Role of Real-World Evidence in Regulatory Decision-Making, Before, During, and After COVID-19

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Declaration of Interest

- I am an employee of Aetion, Inc.
- Opinions are my own and not of my employer or any other entity

Agenda

RWE Before COVID-19

Accelerating the Understanding and Use of RWD and RWE

RWE After COVID-19

RWE Before COVID-19

Study Design vs. Data Collection vs. Study Setting

- **Study Design:** Interventional vs. Non-interventional
  - Randomized vs. Nonrandomized
- **Data Collection:** Primary Data vs. Secondary Data
- **Study Setting:** Real-world vs. Clinical Trial

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It's a spectrum!

What is RWD and RWE and How Can It Be Used for Regulatory Decision-making

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Operational

Clinical trial efficiency

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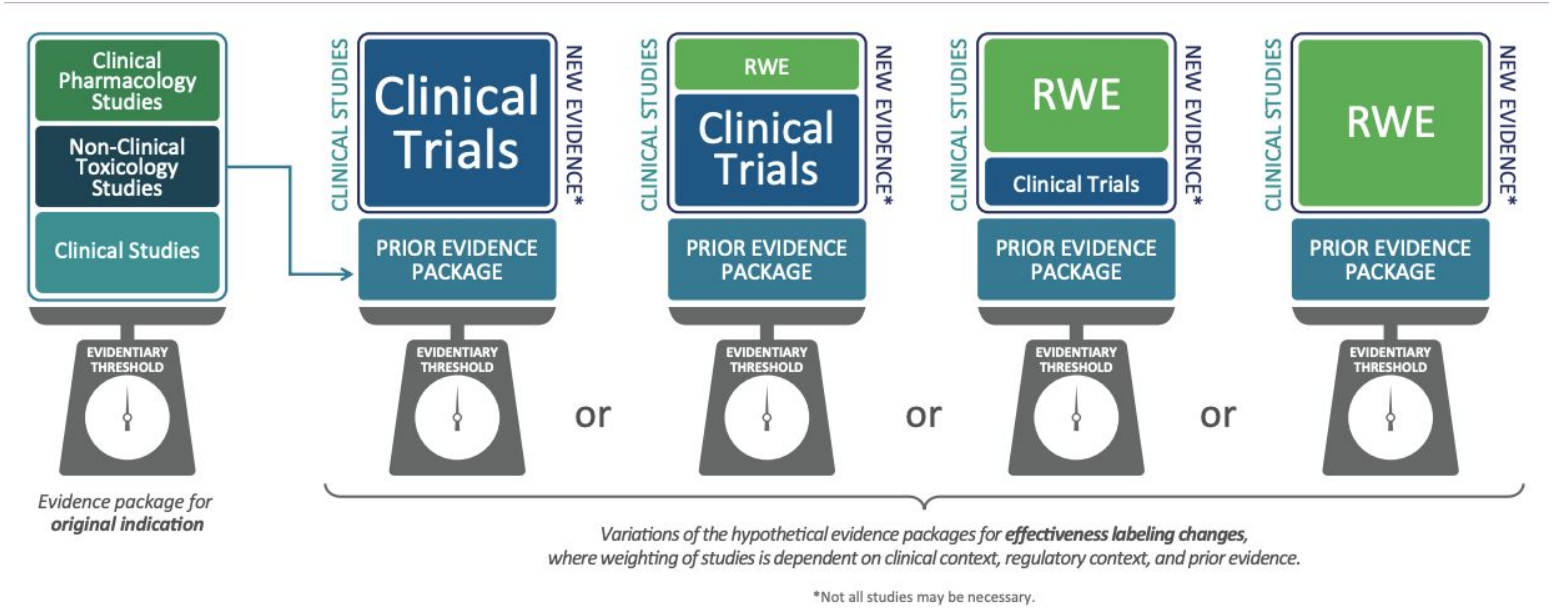
Operational

Clinical trial efficiency

Safety

Effectiveness

RWE Can Complement RCT as Part of an Evidence Package



Duke Margolis Center for Health Policy. Adding Real-World Evidence to a Totality of Evidence Approach for Evaluating Marketed Product Effectiveness. Available at: https://healthpolicy.duke.edu/publications/adding-real-world-evidence-totality-evidence-approach-evaluating-marketed-product

While PDUFA and CURES Mandates FDA to Explore RWE for Effectiveness Decision; RWE is Not New to FDA or to Evidence Packages

5:30PM - 5:45PM **RW3: UNDERSTANDING USE OF REAL-WORLD DATA (RWD) AND REAL-WORLD EVIDENCE (RWE) TO SUPPORT EFFECTIVENESS LABELING CHANGES**

Mercon K, Eckert JC, Mahendraratnam N, Kroetsch AF, Wosińska M, McClellan M
Duke-Robert J. Margolis Center for Health Policy, Washington, DC, USA

OBJECTIVES: To date, use of RWD/RWE in regulatory submissions and decision-making related to product effectiveness is not well tracked or understood. We aim to identify and characterize if and how FDA has used RWD/RWE to support effectiveness labeling changes for marketed products.

METHODS: Submission and use of RWD/RWE in effectiveness labeling changes was identified through a targeted literature review and internet searches supplemented with interviews with regulatory, policy, and methodological experts from the Duke-Margolis RWE Collaborative. Instances were analyzed using descriptive statistics across various characteristics. If and how RWD/RWE was used to inform each labeling change was assessed through qualitative analysis of publicly available information (e.g., summary reviews and press releases) and expert interviews by trained reviewers.

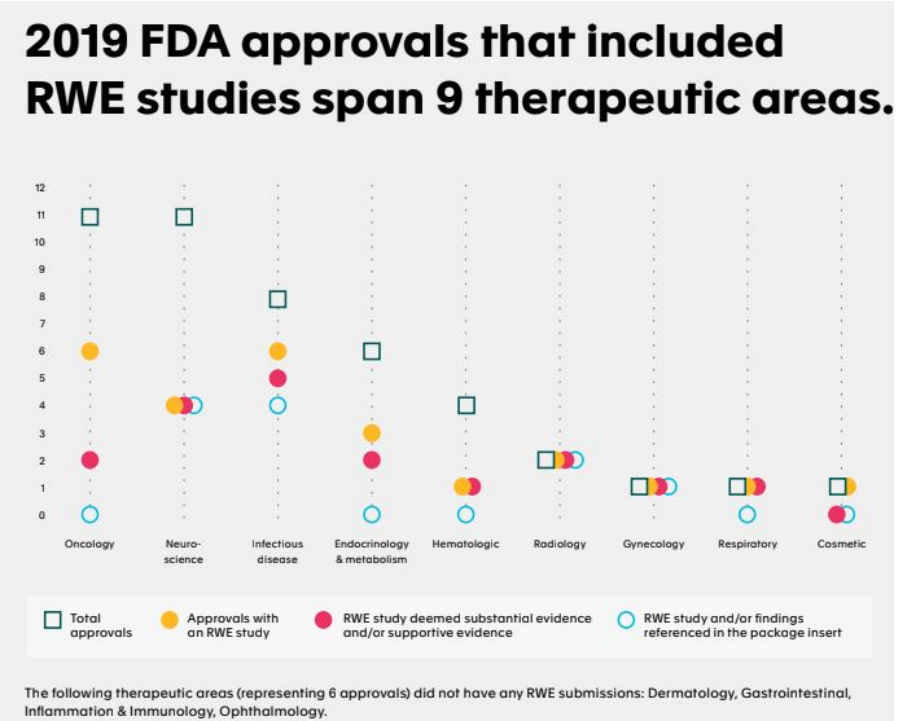
RESULTS: RWD/RWE was submitted in 25 cases to support a labeling change and used in 22 (i.e., 7 biologics, 13 drugs, and 2 vaccines). When RWD/RWE was used, 77% had a rare disease designation. The most common disease states were cancer (18%) and blood diseases (14%). The most common RWD use was for external controls/benchmarks (36%). Across study designs, 32% were case series, 14% were randomized, and 9% were cohort. Reasons for not using submitted RWD/RWE included a lack of study prespecification, unmeasured confounding concern, and data fitness-for-use levels.

CONCLUSIONS: Understanding how FDA has historically used submitted RWD/RWE in effectiveness decision-making is imperative to advancing its use. Currently, there is no standardized tracking mechanism for stakeholders to identify when or how FDA has used RWD/RWE in its decision-making; however, on-going efforts within FDA may improve internal tracking of submissions containing RWD/RWE. Publicly tracking RWD/RWE submissions could demonstrate instances when RWD/RWE was submitted but did not contribute to regulatory decision-making. Greater transparency about how submitted RWD/RWE was or was not used in regulatory decision-making can support future RWD/RWE submissions by offering valuable lessons learned.

Sentinel. "About the FDA Sentinel Initiative." https://www.sentinelinitiative.org/about
Mercon K et al. "Understanding Use of Real-world Data and Real-world Evidence to Support Effectiveness Labeling Changes." 2020 ISPOR Annual Meeting. https://www.valueinhealthjournal.com/article/S1098-3015(20)31681-8/fulltext

Growing Use of RWE to Support Regulatory Decision

- In 2019, 49 percent of FDA-approved NDAs and BLAs included an RWE study
- In 2020, that figure jumped to 75 percent
- In 72 percent of submissions with an RWE study, the study influenced the FDA's approval decision



Aetion. "eBook: The role of Real-World Evidence in FDA Approvals." Available at: https://aetion.com/evidence-hub/ebook-the-role-of-real-world-evidence-in-fda-approvals/

Why Can't We Use Traditional RCTs to Answer All Research Questions?

Intrinsic Value of RWD

- Represents a broader population, and enables sub-population studies
- Collect outcomes that may be prioritized by patients and providers
- Reflects "real-world" prescribing and care
- Studies longer-term outcomes
- Already being collected

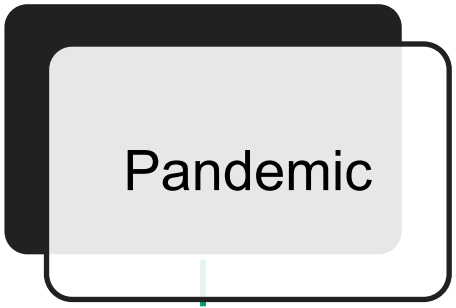
"The COVID-19 pandemic is highlighting longstanding inefficiencies in the US clinical trials enterprise, the result being that only a small fraction of ongoing studies for potential therapeutics are expected to produce actionable data,"

- Janet Woodcock, Director, CDER, US FDA (On-Leave), Therapeutics Lead, Operation Warp Speed

[13] Baumann J. "Reams of Useless Covid Data Drive Reckoning on Clinical Trials." Bloomberg Law. (Summary of Friends of Cancer Research's 24th Annual Cancer Leadership Reception (2020). https://friendsofcancerresearch.org/news/bloomberg-law-reams-useless-covid-data-drive-reckoning-clinical-trials

Accelerating the Understanding and Use of RWD and RWE

COVID-19 Disrupted Traditional Care and Evidence Generation Paradigms



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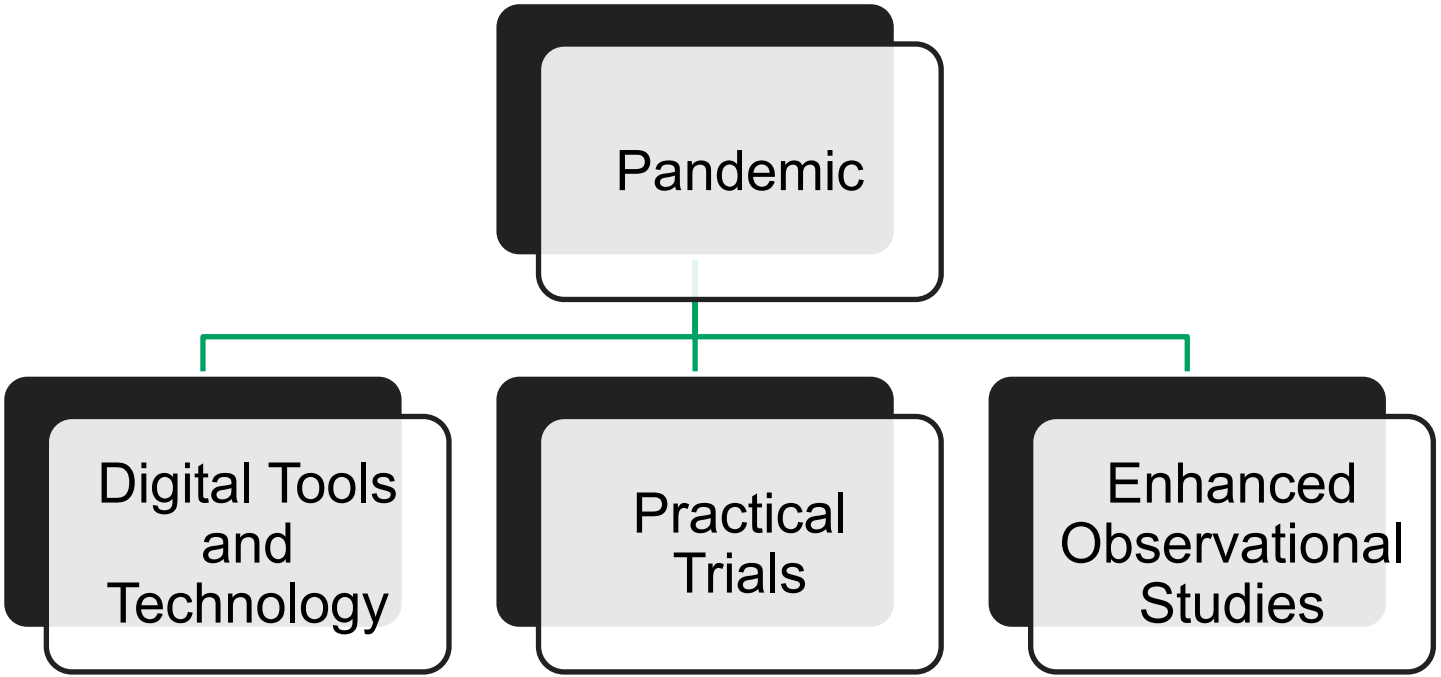
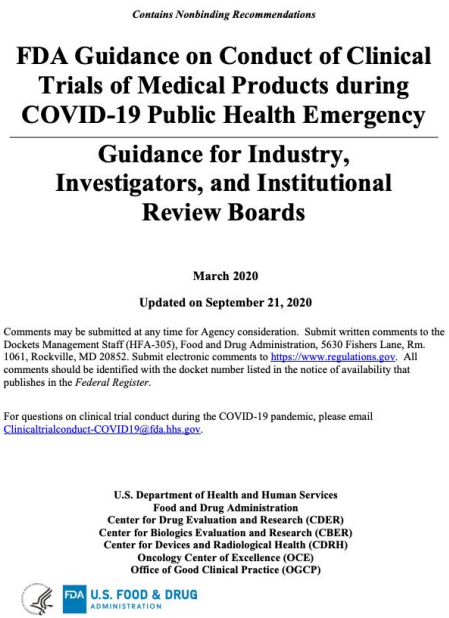


To learn more: Duke Margolis Annual RWE Conference: Applying Lessons Learned from RWE in the Time of COVID-19 to the Future

Digital Tools: Bringing Trial and Real-world Studies to Patients



Contains Nonbinding Recommendations

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

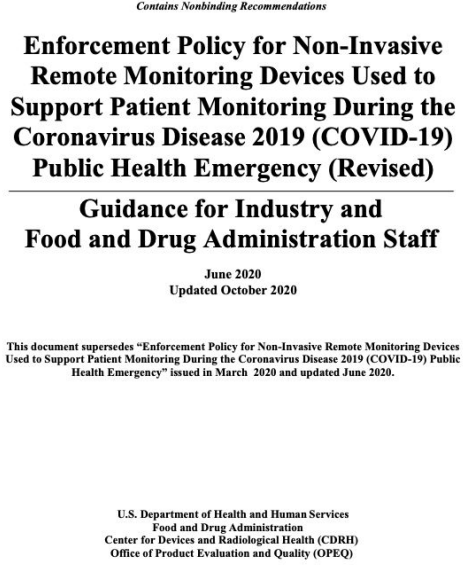
March 2020

Updated on September 21, 2020

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on clinical trial conduct during the COVID-19 pandemic, please email Clinicaltrialconduct-COVID19@fda.hhs.gov.

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)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Good Clinical Practice (OGCP)



Contains Nonbinding Recommendations

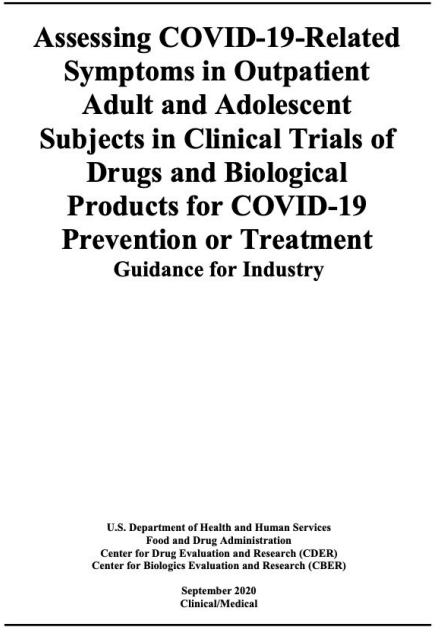
Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (Revised)

Guidance for Industry and Food and Drug Administration Staff

June 2020
Updated October 2020

This document supersedes "Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency" issued in March 2020 and updated June 2020.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)
Office of Product Evaluation and Quality (OPEQ)



Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment

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)

September 2020
Clinical/Medical

Practical Trials: Randomization, Objective Endpoints, and Large Sample Sizes for Decisive Results

- Enhanced, large simple trial
- Randomization
- Streamlined data collection
  - Objective endpoints
  - Serious adverse events
- Embedded in routine clinical care (EHRs)

Duke Margolis Annual RWE Conference: Applying Lessons Learned from RWE in the Time of COVID-19 to the Future

Medicines and Healthcare products Regulatory Agency. "Draft guidance on randomised controlled trials generating real-world evidence to support regulatory decisions." Available at: https://www.gov.uk/government/consultations/mhra-draft-guidance-on-randomised-controlled-trials-generating-real-world-evidence-to-support-regulatory-decisions

Side Bar: COVID Emergency Use Authorizations (EUAs) and RWE

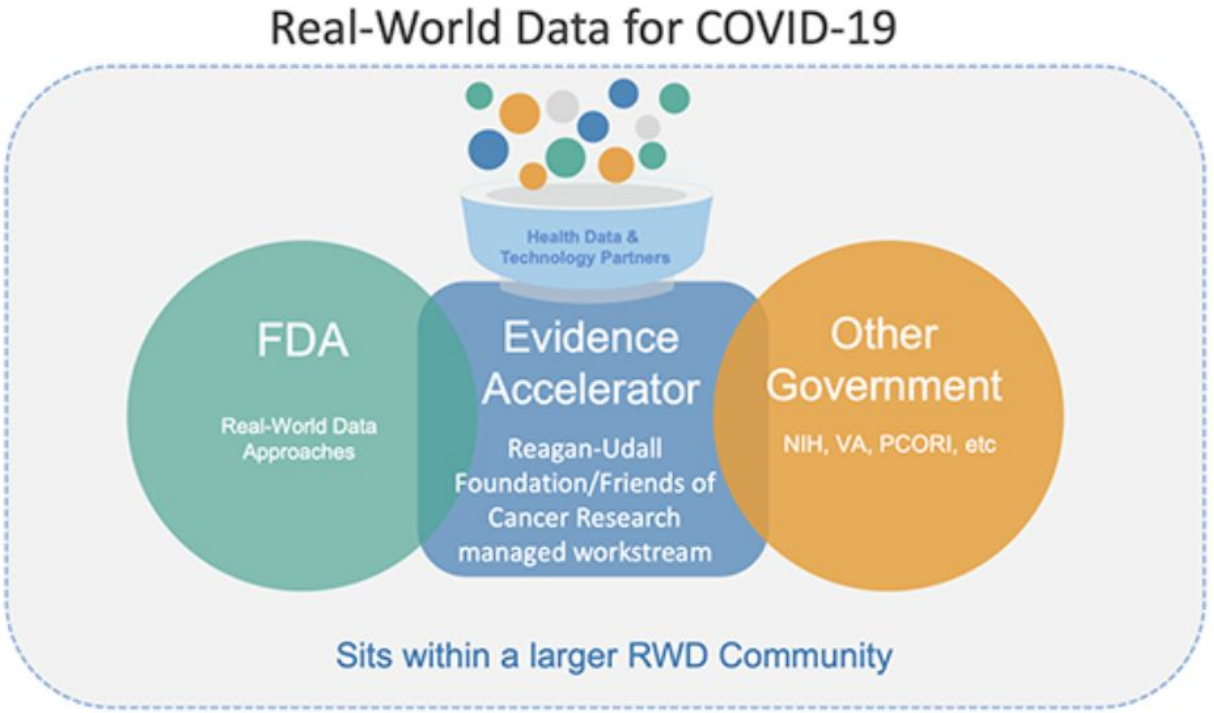
What Is An EUA[1]	EUA vs. Traditional Approval Standard[2]	What Does This Mean?
EUAs "allows the use of unapproved medical products, or unapproved uses of approved medical products to diagnose, treat, or prevent serious or life-threatening diseases when certain criteria are met, including that there are no adequate, approved, and available alternatives"	"If, based on the totality of the scientific evidence available, it is reasonable to believe that the product **may be effective** for the specified use, FDA may authorize its emergency use, provided that other statutory criteria for issuing an EUA also are met"	**Treatments[3]** • New products may enter the market before trial completion (e.g., pre-planned interim analyses) • Safety and effectiveness in specific Covid-19 patients and treatment contexts **Vaccines[4]** • Safety and effectiveness in a clinical trial with at least 30,000 patients and median 2 months follow-up at study conclusion

"Vaccine benefit-risk considerations are different from therapeutics used for life-saving purposes because vaccines are given to healthy people"

– Steve Anderson, Director, Office of Biostatistics and Epidemiology, CBER[5]

1. US FDA. "Emergency Use Authorization." Available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization
2. US FDA. "Emergency Use Authorization of Medical Products and Related Authorizations." Available at: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/faqs-emergency-use-authorizations-euas-medical-devices-during-covid-19-pandemic
3. Duke Margolis. "Building the Critical Path for COVID-19 Therapeutics." Available at: https://healthpolicy.duke.edu/sites/default/files/2020-06/building_the_critical_path_for_covid-19_therapeutics_final.pdf
4. US FDA. "Development and Licensure of Vaccines to Prevent COVID-19,." https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19
5.Anderson S (US FDA) "12th Annual Sentinel Initiative Public Workshop." https://healthpolicy.duke.edu/events/12th-annual-sentinel-initiative-public-workshop

Building a National RWD Infrastructure to Generate RWE



COVID-19 Evidence Accelerator. https://evidenceaccelerator.org

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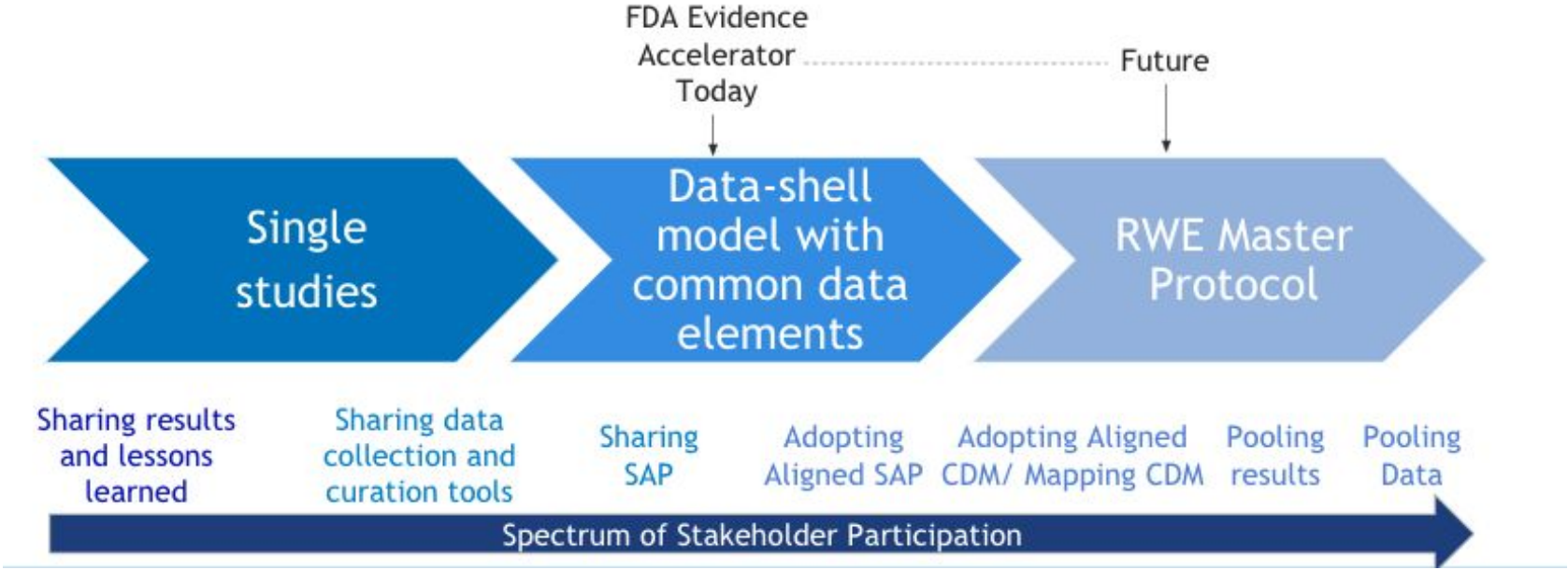

Figure Courtesy of Duke Margolis Center for Health Policy

COVID-19 Spurred Several FDA RWE Engagements

"We are regularly engaging with stakeholders -- medical product industry leaders and scientists, academic researchers, technology companies, state and local governments and patient groups -- to hear from them on how we can come together as a public/private health community to harness the power of data during this emergency."

-Amy Abernethy, Principal Deputy Commissioner, US FDA

FIERCE Biotech

FDA, Aetion dive into the real-world data surrounding COVID-19

by Conor Hale | May 19, 2020 3:38pm

Aetion and the FDA plan to follow medication use and use the evidence generated in evaluations of new potential interventions. (Andrew Harnik, Associated Press)

FDANEWS

FDA Collaborates with HealthVerity to Evaluate Real-World Data

June 10, 2020

The FDA has signed a multiyear agreement with Pennsylvania-based HealthVerity to evaluate real-world data to support the agency's response to COVID-19.

The healthcare data company has access to records from more than 190 million patients, which can be mined for insights into treatment patterns and to understand more about the disease.

HealthVerity is collaborating with Aetion, a New York-based healthcare software company that also entered into an agreement with the FDA last month.

Abernethy A. COVID-19 Update: FDA Collaborations Promote Rigorous Analyses of Real-World Data to Inform Pandemic Response." https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-collaborations-promote-rigorous-analyses-real-world-data-inform

RWE After COVID-19

What Have We Learned, What's Transient, What's Permanent?

Today

- Utility of RWD and RWE - matching the right data with the right question
- Increased familiarity with RWD and RWE
- Multi-stakeholder collaboration

The Future

- Expanding COVID capabilities and experiences to other therapeutic areas
- Adoption of infrastructure and tools to streamline clinical trial and real-world study conduct (e.g., EHR data capture, master protocols, novel technologies)
- Advancing RWD quality and methods to analyze RWD to generate high-quality RWE

Acknowledgements

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Thank you

Contact: Nirosha.Lederer@aetion.com