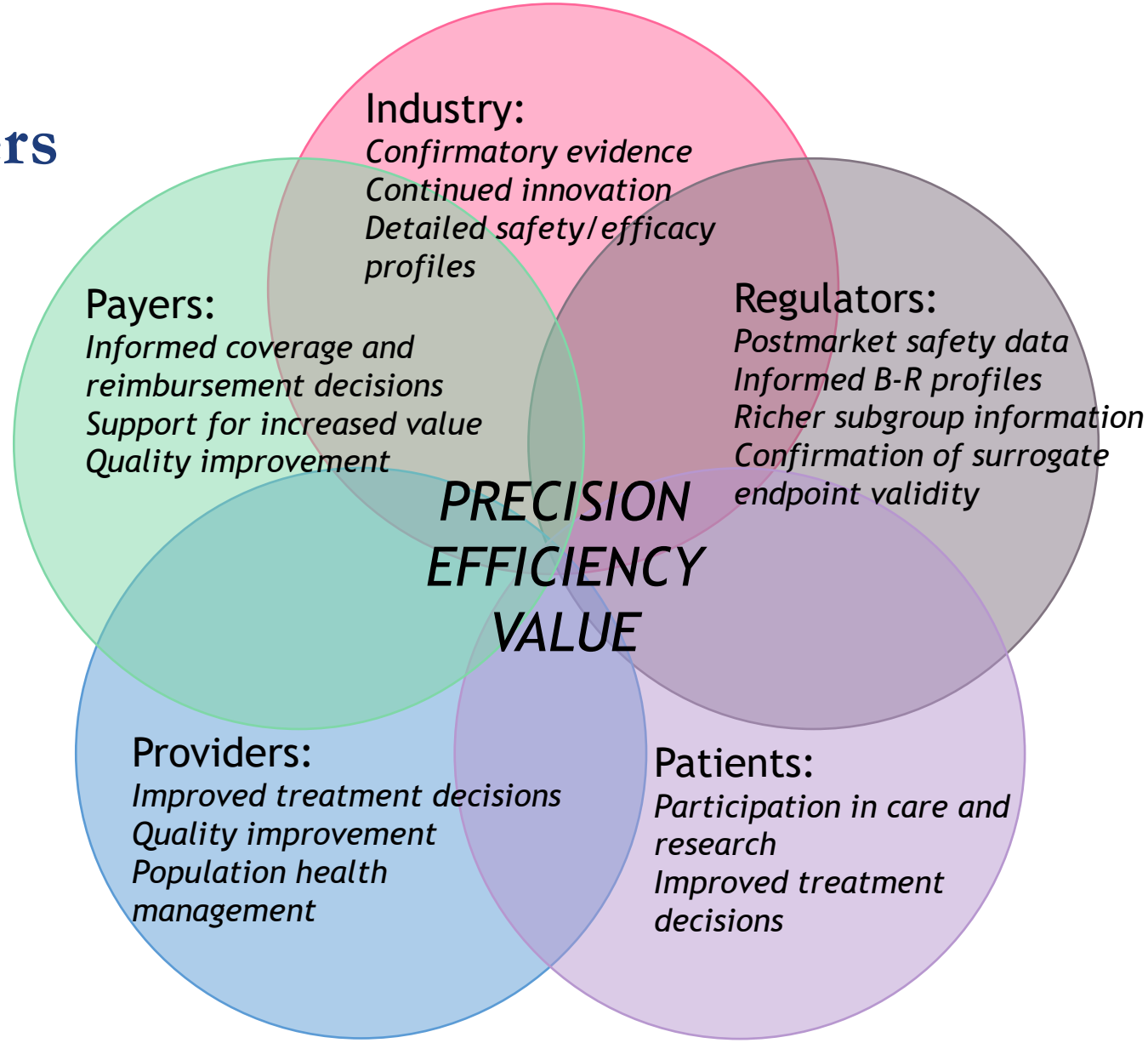
- **Real world data (RWD)** is data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources
  - Electronic health records
  - Payer claims data
  - Registries
  - Mobile apps and digital technologies



- **Real-world evidence (RWE)** is evidence derived from RWD through the application of research methods
- For regulatory applications, RWE can further be defined as clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of RWD

How we define RWD/RWE has follow-on implications for discussing how to develop and use both within stakeholder decision making processes

RWE has value for multiple stakeholders



Duke-Margolis Has Two Complementary RWE Workstreams

RWE Collaborative

The RWE Collaborative engages stakeholders throughout the health care system to guide high-priority efforts aimed at improving the development and use of RWE in regulatory decision-making

FDA-sponsored Cooperative Agreement

Duke-Margolis directly supports the Agency in exploring priorities and commitments through two grants with FDA

Agenda

- Key Note
- Session 1: Advancing Regulatory Acceptability of RWE
- Session 2: Re-imagining Evidence Generation: Opportunities for Developing Shared Evidence and Point of Care Trials
- Session 3: What's Next for the Use of RWE?
  - Panel Discussion 1: Data Considerations
  - Panel Discussion 2: Learning from RWE Pilot Projects

Virtual Meeting Reminders

- Attendees are encouraged to contribute throughout the meeting with questions in the Zoom Q&A function.
  - Audience questions will be incorporated into panel discussions whenever possible

- We also welcome your comments on Twitter, which you can make by tagging @DukeMargolis.

- You can view the meeting agenda, speaker bios, and other meeting materials on our website.

Keynote

Jacqueline Corrigan-Curay

Principal Deputy Center Director in FDA's Center for Drug Evaluation and Research

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RWE and FDA : Moving Forward

Jacqueline Corrigan-Curay
Principal Deputy Center Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Disclaimer

- **Views and opinions expressed are those of the presenter and should not be attributed to the Food and Drug Administration**

- **No conflicts of interest exist related to this presentation**

21st Century Cures Act (2016) – RWE

- **FDA *established* a program to evaluate the potential use of real-world evidence (RWE) to:**
  - **Support a new indication for a drug approved under section 505(c)**
  - **Satisfy post-approval study requirements**
- **Draft framework *issued* in December 2018:**
  - **Describe sources of RWE, challenges, pilot opportunities, etc.**
- **First draft guidances for industry *issued* in September through Dec. 2021**

Background: 'Real-World' Definitions (FDA 2018)

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
- patient-generated data, including from in-home settings
- other sources that can inform on health status, such as "wearable" devices

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 different study designs, including but not limited to randomized trials (e.g., pragmatic clinical trials), externally controlled trials, or observational studies

Current Status of Real-World Evidence

Real-World Evidence — Where Are We Now?

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

<u>Issue being addressed</u>: More than five years after passage of the 21st Century Cures Act, the terms RWD and RWE are being used inconsistently and interchangeably and the lack of precision in our communication about RWE complicates our efforts to assess the impact of such data and evidence and hinders attempts to track their use.

Misconceptions need to be corrected as we continue to work with stakeholders to advance this work through guidance, demonstration programs and identification of applications where RWE is fit for use

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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**

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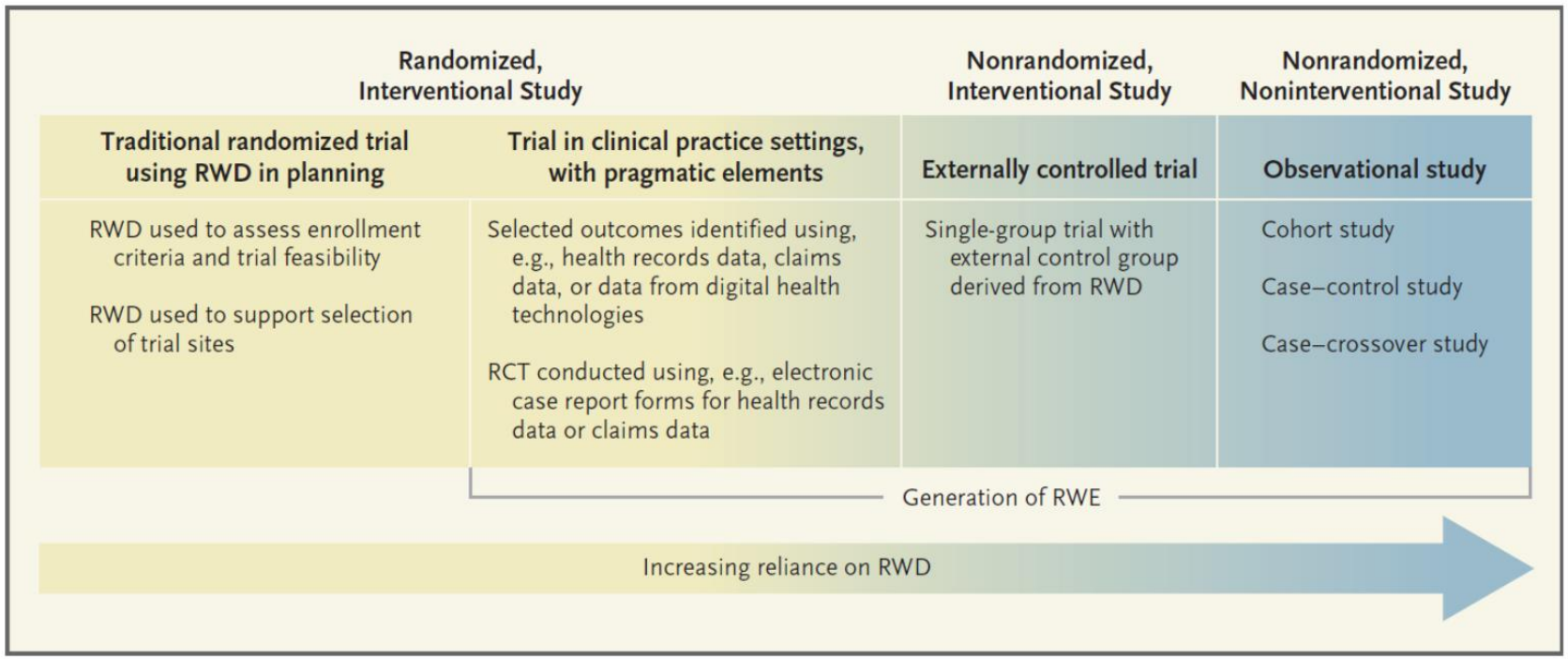
Current Status of Real-World Evidence (cont'd)

<u>Comment on terminology</u>: Including 'RWD' or 'RWE' in the description of a study, by itself, doesn't tell us exactly where the data came from or what kind of study architecture is involved



Reliance on RWD in Representative Types of Study Design.

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

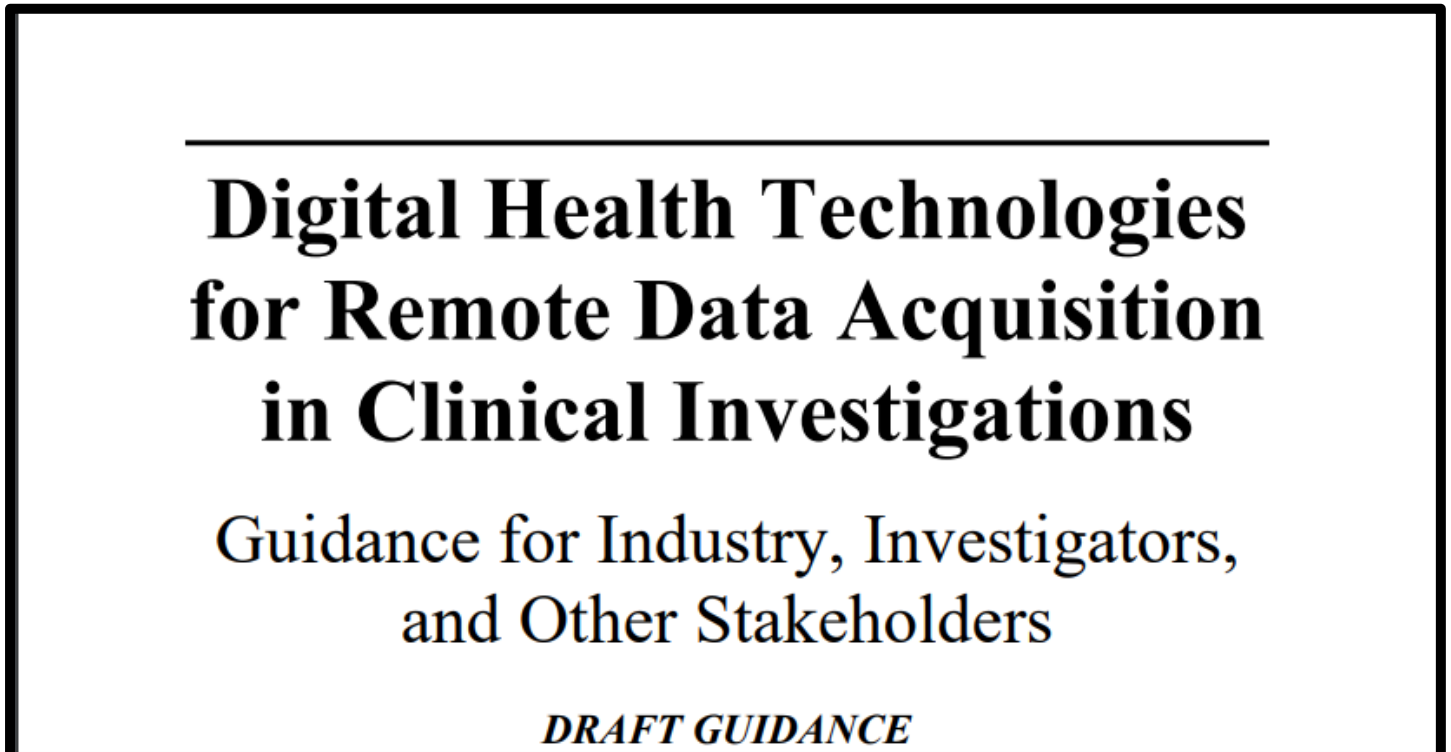
Enabling Point of Care Trials

How do we create a research infrastructure that can support point-of-care trials and provide reliable, persuasive results?

- **Randomization methods suitable for use at clinical sites**
- **If blinding needed – adapted to practices, such as central dispensing to patients**
- **Simpler monitoring – focused on endpoints that matter, but collected reliably**
- **Appropriate safety monitoring – more feasible in later stages of development**
- **Supplement data collection through use of digital tools – in-home collection**

Current Status of Real-World Evidence (cont'd)

<u>Additional comment</u>: Data generated by digital health technologies (e.g., software applications, sensor hardware) don't meet the strict definition of RWD if provided in the context of a clinical trial, but such technologies—when the data they generate are verified and valid—offer considerable opportunities for drug development.



Ongoing RWE Demonstration Projects - Examples

- ‘OneSource’ project
- Linking RCTs w/ RWD
- ‘ICAREdata’ project

- RCT-DUPLICATE trial emulations
- Statistical approaches for RCT designs w/ hybrid controls

- Evaluating confounded treatment effects
- Targeted learning framework for causal effect estimation

Recent RWE Demonstration Project Awards

Funding Opportunity Title ('U01'): Exploring the use of Real-World Data to Generate Real-World Evidence in Regulatory Decision-Making

N=31 applications received; n=4 applications funded

Applicant	Project Title
Brigham and Women's Hospital	Enhancing evidence generation by linking RCTs to RWD
Genentech-UNC	Applying novel statistical approaches to develop a decision framework for hybrid RCT designs, combining internal control arms with data from RWD sources
Verantos, Inc.	Transforming RWE with *U*nstructured and *S*tructured data to advance *T*ailored therapy (TRUST)
Critical Path Institute	Advancing standards and methodologies to generate RWE from RWD through a neonatal pilot project

FDA 'RWE' Guidance: Sep-Dec 2021

Guidance for Industry

DRAFT GUIDANCE

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

Data Standards for Drug and Biological Product Submissions Containing Real-World Data
Guidance for Industry

Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

FDA Guidance on RWD/RWE – 2021

Recent CDER-CBER guidance on RWD/RWE:

"EHR/claims data" draft guidance: Considerations for selecting fit-for-use real-world data from EHR or medical claims databases to help answer research questions of interest. Sep 2021; https://www.fda.gov/media/152503/download

"Registry data" draft guidance: Considerations when designing a registry or proposing to use an existing registry to support a regulatory decision. Nov 2021; https://www.fda.gov/media/154449/download

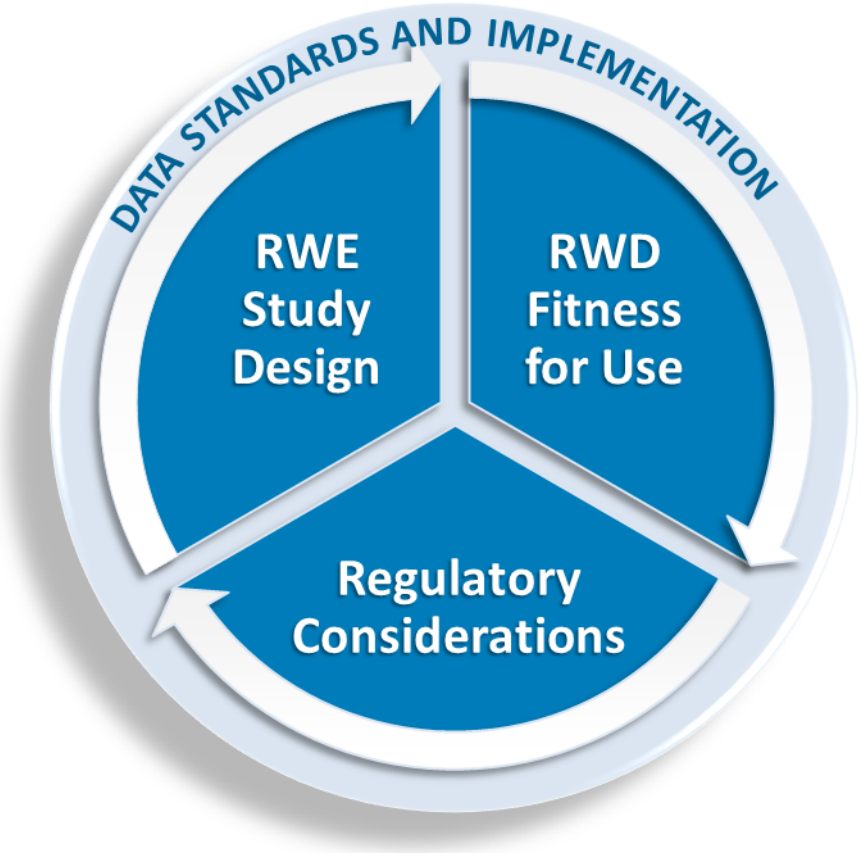
FDA Guidance on RWD/RWE – 2021 (cont'd)

Recent CDER-CBER guidance on RWD/RWE:

"Data standards" draft guidance: Recommendations for complying with the Federal Food, Drug, and Cosmetic Act when submitting study data derived from real-world data sources in an applicable regulatory submission. Oct 2021; https://www.fda.gov/media/153341/download

"Regulatory considerations" draft guidance: Expectations for the design and conduct of non-interventional (observational) studies that are not subject to FDA's investigational new drug regulations. Dec 2021; https://www.fda.gov/media/154714/download

FDA Approach to Evaluating RWE



Key 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**

New Indication for Tacrolimus Based on RWE

- **Prograf® (tacrolimus) approved for prophylaxis of organ rejection in patients receiving liver transplants in 1994 (later for kidney & heart) based on RCT evidence, and the drug is used widely in clinical care**
- **RCTs not done for lung transplant, but sponsor (Astellas Pharma US) submitted supplemental New Drug Application to FDA with non-interventional 'RWE' study**
- **Study data and design were evaluated according to FDA standards**
- **Approval for preventing rejection/death in lung transplant granted 16 Jul 2021**

New Indication for Prograf Based on RWE (cont'd)

Data: US Scientific Registry of Transplant Recipients (SRTR) data on all lung transplants in US during 1999–2017

Design: non-interventional (observational) treatment arm, compared to historical controls

Review: FDA determined this non-interventional study w/ historical controls to be adequate and well-controlled. Of note, outcomes of organ rejection and death are virtually certain without therapy, and the dramatic effect of treatment helps to preclude bias as explanation of results.

RWE IN PDUFA VII – OVERARCHING OBJECTIVES

a. By no later than December 31, 2022, FDA will establish and communicate publicly a pilot Advancing RWE Program intended to:

   i. 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;

   ii. Develop agency processes that promote consistent decision-making and shared learning regarding RWE;

   iii. 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.

RWE IN PDUFA VII – KEY COMPONENT

b. The Advancing RWE Program will include but not be limited to the following activities and components:

   i. FDA will solicit applications for the Advancing RWE Program twice (i.e., two cycles) each year, asking sponsors to describe—before protocol development or study initiation—the regulatory question(s) they seek to address with RWE, the proposed RWE study design, and the potential real-world data (RWD) source(s) to support that design;

   ii. FDA will use a structured review process to evaluate and rank applications, based on the information they present that the data may be fit-for-use, the study design will be adequate, and the proposed study conduct can be anticipated to meet regulatory requirements. Consideration will be given to promoting diversity of data sources, study designs, analytical methodologies and regulatory indications, as well as to diversity of diseases under study and FDA Centers and Offices involved;

RWE IN PDUFA VII: OTHER COMPONENTS

- After establishing the Advancing RWE Program, FDA will also complete the following:

By June 30, 2024:

FDA will **report aggregate data on an annual basis**, anonymously describing program submissions (for CDER and CBER). The reports will include types of data sources used, study designs employed, and 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 RWE Pilot Program to **update existing, or generate new, RWE-related guidance documents**

RWE – Looking Forward

Closing paragraph from recent 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."**

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CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

Session 1: Advancing Regulatory Acceptability of RWE

Moderator:

Rachele Hendricks-Sturrup

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An Overview of Stakeholder Comments to FDA RWE Draft Guidance

Trevan Locke, PhD

Adam Aten, MPH, MSc

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Outline

- Recent guidance overview
- Key themes from comment letters
- Conclusion

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

- Covered the following topics related to the potential use of data from EHRs and medical claims in clinical studies to support regulatory decisions:
  - Selection of data sources that appropriately address the study question and sufficiently characterize study populations, exposure(s), outcome(s) of interest, and key covariates
  - Development and validation of definitions for study design elements (e.g., exposure, outcomes, covariates)
  - Data provenance and quality during data accrual, data curation, and into the final study specific dataset
- This draft guidance did not provide recommendations on choice of study design or type of statistical analysis, and it does not endorse any type of data source or study methodology.

https://www.fda.gov/media/152503/download

Data Standards for Drug and Biological Product Submissions Containing Real-World Data

- Provides recommendations to sponsors for complying with section 745A(a) of the FD&C Act (21 U.S.C. 379k-1(a)) when submitting RWD as study data in applicable drug submissions.
- Addresses considerations for the use of data standards currently supported by FDA in applicable drug submissions containing study data derived from RWD sources.
- States current allowable study data standards found in the Data Standards Catalog

https://www.fda.gov/media/153341/download

Real-World Data: Assessing Registries To Support Regulatory Decision-Making for Drug and Biological Products

- Considers a registry's fitness-for-use in regulatory decision-making, focusing on attributes of a registry that support the collection of relevant and reliable data
- Considerations when linking a registry to another data source for supplemental information, such as data from medical claims, electronic health records (EHRs), digital health technologies, or other registries
- Considerations for FDA review of submissions that include registry data

https://www.fda.gov/media/154449/download

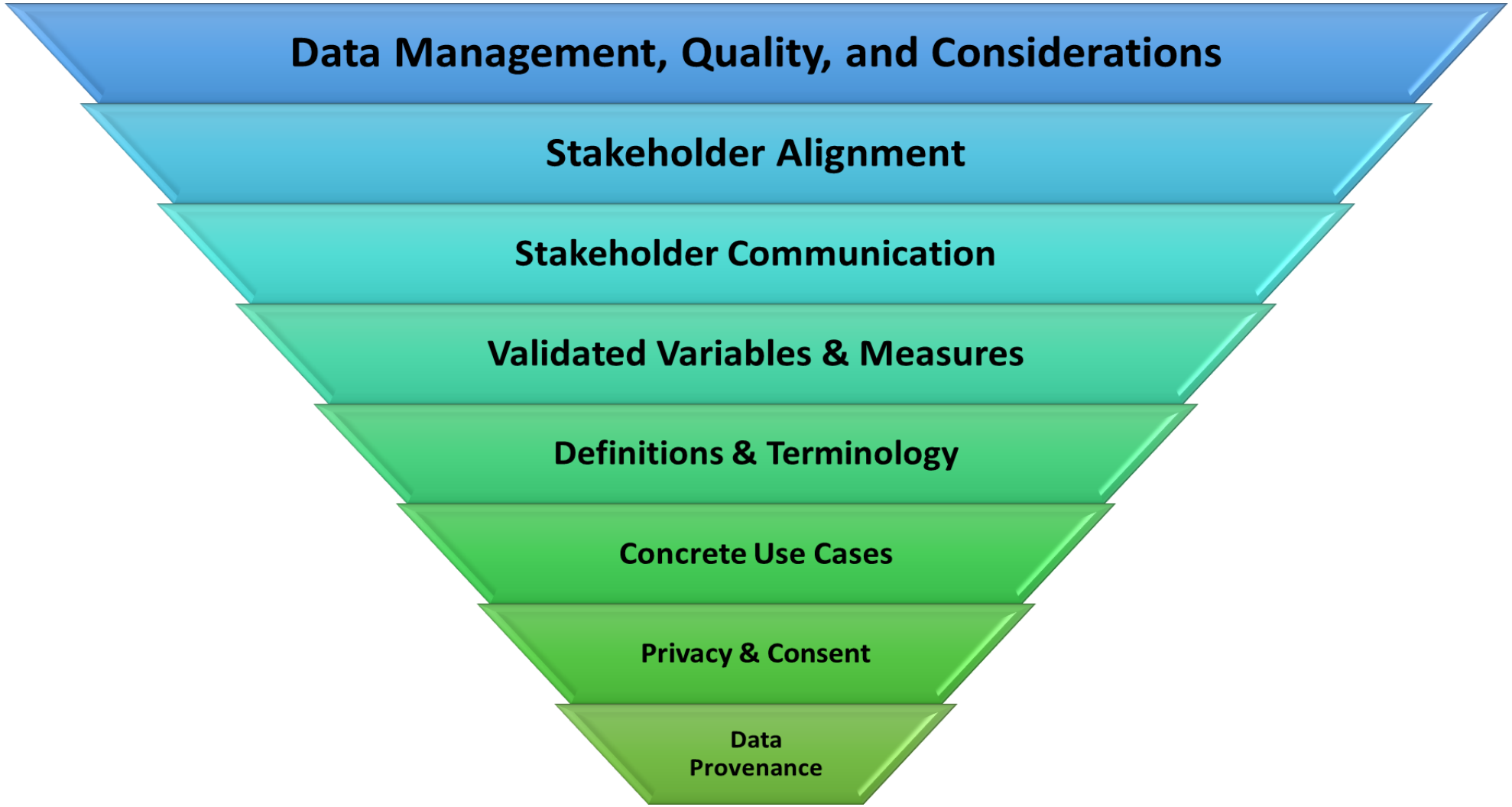
Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

- Discusses the applicability of FDA's investigational new drug application (IND) regulations under part 312 (21 CFR part 312) to various clinical study designs that utilize RWD.
- Clarifies the Agency's expectations concerning clinical studies using RWD submitted to FDA in support of a regulatory decision regarding the effectiveness and safety of a drug (e.g., as part of a new drug application (NDA) or biologics license application (BLA)) when such studies are not subject to part 312.
- Focuses primarily on clinical study designs that are non-interventional.

https://www.fda.gov/media/154714/download

Public Stakeholder Comments: Key Themes and Broad Domains

Key Action Themes: Public Stakeholder Comments



Broad Action Domains Based on Stakeholder Comments

- **Stakeholder Alignment and Shared Understanding of RWD**
  - Communication between key stakeholders
  - Harmonizing defined terminology
- **Overarching Data Considerations**
  - Data source type considerations
  - Linking RWD sources
  - Data provenance
  - Data privacy and consent
- **Standardization, Technology, and Analytical Methods**
  - Data standards and technology
  - Analytical approaches for curation, data mapping, and transformation
  - Validation of measures and variables
- **Trust and Transparency**
  - Documentation needs to support regulatory review and enable study replication
  - Protocol readability
- **Concrete Use Cases**

Stakeholder Alignment and Shared Understanding of RWD

Communication Between Key Stakeholders

- To date, RWD/RWE advancement has been driven by stakeholder collaboration.
- Despite progress, comment letters make clear that there is still a need for stakeholders to align on a range of topics from data standards, to validation methods, to data privacy.
- Likewise, government stakeholders at the FDA and other agencies need to continue aligning on expectations for RWD and RWE and make clear those expectations not only to sponsors, but other owners of RWD sources.

Harmonizing Defined Terminology

- Concepts like “interoperability” and “traceability” could still benefit from consistently accepted definitions.
- Need clarity between “registry” and “registry-based study”
- While there are similarities, these data sources have unique considerations for use. Particularly for EHR and claims data, there are opportunities to clarify their strengths and weaknesses in further work.

Overarching Data Considerations

Data Source Type Considerations

Electronic Health Records

- Unable to ascertain certain information without linkage to other sources, but interoperability rules should enable easier linkage between EHR systems
- Room to consider similarities/differences with data captured electronically for clinical trials

Claims Data

- Claims data is broad and there may be unique considerations for medical claims versus pharmacy claims
- Providing background information on claims data aggregated from many health systems may be unfeasible.

Registry Data

- Unique considerations for adapting existing registries vs. developing new purpose-built registries.
- Need clearer delineations on responsibilities for sponsors and registry managers.
- Encourage new registries to cover outcomes not traditionally found in other sources (ex. PROs)

Linking RWD Sources

- Gaps and fragmentations exists within these data sources, so data linkage is vital to building more comprehensive datasets.
- However, linking comes with challenges as well including differences in data source purpose as well as accurately matching individual patient records - including the privacy considerations that come with that.

Data Provenance

- Data systems change overtime to meet enterprise needs. The impact of these changes on determining data provenance needs to be a key consideration for studies that span multiple years.
- Any use of patient level data for provenance information should have appropriate patient privacy protections in place.

Data Privacy and Consent

- As noted throughout this presentation, there are important privacy considerations in multiple aspects of RWD use.
- Community needs to work together to develop appropriate privacy frameworks including processes for patients' consenting to their data being used.
- For RWD to be the most successful, the stakeholder community must work to implement patient privacy protections that also enable RWD-powered research

Standardization, Technology, and Analytical Methods

Data Standards and Technology

- Current data standards specified in the Data Standards Catalog may not align fully align with standardization needs for RWD sources.
  - FDA Data Catalog standards: CDISC controlled terminologies are geared towards data collection efforts for clinical trials (e.g., MedRA and WHO Drug vocabularies).
  - RWD example standards: SNOMED, RxNorm, HL7 FHIR

- Potential opportunities to consider alternate approaches resulting from improving technology innovations that can enable insights to be gained from source data in its native format.

Analytical Approaches for Curation, Data Mapping, and Transformations

- Need for a shared understanding of appropriate approaches to curate RWD and data mapping from RWD standards to FDA approved submission standards.
- Acceptable analytic approaches for data missingness and utilizing proxy variables.
- Stakeholder understanding needed on what constitutes 'regulatory grade' data quality to align data practices with reliability requirements.

Validation of Measures and Variables

- Stakeholder collaboration needed to improve understanding of how validation might apply to different RWD sources.
  - Potentially unique to specific RWD sources and when linking RWD sources.
  - Can be specific to data standards or common data models.

- Metrics for evaluating algorithm performance.

Trust and Transparency

Documentation Needs to Support Regulatory Review and Enable Study Replication

- Describing the suitability of RWD sources, analytical approaches, methods considerations, and key decisions.
- Different dimensions of documentation:
  - Background on health systems.
  - Approaches for data model mapping, cleaning data and transformations, data missingness, etc.
  - Quality metrics and validations.

Protocol Readability and Reproducibility

- Where does this documentation go in the protocol?
- Increasingly important to find ways to improve the readability of the protocol.
- Increasingly important to have transparency mechanisms in place to support the reproducibility of results.

Concrete Use Cases

Concrete Use Cases

- Developing examples of successful or unsuccessful use of RWD and RWE can help practically address these challenges and provide greater comfort to the larger stakeholder community on the value of RWD and RWE
- Use cases to examine and illustrate data quality, study designs, and supporting tools are key to progress.

Example: RCT-DUPLICATE

- Led by Brigham and Women's Hospital in collaboration with U.S. FDA and Aetion.
- Strategic goal: Better understand and improve the validity of RWE studies for purposes of supporting regulatory decision making.
- Approach: Emulated 30 RCTs using clinical practice data and rigorous epidemiological methods to compare treatment effect estimates.

https://rctduplicate.org/

Example: Friends of Cancer Research RWE Pilot Projects

- Use case focused on establishing the utility of real-world endpoints and framework for evaluating their use.
- Strategic goal: Gain experience using curated data to determine how real-world endpoints correlate with major oncology clinical trial endpoints.
- Approach: Work with a multi-stakeholder set of partners to develop datasets to apply real-world endpoints definitions and analysis methods.

https://friendsofcancerresearch.org/rwe/

Conclusions and Next Steps

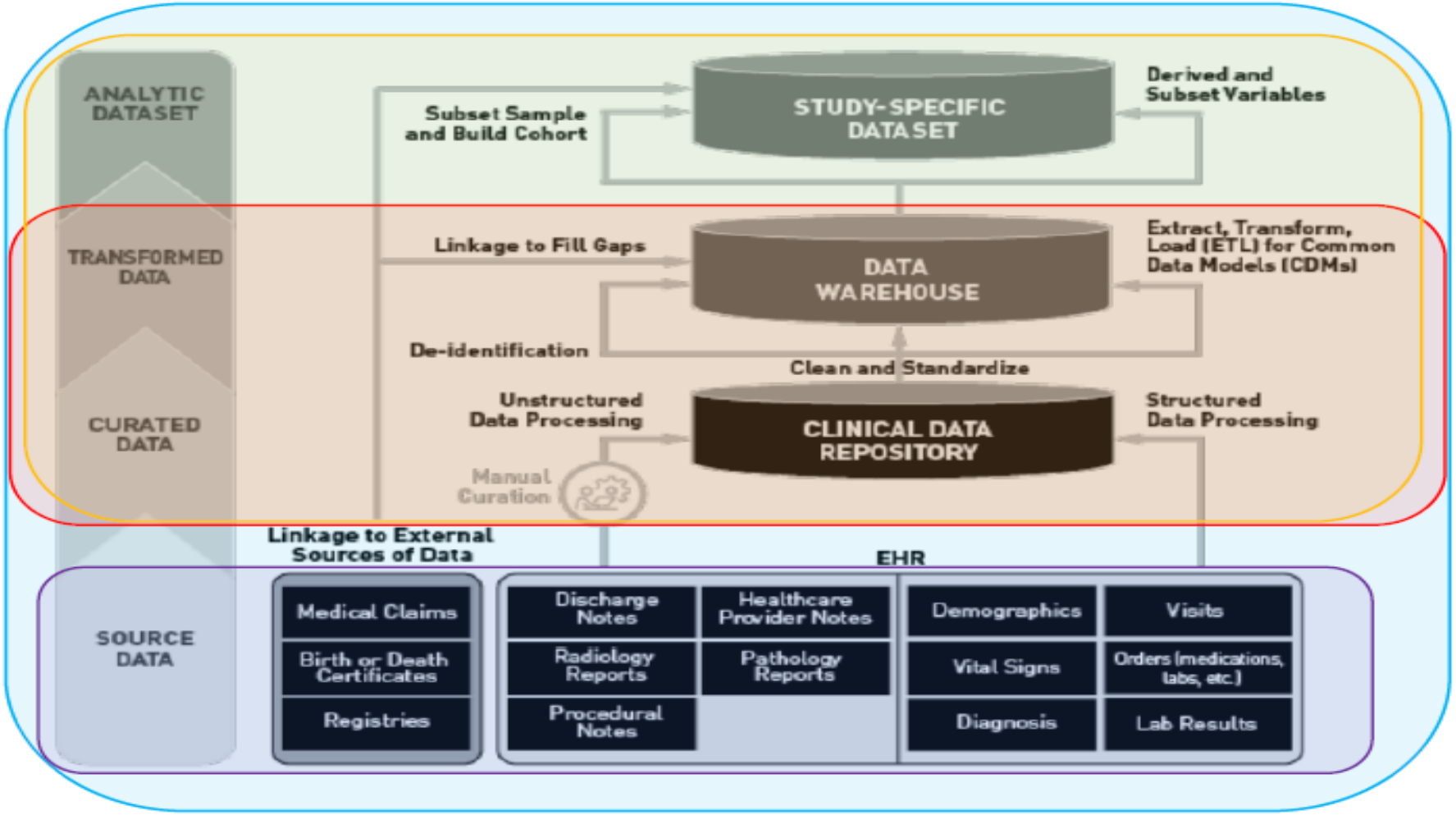
Visualizing Key Themes

Trust and Transparency

Stakeholder Alignment and Shared Understanding of RWD

Standardization, Technology, and Analytical Methods

Overarching Data Considerations



https://www.fda.gov/media/152503/download

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Conclusions and Next Steps

- Strategic efforts are needed to build on the areas of stakeholder consensus and alignment discussed today, which can serve as guiding themes for multi-stakeholder collaborations involving RWD/RWE.
- The following panel will further explore these topics to kick off the rest of the day's discussion.

Session 1: Advancing Regulatory Acceptability of Real-World Evidence

- **Angela Dobes,** Vice President or IBD Plexus, Cohn's & Colitis Foundation
- **Nancy Dreyer,** Senior Vice President and Chief Scientific Officer for Real World Evidence, IQVIA
- **Jeremy Rassen,** Co-Founder and President, Aetion
- **Nicole Mahoney,** Executive Director for Regulatory Policy, Novartis
- **Richard Willke,** Chief Science Officer, ISPOR

ISPOR/ISPE Joint Special Task Force on Real-World Evidence in Healthcare Decision Making

VALUE IN HEALTH 20 (2017) 1003–1008

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

ELSEVIER

Original Report

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

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

PDS Pharmacoepidemiology & Drug Safety

ORIGINAL REPORT

Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0

Shirley V. Wang[1,2] | Sebastian Schneeweiss[1,2] | Marc L. Berger[3] | Jeffrey Brown[4] | Frank de Vries[5] | Ian Douglas[6] | Joshua J. Gagne[1,2] | Rosa Gini[7] | Olaf Klungel[8] | C. Daniel Mullins[9] | Michael D. Nguyen[10] | Jeremy A. Rassen[11] | Liam Smeeth[6] | Miriam Sturkenboom[12] |

on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making

Transparency of Study Processes

Reproducibility of Study Implementation

Real-World Evidence Transparency Initiative

RWE Registry www.ispor.org/RWEregistry

Break

We will be back momentarily.

The next panel will begin at 2:10 p.m. (U.S. Eastern Time)

Session 2: Re-imagining Evidence Generation: Opportunities for Developing Shared Evidence and Point of Care Trials

Moderator:

Rachele Hendricks-Sturrup

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Key Insights From the Latest and Forthcoming Duke-Margolis Real-World Evidence White Papers

Dr. Rachele Hendricks-Sturrup

Research Director, Real-World Evidence

An Overview

- Introduction
- Point-of-Care Clinical Trials: Integrating Research and Care Delivery
- Aligning to Address Shared Evidentiary Needs Among Payers and Regulators

Point-of-Care Clinical Trials: Integrating Research and Care Delivery

Point-of-Care Trials Landscape Review: Key Initial Findings

- Point-of-care trials are not consistently defined in the literature.
  - Often-recognized key components include integration with EHR and conduct in usual care conditions.
  - Additional often-used components include randomization at the health care encounter, elimination of research-only visits, and utilization of Bayesian adaptive methods.
- Point-of-care trials that have already been conducted provide insight into the successes and challenges of the model.
  - Key exemplar trials: VA insulin study, Retropro, eLung, MOMs, and INFANTs studies.
  - Clinicians noted that regulatory and technological challenges were the most obstructive factors to the point-of-care approach.
  - Overall, participating clinicians were supportive of the model and see these trials as an important step toward establishing a learning health care system.

Point-of-Care Trials White Paper: Establishing a Definitional Framework

- A point-of-care trial is not a type of trial design, but rather an operational approach to integrate clinical research into routine health care delivery
- The point-of-care approach:
  - Can be used to support different types of trials, including pragmatic and explanatory trial methodologies.
  - Focuses on enhancing key clinical trial operations (including patient screening, consent, randomization, and data collection) and their incorporation into routine care that can be applied to various trial methodologies.
- Fundamental components of point-of-care trials include:
  - EHR integration to facilitate multiple aspects of the trial (e.g., enrollment, randomization, and data collection).
  - Trial is completed in usual care conditions.
  - Integrating research into clinical workflows.

When is the point-of-care approach appropriate?

1. What types of interventions and therapeutic areas might be well-suited for trial conduct in routine clinical care settings?
2. What procedures might be needed beyond routine care and how can these procedures be integrated without interrupting clinician workflow?
3. What clinical endpoints and available covariates can inform effectiveness and be reliably captured in practice (and if endpoint measurement would be influenced by a lack of blinding?
4. Would safety monitoring for the product as part of clinical practice be sufficient and adequately recorded?
5. Are systems in place to extract the RWD reliably?
6. Are source records available for inspections to support data provenance?

Point-of-Care Trials White Paper: Next Steps in Improving and Scaling the Approach

- Solutions for improving the point-of-care approach:
  - Supplement EHR data with other sources (i.e., PROs, wearables)
  - Use data surveillance systems and establishing a minimum set of common data elements
  - Align incentives internal and external to health systems
  - Adopt a risk-proportionate regulatory framework
  - Streamline eligibility criteria and the consenting process
- Solutions for scaling the point-of-care approach:
  - Secure key investments in reusable trial infrastructure
  - Align incentives to support trial networks that will monitor long-term patient outcomes
  - Create an engagement framework to build capacity for future point-of-care research
  - Create a national point-of-care trials network and hub to establish standards for data collection, tools, and supports
  - Develop ongoing partnerships between sponsors, clinicians, patients, and other stakeholders
  - Foster a culture of patient engagement and trust

Aligning to Address Shared Evidentiary Needs Among Payers and Regulators

Shared Evidentiary Opportunities

- Data requirements for stakeholders is largely dependent on how they use the data, which can result in parallel data collection efforts at the provider level.
- Efforts to generate evidence across stakeholders are often misaligned, which can result in duplicative efforts and increased administrative burden for providers.
- There is significant overlap in actual datapoints being collected.
- There is an opportunity to develop a common protocol or a dataset across disease spaces that have similar evidentiary characteristics and that addresses multiple stakeholders' data requirements.

Why Evidence Alignment is Important

- Data generated for FDA approval may not be sufficient to inform payer coverage or clinical decision making.
- The long-term safety, effectiveness, and durability of treatment effect for newly approved therapies is often unknown at the time of market approval.
- Consequently, payers may not have sufficient evidence to determine whether the technology is appropriate for some or all segments of the beneficiary population.
- Providers may also lack sufficient evidence to understand patient, practice, and facility level variables that impact outcomes to make treatment decisions.

Systematic combinations of real-world data with clinical trial data for novel or newly approved therapies will produce real-world evidence that is insightful to payers, regulators, and other key stakeholders.

Key Themes and Considerations

- Post-regulatory approval evidence generation to inform payer and regulator decision-making.
- Data system interoperability to facilitate the use, sharing, and exchange of RWD across multiple systems.
- Linking databases to maximize data analysis capabilities.
- Standardized endpoints and outcomes measures to evaluate real-world effectiveness.

Key Themes and Considerations, cont.

- Strategic partnerships to facilitate data collaborations and sharing.
- Building on existing databases as a starting point toward more robust data collection.
- Payment models and incentives to support long-term RWD collection and analysis.
- Data governance and management are ongoing challenges yet are critical to generating shared evidence.

Policy Recommendations and Key Takeaways

- Provide resources needed to support electronic health record interoperability between clinical research networks and central claims data repositories.
- Fund initiatives that focus on not only safety, but also effectiveness (e.g., registries or observational studies that monitor the safety and effectiveness of therapies granted accelerated approval).
- Reconsider existing bans on unique patient identifier funding and encourage the Department of Health and Human Services through the Office of the National Coordinator for Health IT to advance unique patient identifier development.
- Harmonize stakeholder goals and initiatives by cultivating and supporting pre-competitive public-private partnerships.

Session 2: Re-imagining Evidence Generation: Opportunities for Developing Shared Evidence and Point of Care Clinical Trials

- **Marc Berger,** semi-retired, part-time consultant and scientific advisor, ISPOR
- **Gracie Lieberman,** retired Biostatistician, formerly Genentech
- **Sally Okun**, Executive Director, Clinical Trials Transformation Initiative

Session 3: What's Next For the Use of RWE?

Moderators:

Rachele Hendricks-Sturrup and Mark McClellan

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Overview of draft legislative proposals and RWE commitments

Dure Kim, PharmD

Assistant Research Director

Legislative and Policy Advancement of RWE

- Prescription Drug User Fee Act (PDUFA) Commitment Letter
- H.R. 7667 – Food and Drug Amendments 2022
- H.R. 6000 – Cures 2.0
- S.3799 – Prepare for and Respond to Existing Viruses, Emerging New Threats, and Pandemics Act – PREVENT Pandemic Act

PDUFA VII (2023-2027) Commitment Letter

- Final performance goal letter transmitted to Congress on Jan 12, 2022
- Advancing RWE Program
  - New processes for RWE based decision making
  - Call for RWE study proposals with regulatory applicability
- Promotion of RWE submission acceptability
  - Annual report of submissions with RWE
  - Regulatory grade RWE Public workshops

PDUFA VII (2023-2027) Commitment Letter

- Optimizing the Sentinel Initiative using RWE
  - Maintenance of the Sentinel Initiative Capabilities and Continued Integration into FDA Drug Safety Activities
  - Analytic Capabilities Enhancement to Address Product Safety and Effectiveness
    - Post-market Pregnancy studies and use of negative controls
- Additional policy implications for RWE
  - Patient Focused Drug Development meeting
  - Update on the Expedited Programs for Regenerative Medicine Therapies for Serious Conditions Industry Guide
  - Digital Health Technologies to Support Drug Development

H.R. 7667 – Food and Drug Amendments of 2022

- Sec. 503 – Public Workshops to Enhance Clinical Trial Diversity
  - Utilization of RWE as a topic for discussion at a public meeting on trial diversity
- Sec 804 – Post-Approval Studies and Program Integrity for Accelerated Approval Drugs
  - RWE augmenting or supporting post approval studies for accelerated approval
  - Report on when and how RWE was used to support post-approval studies
  - Use of RWD/E to support endpoint development in rare diseases
- Sec 805 – Facilitating the use of Real World Evidence
  - Guidance on RWD/E use to support regulatory decision making
  - Report to Congress on applications using RWE to support decision making

H.R. 6000 – Cures 2.0

- Sec 302 – Prioritize grants for novel trial designs and other innovation, such as digital health technologies and RWE, in drug development
- Sec 304 – Increasing Use of Real World Evidence
  - Guidance on the use of real world evidence in evaluating the safety and effectiveness of breakthrough devices and drugs
  - Identification and implementation of approaches
  - RWE Task Force
- Sec 309 – RWE in post-approval study requirements for accelerated approval

S.3799 – PREVENT Pandemics Act

- Sec 505 – Facilitating the Use of RWE

Summary

- Enhancement of RWE/D quality and methodology
- RWE submission efficiencies and transparency
- Promotion of broader utility of RWE in regulatory science and decision making

Session 3: What's Next for the Use of RWE?
Panel 1: Data Considerations

- **Jeffrey Brown,** Chief Scientific Officer, TriNetX
- **Elise Berliner,** Global Senior Principal for Real World Evidence Strategy, Cerner Enviza
- **Luca Foschini,** Co-Founder and Chief Data Scientist, Evidation
- **Lauren Silvis,** Senior Vice President of External Affairs, Tempus

Session 3: What's Next for the Use of RWE?
Panel 2: Learning from RWE Pilot Projects

- **Stephanie Reisinger,** Senior Vice President and General Manager of Real-World Evidence, Flatiron Health
- **Shirley V Wang,** Associate Professor, Brigham and Women's Hospital; Co-lead of 1st and 2nd joint task forces, ISPE and ISPOR
- **Laura Roe,** Clinical Studies Platforms Strategy and Operations, Verily
- **Solomon Iyasu,** Vice President and Global Head of Epidemiology, Merck and Co.

Closing Remarks & Meeting Adjournment

Mark McClellan, MD, PhD

Director, Duke-Margolis Center for Health Policy

Thank You!

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