Regulation in the Age of Exponential Innovations

Artificial Intelligence

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Director -Office of Medical Policy
CDER | US FDA

February 2022

The views expressed in this presentation do not necessarily represent the policies of the FDA or HHS. Mentions are not endorsements.

Disclosures: None

For today…

- Convergence of exponential technologies
- Real-World Evidence
- AI in therapeutic development
- Shaping the future

Exponential technologies?

*"Exponential technologies are those that enable change at a rapidly accelerating, nonlinear pace facilitated by substantial progress (and cost reduction) in areas such as computer power, bandwidth and data storage."**

Data Availability – Computing Power – Advanced Methodologies – Digital Health Tools – Digital Data Platforms – Real-Time Data Capture – Frequent Improvements

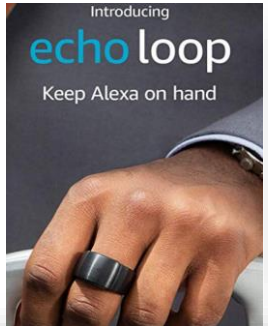
Complex Therapeutics – Combination Products – Therapeutic Experience – Adherence ---

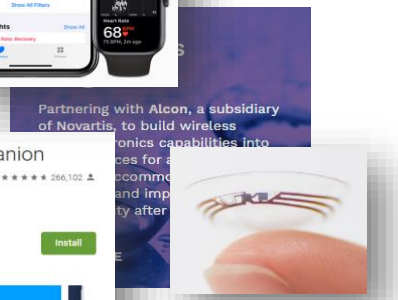
*https://www2.deloitte.com/content/dam/Deloitte/us/Documents/manufacturing/us-mfg-advanced-manufacturing-technologies-report.pdf

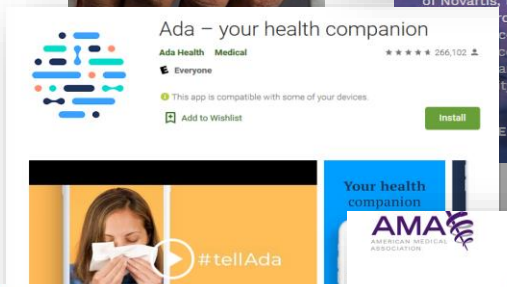
Responsive Framework for a Rapidly Evolving Ecosystem

Advancing Evidence Generation Paradigm*

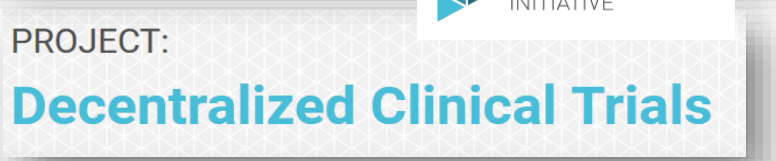
Increasingly Digital World*

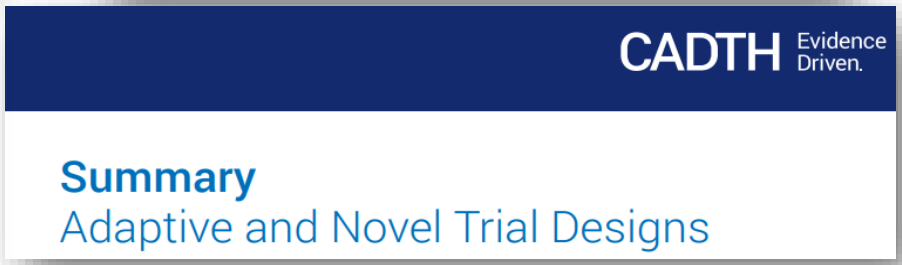






Innovative Clinical Trial Designs*

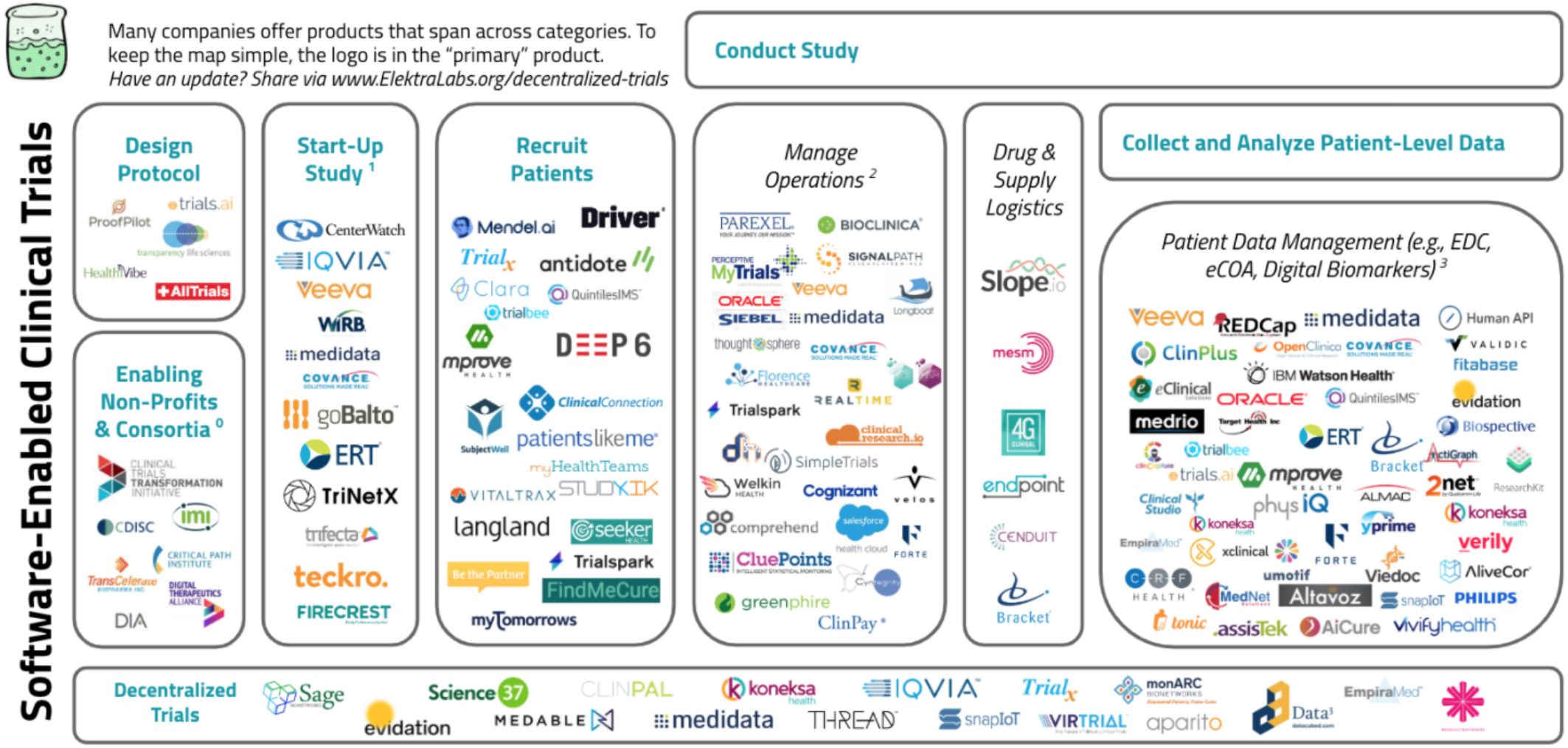




* Examples – not fully inclusive

The writing on the wall

"on the go data capture & analytics"



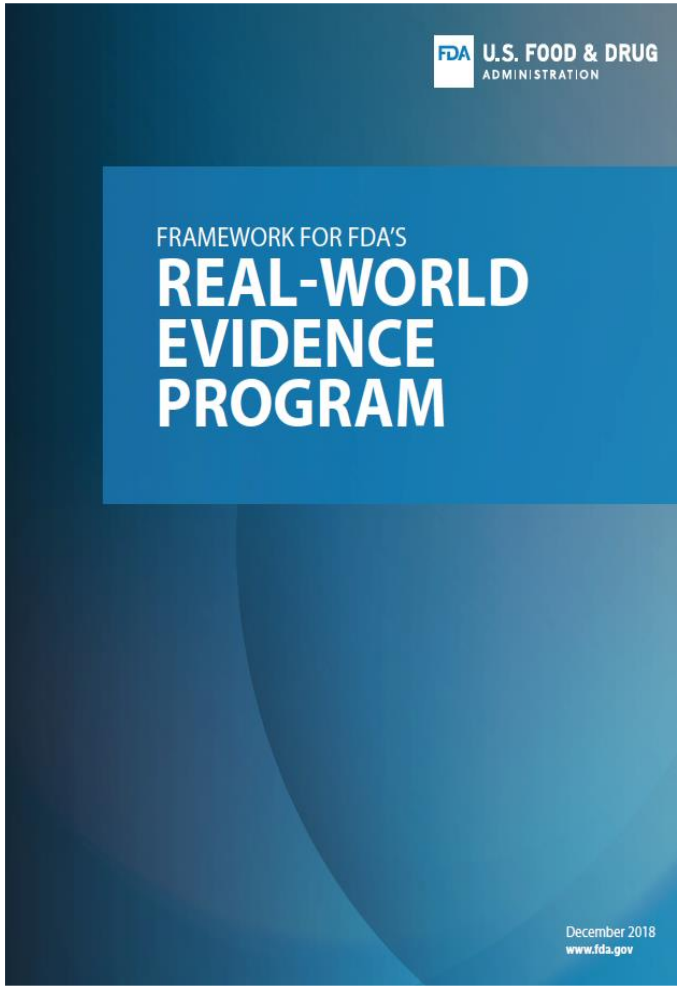
elektralabs

https://blog.andreacoravos.com/software-enabled-clinical-trials-8da53f4cd271

U.S. 21st Century Cures Act (2016)

- **Food & Drug Administration (FDA) shall establish a program to evaluate the potential use of real-world evidence (RWE) to:**
  - **Support new indication for a drug approved under section 505(c)**
  - **Satisfy post-approval study requirements**
- **Draft framework to be issued by Dec 2018:**
  - **Describe sources of RWD/RWE, challenges, pilot opportunities, etc.**
- **Draft guidance for industry to be issued by Dec 2021**
- **Standard for *substantial evidence* remains unchanged; commitments are aligned with Prescription Drug User Fee Act (PDUFA)**

FDA RWE Framework (2018)



- Applies to Center for *Drug* Evaluation and Research (CDER) and Center for *Biologics* Evaluation and Research (CBER) Multifaceted program to implement RWE:
  - internal processes
  - external stakeholder engagement
  - demonstration projects
  - guidance development

The framework will include consideration of the following:

1. Whether the RWD are fit for use
2. Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question
3. Whether the study conduct meets FDA regulatory requirements (e.g., for study monitoring and data collection)

‘Real-World’ Definitions (from FDA’s 2018 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

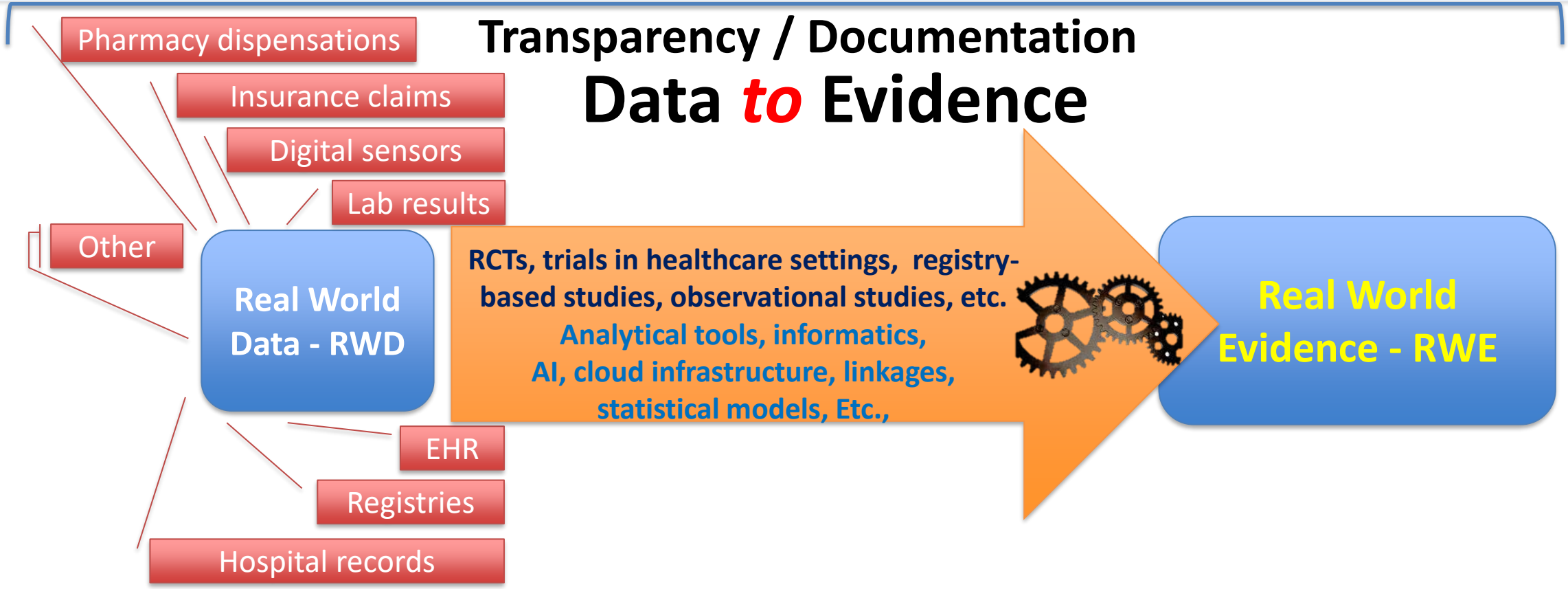
- electronic health records (EHRs)
- medical claims data
- product and disease registries
- patient-generated data, including from in-home settings
- other sources that can inform on health status, such as “wearable” devices

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., large simple trials, pragmatic trials), externally controlled trials, or observational studies

Exploring Multiple Streams of Data

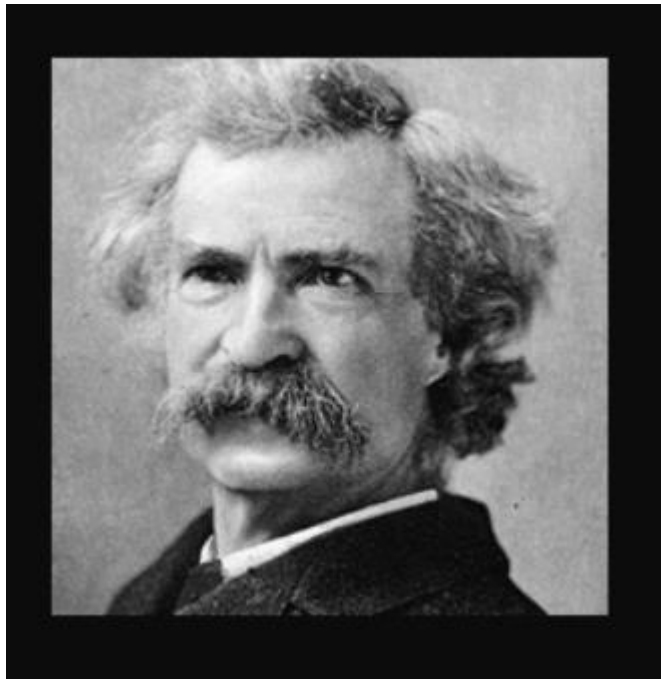
Real World Data / Evidence



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

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

Real World Data

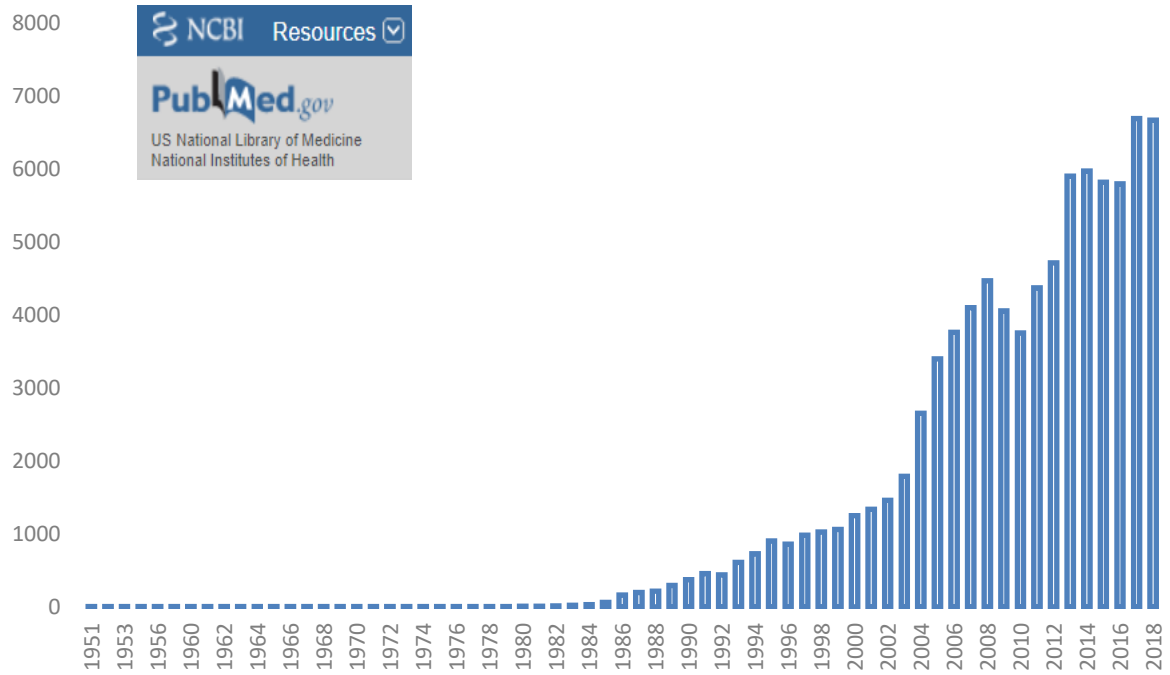


~ Mark Twain

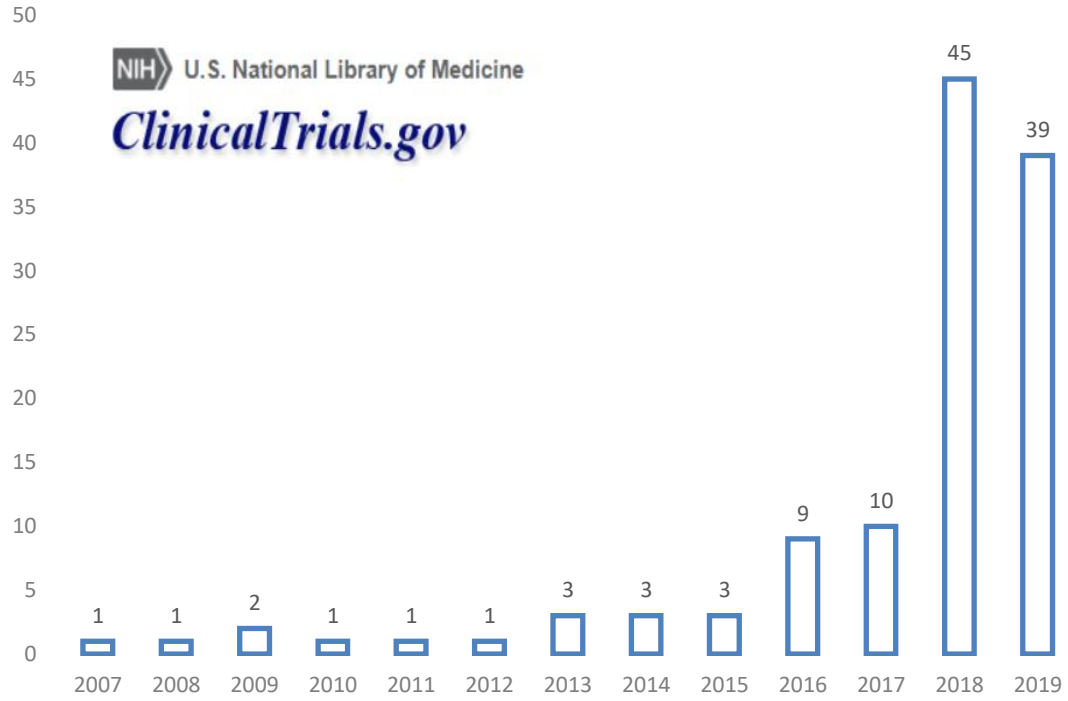
In the real world, nothing happens at the right place at the right time . . .

Beyond the Hype – Artificial Intelligence

Number of Scientific Papers with the Term Artificial Intelligence



Clinical Trials Incorporating AI



AI Across the Drug Development Lifecycle

Discovery, Development, and Preclinical Research

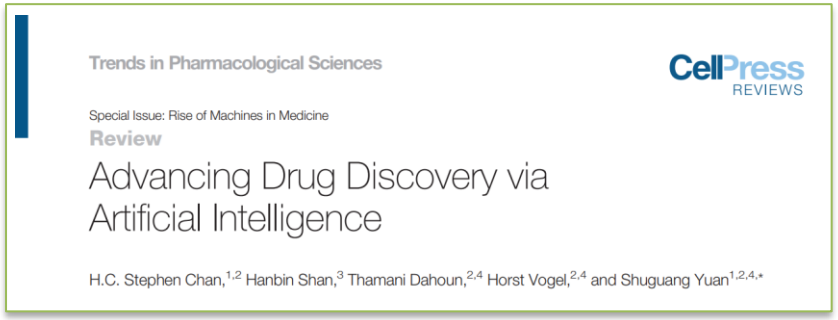
- Pathogenesis
- PK/PD modeling
- Biomarker identification
- Compound identification, screening, and design

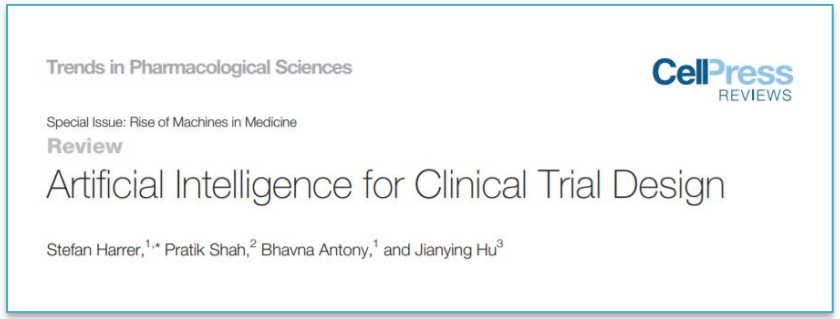
Clinical Research

- Biomarker qualification/DDTs
- Recruitment and retention
- Adherence and compliance
- Facilitating the use of RWD
- Clinical trial monitoring
- Safety monitoring

Manufacturing & Post Market

- Identification of long-term safety trends
- Utilization as a part of care
- Continuous monitoring of safety and effectiveness
- Manufacturing





Context is important

News > Medscape Medical News

Skin Imaging Working Group Releases First Guidelines for AI Algorithms Used in Dermatology

Jeff Craven
December 22, 2021

The International Skin Imaging Collaboration (ISIC) Artificial Intelligence Working Group has released the first-ever guidelines for developing artificial intelligence (AI) algorithms used in dermatology.

RESEARCH Open Access

Detecting compensatory movements of stroke survivors using pressure distribution data and machine learning algorithms

Siqi Cai[1], Guofeng Li[1], Xiaoya Zhang[2], Shuangyuan Huang[1], Haiqing Zheng[2], Ke Ma[1] and Longhan Xie[1*]

FDA

This Issue | Views 868 | Citations 0 | Altmetric 41

Consensus Statement

December 1, 2021

Checklist for Evaluation of Image-Base Intelligence Reports in Dermatology

CLEAR Derm Consensus Guidelines F International Skin Imaging Collaborat Intelligence Working Group

Roxana Daneshjou, MD, PhD[1,2]; Catarina Barata, PhD[3]; Brigid Betz-Stablein, PhD[4]; et al

Author Affiliations

JAMA Dermatol. 2022;158(1):90-96. doi:10.1001/jamadermatol.2021.4915

HHS Public Access

Author manuscript

Curr Psychiatry Rep. Author manuscript; available in PMC 2020 November 07.

Published in final edited form as:

Curr Psychiatry Rep. ; 21(11): 116. doi:10.1007/s11920-019-1094-0.

Artificial Intelligence for Mental Health and Mental Illnesses: An Overview

Machine Learning

Just in time crisis response: suicide alert system for telemedicine psychotherapy settings

Niels Bantilan, Matteo Malgaroli, Bonnie Ray & Thomas D. Hull

Pages 289-299 | Received 31 Dec 2019, Accepted 06 Jun 2020, Published online: 19 Jun 2020

Download citation | https://doi.org/10.1080/10503307.2020.1781952 | Check for updates

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https://jamanetwork.com/journals/jamadermatology/article-abstract/2786912
https://www.medscape.com/viewarticle/965407
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https://www.tandfonline.com/doi/full/10.1080/10503307.2020.1781952?scroll=top&needAccess=true
https://jneuroengrehab.biomedcentral.com/track/pdf/10.1186/s12984-019-0609-6.pdf

Understanding the Complexities

Opinion | Ruth Bader Hat Guy? Let Our Algorithm Choose Your Hallo...

Machine learning has a spooky side. These algorithmically generated Halloween costumes show how artificial intelligence can reinforce human...

nytimes.com

Sometimes, the ways algorithms work can have unexpected and disastrous consequences. In 2013, M.I.T. researchers trained an algorithm that was supposed to figure out how to sort a list of numbers. The humans told the algorithm that the goal was to reduce sorting errors, so the program deleted the list entirely, leaving zero sorting errors. And in 1997, another algorithm was supposed to learn to land an airplane on an aircraft carrier as gently as possible. Instead, it discovered that in its simulation it could land the plane with such huge force that the simulation couldn't store the measurement, and would register zero force instead.

- **Prediction algorithms predict the most likely outcome/decision based on input data - not necessarily the accurate answer.**

- **AI may produce unpredictable or unconventional "solutions".**

https://www.nytimes.com/interactive/2018/10/26/opinion/halloween-spooky-costumes-machine-learning-generator.html

GMLP & Real-World Performance

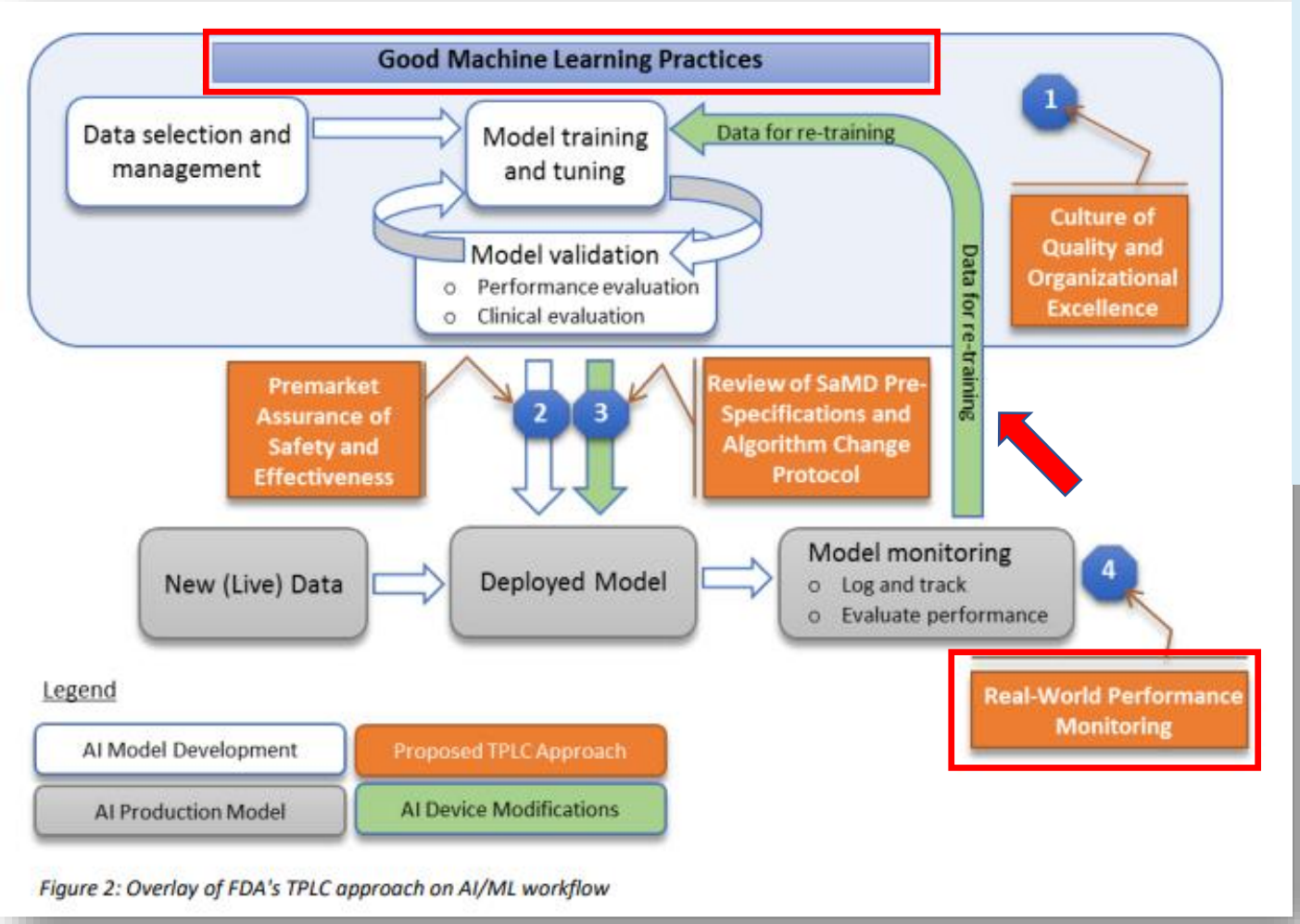

Figure 2: Overlay of FDA's TPLC approach on AI/ML workflow

Artificial Intelligence and Machine Learning (AI/ML) Software as a Medical Device Action Plan

The U.S. Food and Drug Administration (FDA) issued the "Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan" f… Health Center of Excel…

The Action Plan is a d… discussion paper, "Pro… Intelligence/Machine … five actions the FDA in…

https://www.fda.gov/media/122535/download
https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device

Regulations, Transparency, and Documentation

- Consolidated Standards of Reporting Trials (CONSORT)
- Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

The CONSORT-AI Extension
&
SPIRIT-AI Extension

http://nautil.us/issue/66/clockwork/we-need-an-fda-for-algorithms

FDA Continues to Respond to an Increasingly Digital World

U.S. FOOD & DRUG ADMINISTRATION

s | Drugs / Drug Development Tool (DDT) Qualification Programs / Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program

Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program

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Examples of submissions that might be considered for ISTAND include, but are not limited to:

Tools that may help enable remote or decentralized trials
•Application of patient-performed digital photography in dermatology trials
Tools that may advance our understanding of drugs
•Use of tissue chips (i.e., microphysiological systems) to assess safety or efficacy questions
•Development of novel nonclinical pharmacology/toxicology assays
Tools that leverage digital health technologies
•Use of artificial intelligence (AI)-based algorithms to evaluate patients, develop novel endpoints, or inform study design
•Use of novel digital health technologies (e.g., wearables) for patient assessment
Development programs needed for evaluation of adherence sensors

NATIONAL ARCHIVES

FEDERAL REGISTER
The Daily Journal of the United States Government

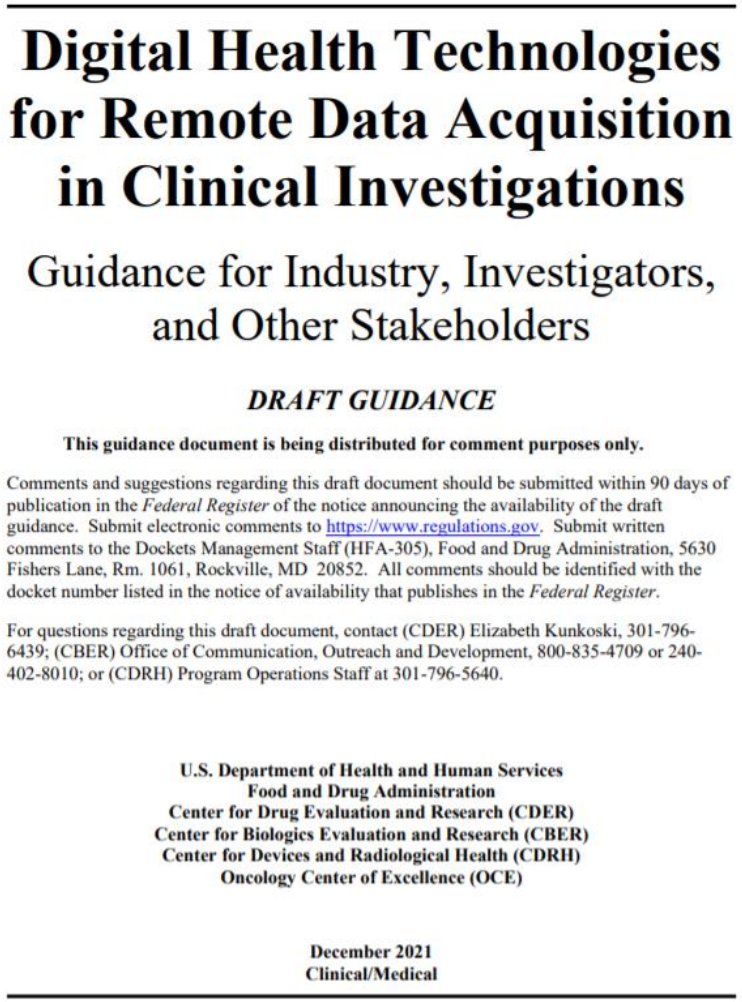
Notice

Prescription Drug-Use-Related Software; Establishment of a Public Docket; Request for Comments

A Notice by the Food and Drug Administration on 11/20/2018

The framework proposed in this notice focuses not on prescription drug-use-related software itself, but rather **on the output of such software that is presented to the end user**. For purposes of the notice, prescription drug-use-related software refers to software disseminated by or on behalf of a drug sponsor that accompanies one or more of the sponsor's prescription drugs (including biological drug products).

FDA Continues to Respond to an Increasingly Digital World



Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Guidance for Industry, Investigators, and Other Stakeholders

DRAFT GUIDANCE

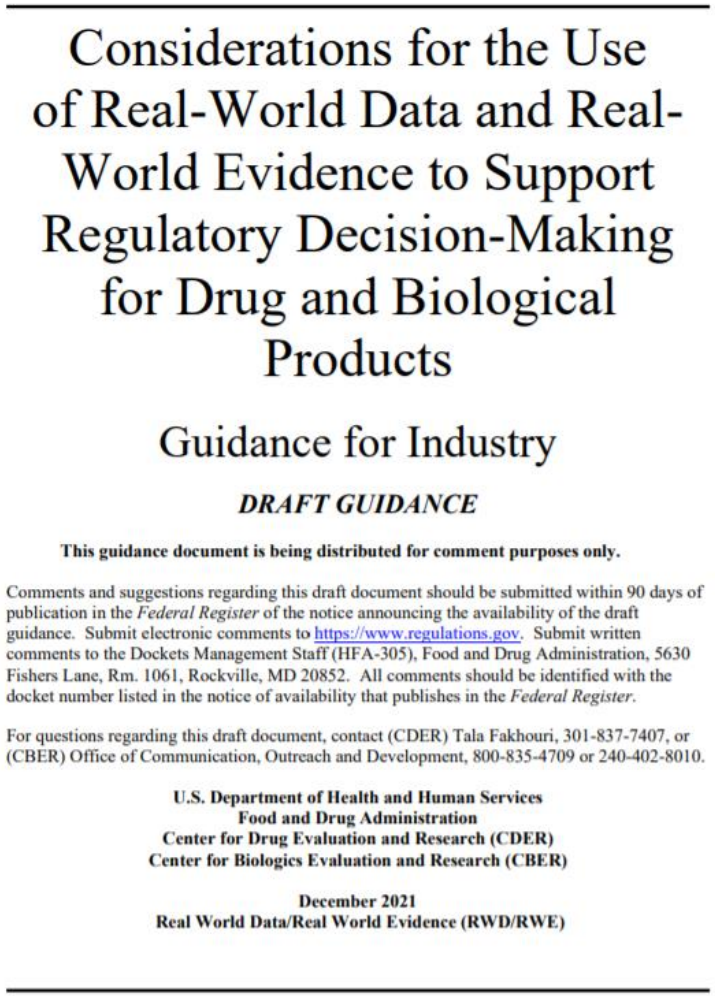
This guidance document is being distributed for comment purposes only.

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) Elizabeth Kunkoski, 301-796-6439; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Program Operations Staff at 301-796-5640.

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)

December 2021
Clinical/Medical



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

Guidance for Industry

DRAFT GUIDANCE

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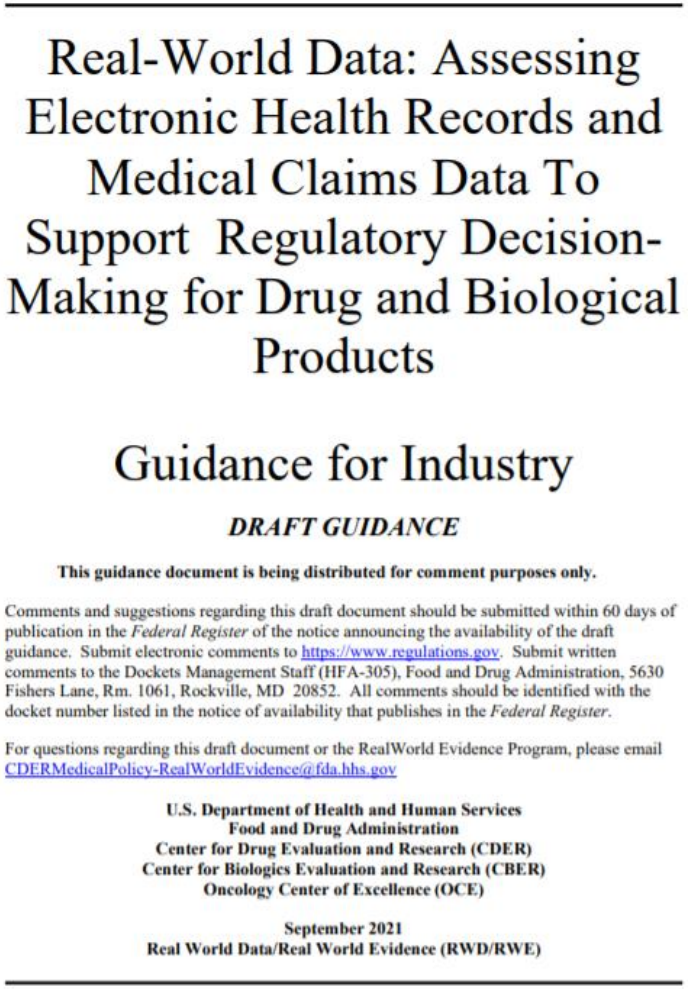
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2021
Real World Data/Real World Evidence (RWD/RWE)



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

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document or the RealWorld Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@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)
Oncology Center of Excellence (OCE)

September 2021
Real World Data/Real World Evidence (RWD/RWE)

https://www.fda.gov/media/155022/download
https://www.fda.gov/media/154714/download
https://www.fda.gov/media/152503/download

CDER AI

- **Established the AI Steering Committee (AISC) to coordinate efforts around AI uses across therapeutic development.**
- **Identifying current and emerging uses of AI across the therapeutic development cycle, including approaches to validating and benchmarking AI tools**
- **Understanding the impact of AI use in clinical practice on the analyses of real-world data (RWD) and the generation of real-world evidence (RWE)**
- **Focusing on a risk-based approach that considers intended use of AI across the spectrum of drug development**
- **Identifying ways to address regulatory science needs when evaluating the use of AI in drug development**
- **Engage stakeholders and encourage mutual learning**

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- *Tala Fakhouri*
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- *John Concato*
- *Karen Boyd*
- *Scott Steele*