U.S. FOOD & DRUG ADMINISTRATION

Seminar on Real-World Data and Evidence Generation in Medical Product Development: Past, Present, and Future

Evolution of Evidence Generation

2 December 2024

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies
- No conflicts of interest exist regarding this presentation
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Outline of Presentation

- **Hierarchies of study design**
- **Emergence of real-world evidence (RWE)**
- **Selected aspects of FDA's RWE Program**
- **Real-world data (RWD) in the context of clinical trials and non-interventional studies**

Outline of Presentation

- **Hierarchies of study design**

‘Case Study’ – Streptomycin & Tuberculosis

Evidence generation:

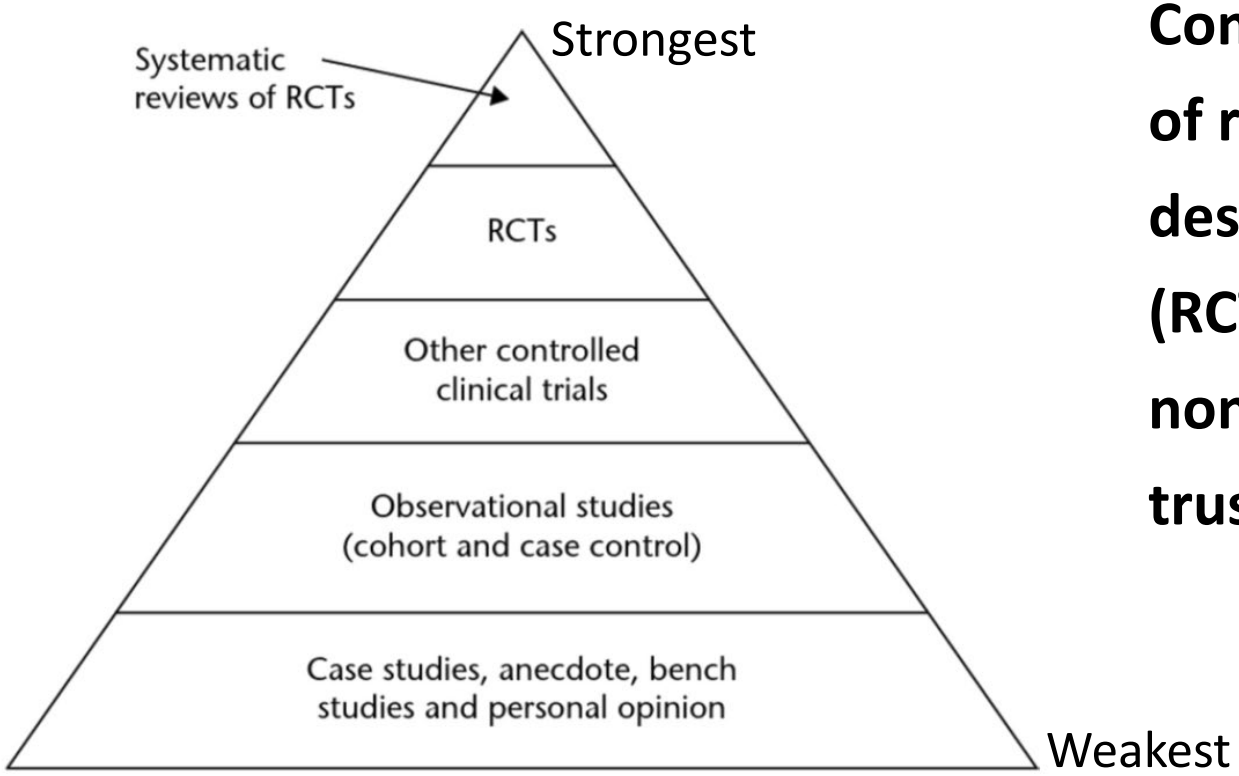
- **U.K. Medical Research Council trial of streptomycin to treat tuberculosis (*BMJ* 1948;2:769-782)**

  - often cited as first modern randomized, controlled trial

  - excerpt: “The Committee of the Medical Research Council decided then that a part of the small supply of streptomycin allocated to it for research purposes would be best employed in a rigorously planned investigation with concurrent controls”

Hierarchies of Study Design – Circa 1990

Strength of Evidence



Comment: Overly simplistic hierarchies of research design evolved in the 1990s, designating randomized controlled trials (RCTs) as "gold standard" and suggesting non-randomized study designs are not trustworthy

Adapted from Greenhalgh, Wiley-Blackwell (2010)

Selected Publications – 1990s

Evidence-Based Medicine

"It is now accepted that virtually no drug can enter clinical practice without a demonstration of its efficacy in clinical trials."

2420 JAMA, November 4, 1992—Vol 268, No. 17

Developing Improved Observational Methods for Evaluating Therapeutic Effectiveness

"[…] an observational cohort method based on the design principles and patient assembly procedures of a randomized clinical trial closely approximates the results of the experimental trial"

630 November 1990 The American Journal of Medicine Volume 89

Selected Publications – 2000s

RANDOMIZED TRIALS OR OBSERVATIONAL TRIBULATIONS?

Editorial in *New Engl J Med* (2000): "Only randomized treatment assignment can provide a reliably unbiased estimate of treatment effects."

Volume 342 Number 25 · **1907**

RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES, AND THE HIERARCHY OF RESEARCH DESIGNS

"The results of well-designed observational studies (with either a cohort or a case–control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic."

(N Engl J Med 2000;342:1887-92.)

Selected Publications – 2020s

The Magic of Randomization versus the Myth of Real-World Evidence

"However, because of the potential biases inherent in observational studies, such studies cannot generally be trusted […]"

N ENGL J MED 382;7 NEJM.ORG FEBRUARY 13, 2020

Target Trial Emulation
A Framework for Causal Inference From Observational Data

"The goal of target trial emulation is to avoid making fundamental errors that can result in erroneous causal conclusions."

2446 JAMA December 27, 2022 Volume 328, Number 24

Outline of Presentation

- Hierarchies of study design
- **Emergence of real-world evidence (RWE)**

Observational Studies – 'Old' Dogma

A COMPARISON OF OBSERVATIONAL STUDIES AND RANDOMIZED, CONTROLLED TRIALS

KJELL BENSON, B.A., AND ARTHUR J. HARTZ, M.D., PH.D.

RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES, AND THE HIERARCHY OF RESEARCH DESIGNS

JOHN CONCATO, M.D., M.P.H., NIRAV SHAH, M.D., M.P.H., AND RALPH I. HORWITZ, M.D.

<u>Accompanied by editorial</u>: *Randomized trials or observational tribulations*?

"Only randomized treatment assignment can provide a reliably unbiased estimate of treatment effects […] perhaps we have not tried hard enough to convert the skeptics." (Pocock & Elbourne, *New Engl J Med* 2000;342:1907)

Observational Studies – Contemporary Debate

'The Magic of Randomization versus the Myth of Real-World Evidence'

"[…] because of the potential biases in observational studies, such studies cannot generally be trusted […] replacement of randomized trials with nonrandomized observational analyses is a false solution to the serious problem of ensuring that patients receive treatments that are both safe and effective."
(Collins, et al., *New Engl J Med* 2020;382:674)

'Misunderstanding randomized controlled trials'

"We argue that any special status for RCTs is unwarranted. Which method is likely to yield a good causal inference depends on what we are trying to discover as well as on what is already known." (Deaton & Cartwright, *Soc Sci Med*, 2018;210:2)

What's Changed? – Availability of 'Big Data'

Origin: Term appeared in computer science literature during 1990s, often referring to data too large to be stored in then-conventional storage systems

Contemporary usage: *Big Data* represents "[…] shorthand for advancing trends in technology that open the door to a new approach to understanding the world and making decisions" (Lohr S, *New York Times*, 11 Feb 2012)

Perspective: Modern technology has increased quantity and forms of available data as well as the speed to merge and manipulate data, yet integration and analysis of large-scale data has always been integral to epidemiology

What's Changed? – Views on Observational Studies

Cochrane Collaboration – 2014:

- **"[…] on average, there is little evidence for significant effect estimate differences between observational studies and RCTs […]"**
- **"Factors other than study design *per se* need to be considered when exploring reasons for a lack of agreement between results of RCTs and observational studies"**

Citation: Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: MR000034. DOI: 10.1002/14651858.MR000034.pub2.

Example – Hormone Replacement Therapy (HRT)

The HRT controversy: observational studies and RCTs fall in line

"For randomised trials, [the start of HRT] is the natural analysis because therapy starts at randomisation…the first years of hormone replacement by combined oestrogen-progestin did increase coronary heart disease, which then waned"

"Most current users [in observational studies] were past the window wherein coronary heart disease risk was increased […] when data from the observational part of the [randomized trial] were re-analysed according to time since start of therapy, the same pattern emerged of an initial increase in risk, followed by a decrease"

Vandenbroucke *Lancet* 2009;373:1233

What's Changed? – New Terminology

Origin: "Real world" is a non-specific term; "real-world data (RWD)" and "real-world evidence (RWE)" appeared in medical literature as of the 1970s or earlier, in various contexts

Contemporary usage: RWD and RWE have specific regulatory implications

Perspective: Older epidemiologic terms were sufficient, but emergence of big data, changing views on study design, and regulatory initiatives have led to sometimes confusing use of different taxonomies for study design

Publication – Study Design in the Era of RWE

Randomized, observational, interventional, and real-world—What's in a name?

John Concato[1] | Peter Stein[2] | Gerald J. Dal Pan[3] | Robert Ball[3] | Jacqueline Corrigan-Curay[1]

In the current era of RWE, the FDA is evaluating whether and how observational studies intended to evaluate efficacy can contribute persuasive results from scientific and regulatory perspectives. In this context, a "randomized trial versus observational study" dichotomy is overly simplistic as short hand for strength of study design to support causal inference. Clarity is needed regarding interventional or noninterventional design, primary collection or secondary use of data, and characteristics of comparison group(s), as well as an assessment of prognostic determinism for the corresponding cause-effect association.

Pharmacoepidemiol Drug Saf. 2020;29:1514–1517

Emergence of Real-World Evidence – Summary

Interest in real-world evidence (RWE) can be attributed to:

- **Improved access to, and rapid analysis of, information in the era of big data**
- **Research showing observational studies can generate results similar to those of randomized controlled trials (RCTs)**
- **21st Century Cures Act mandating U.S. Food and Drug Administration (FDA) evaluate the potential use of RWE for medical product approvals**
- **Popularity of "real-world" as a term; other factors, including COVID-19**

Note: Confusion exists when using the terms "RWD" and "RWE," but most of the underlying methodology isn't new

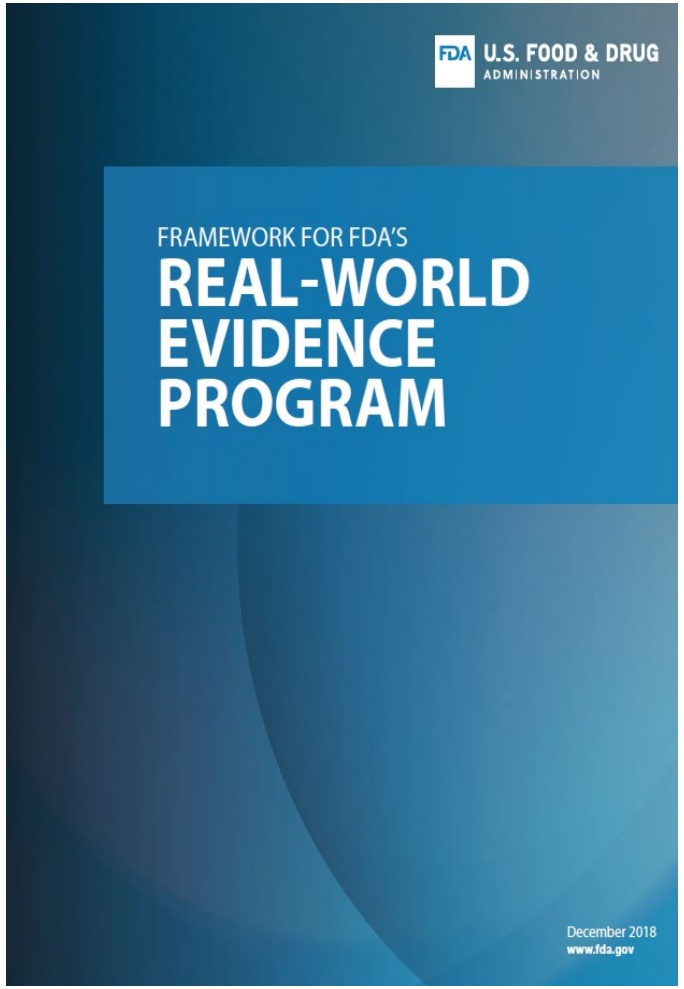
Outline of Presentation

- Hierarchies of study design
- Emergence of real-world evidence (RWE)
- **Selected aspects of FDA's RWE Program (*Note: Marie Bradley to provide additional details*)**

21st Century Cures of 2016 – 'Mandates Met'

- **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 2018:**
  - **Describe sources of data, challenges, opportunities, etc.**
- **Draft guidance for industry issued 2021-2024**
- ***Note: Standard for substantial evidence to approve drug & biologics unchanged***

FDA's RWE Framework For Drugs & Biologics (2018)



- **Applies to:**
  - **Center for Drug Evaluation & Research (CDER)**
  - **Center for Biologics Evaluation & Research (CBER)**
  - **Oncology Center of Excellence (OCE)**
  - ***Center for Devices & Radiological Health (CDRH) has separate regulations & RWE program***

- **Multifaceted program to implement RWE:**
  - **internal agency processes**
  - **external stakeholder engagement**
  - **demonstration (research) projects**
  - **guidance development**

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

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

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

- **electronic health records (EHRs)**
- **medical claims data**
- **product and disease registries**
- **data from digital health technologies in non-research setting**
- **other data sources that can inform on health status, such as questionnaires**

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

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

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

New Indication for Prograf® Based on RWE


FDA approves new use of transplant drug based on real-world evidence

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

https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence

Representative Challenges with Use of RWD

Real-world data sources:

- data reliability and clinical relevance
- missing or "mistimed" data
- suitable capture of endpoint data
- need for linkage with other data sources

Design and interpretation of non-randomized studies:

- residual confounding
- problems with index date ("zero time")
- use of inappropriate comparator

Conduct of non-randomized studies:

- protocol and analysis plan not *pre-specified*
- access to patient-level data and ability to inspect RWD sources

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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"**

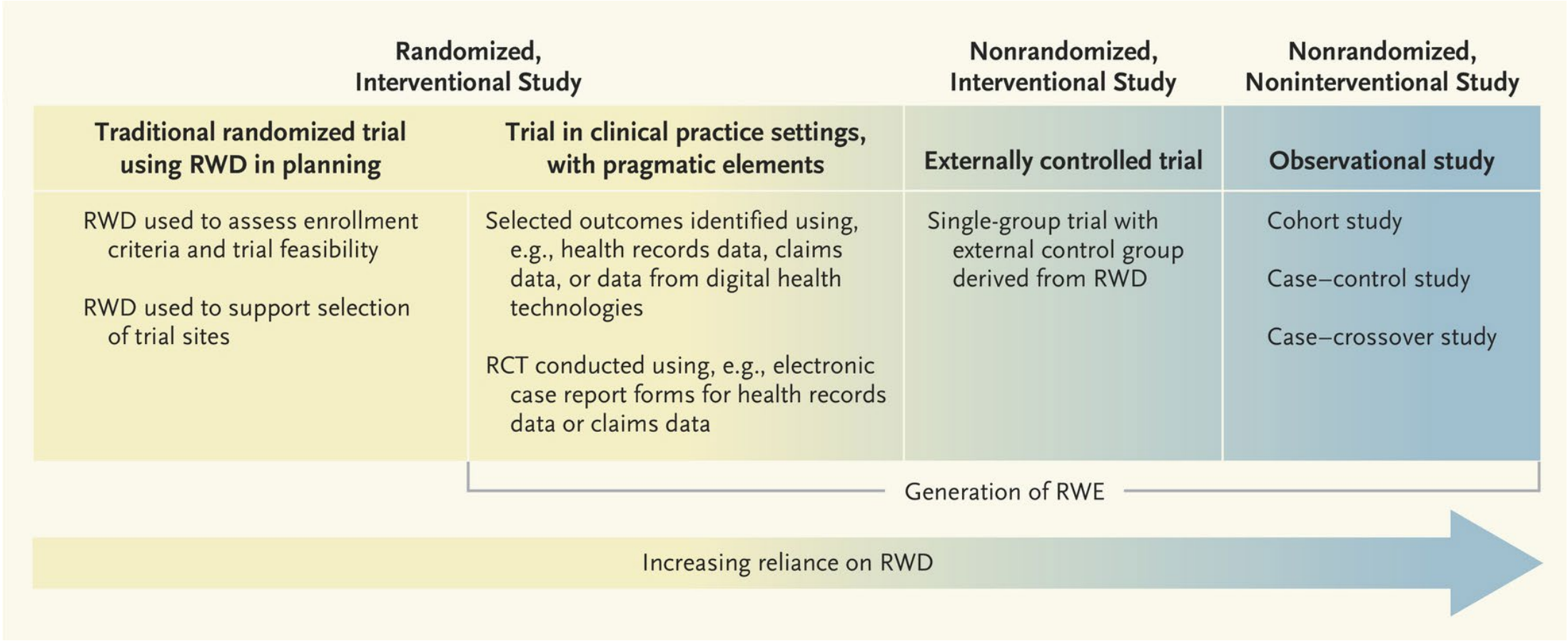
- ***Misconception #2 – A simple dichotomy of randomized trials vs. observational studies exists*: "In reality, clinical trials are defined by assignment of treatment according to an investigational protocol, and single-arm trials face challenges similar to those in observational studies in determining whether difference in clinical outcomes (compared to an external control group) represent actual treatment effects"**

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

When Does RWD Generate RWE?

Real-World Evidence — Where Are We Now?

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



Reliance on RWD in Representative Types of Study Design.

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

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

'Case Study' – *revisited*

Evidence generation:

- **Medical Research Council trial of streptomycin to Rx tuberculosis (*BMJ* 1948;2:769-782)**
  - **often cited as 1st modern trial**
- **Observational study reached same conclusion (*Am Rev Tuberc* 1948:58:64-76)**
  - **rarely cited in the literature**

Excerpt from Essay:

A balanced view regarding study design in patient-oriented research is represented by statements such as: "The importance lies not in arguing about which methodology is better than the other, but what can be learned about disease activity and therapy from each type of study" (10), and "Decision makers need to assess and appraise all the available evidence irrespective of whether it has been derived from randomised controlled trials or observational studies; and the strengths and weaknesses of each need to be understood" (12). These cogent recommendations can even be applied retrospectively to data from the 1940s, when the landmark RCT conducted by the United Kingdom Medical Research Council (55) and the observational study conducted by the U.S. Department of Veterans Affairs (56) both showed that streptomycin was effective in treating tuberculosis. Pulmonary medicine therefore has the distinction of perhaps having the earliest medical evidence refuting a hierarchy of research design.

Am J Respir Crit Care Med Vol 187, Iss. 11, pp 1167–1172, Jun 1, 2013

Looking Forward

Closing paragraph from 2022 NEJM article:

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

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

Summary

- In addition to the randomized trial paradigm, availability of big data and passage of 21st Century Cures Act reflect & contributed to emergence of “real-world evidence”
- FDA’s RWE Program is advancing as outlined in the 2018 *Framework for FDA’s Real-World Evidence Program*, including guidance and demonstration projects
- Whether based on clinical trials or observational studies, and with or without real-world data, FDA approves drugs and biological products using an existing evidentiary standard

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Innovative approaches to clinical trials

Leonard Sacks MD

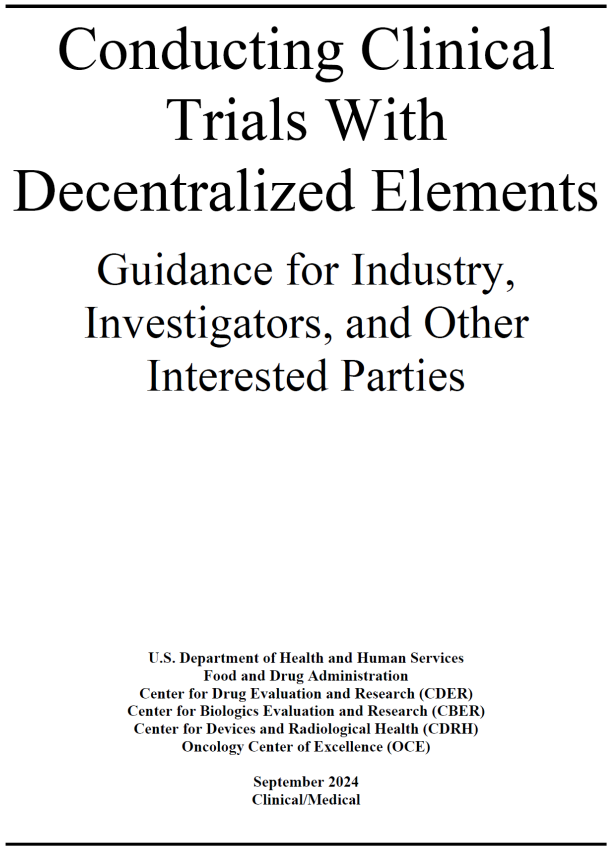
Office of Medical Policy

CDER

FDA

Clinical Trials with Decentralized Elements

Decentralized elements allow trial-related activities to occur at locations other than traditional clinical trial sites that are convenient for trial participants



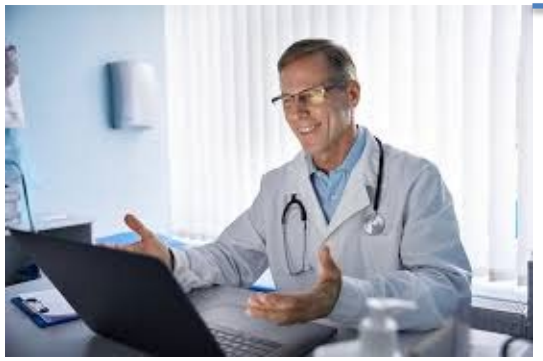
Conducting Clinical Trials With Decentralized Elements

Guidance for Industry, Investigators, and Other Interested Parties

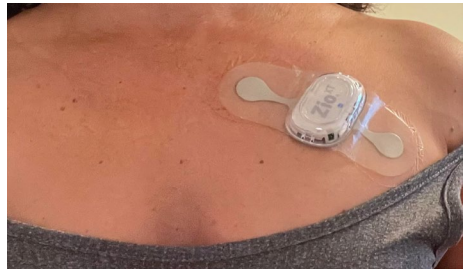
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

September 2024
Clinical/Medical

Decentralized clinical trials -a bundle of strategies



Remote telehealth visit with investigator



Digital Health Technology

Electronic informed consent

Home delivery of drug

Local clinic

Local Health Care Provider

Use of local healthcare providers and facilities

- There are resources and qualified healthcare providers in the clinical care environment who may be used in trials
- Delegation routine clinical activities to patient's local clinic or healthcare provider for routine procedures- e.g., X ray, clinical examination, laboratory tests)
- Ensuring appropriate qualifications
- Regular review of data

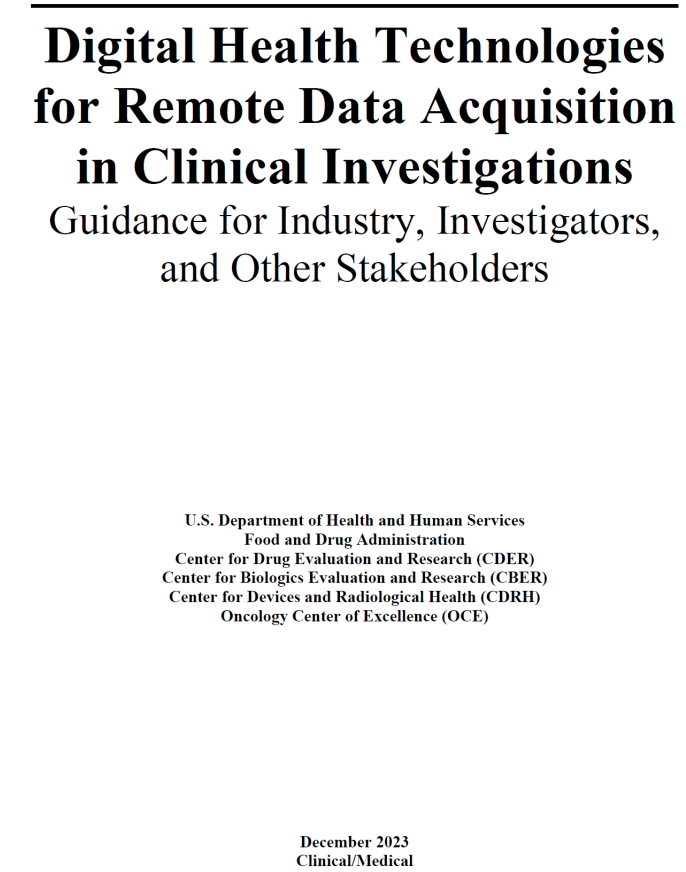
Home visits

- Novel approach
- Either dedicated trial staff or contracted healthcare providers
- Mobile trial units are being developed
- Extend the physical reach of the trial

Digital Health Technologies

"Digital health technologies (DHTs) are systems that use computing platforms, connectivity, software, and/or sensors for health care and related uses"

In the context of clinical trials, we are interested in DHTs such as wearables, interactive applications, and instruments placed in the patient's environment that measure clinical features of interest in a clinical trial



Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Guidance for Industry, Investigators, and Other Stakeholders

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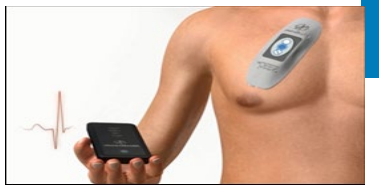
Oncology Center of Excellence (OCE)

December 2023
Clinical/Medical

Transducer	output	Clinical feature to be measured	Data processing	Clinical DHT
Galvanometer	voltage/ current/ impedance	Heart rhythm	Algorithm	
Accelerometer	Voltage/ current/ impedance	Walking, Scratching Sleep Tremor	Algorithm	
Photoelectric cell	Voltage/ current/ impedance	Blood oxygen saturation	Algorithm	
Electrochemical sensor	Voltage/ current/ impedance	Blood glucose	Algorithm/ calibration curves	
Thermocouple	Voltage/ current/ impedance	Temperature	Algorithm	

As far as biosensors go, they measure clinical features

Discrete events

- **Steps**
- **Breaths**
- **Coughs**
- **Pulse beats**
- **Seizures**
- **Tremor**
- **FEV1**

Continuous readings

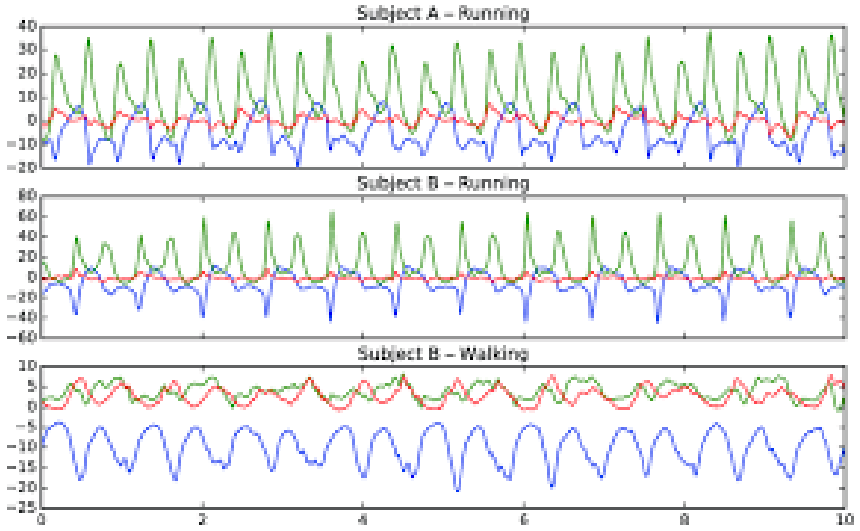
- **Glucose**
- **pO_2**
- **Temperature**
- **ECG**
- **Blood pressure**

Novel types of data that biosensors can provide

Opportunities	Examples
Rich continuous data instead of snapshots	average steps per day v.s. 6MWD, continuous glucose monitoring v.s. HBA1C
Ability to detect rare events	Falls, arrhythmias, seizures, apneic spells
Data from patients who cannot report	scratching in infants with atopic dermatitis, sleep in patients with dementia
Dose response information	on/off effects in Parkinson's
New types of measurement	gait stability that may predict falls, coughing, sneezing, tremor Behavior patterns in dementia or depression
Early detection of functional abnormalities	coordination, gait, reaction time

Example of Analytical Validation Study- confirms that the interpretative algorithm is working as needed

Raw signal



Interpretive Algorithm

Step count in 5 minutes = 480

Ground truth

Observer report

Step count in 5 minutes = 477

Is the DHT suitable for use in the trial? (Operational issues)

- Ugly or elegant?
- Easy to put on?
- Easy to operate?

- Comfortable to wear for the required time period?
- Battery life?
- Syncing data?
- “Bring your own” devices?

Measurement tool versus clinical endpoint

- **Important to distinguish between the instrument used to measure a clinical feature, and the clinical feature used to evaluate the effect of a drug.**
  - **Verification and Validation are technological assessments. They address how well the technology measures the clinical feature of interest.**

  - **Justification of an endpoint (or a clinical outcome assessment) is a clinical issue. It addresses whether the clinical feature is a meaningful way to assess the response to treatment (nothing to do with the DHT).**

EMA qualified 95th centile of stride velocity as primary endpoint in studies in ambulatory Duchenne muscular dystrophy

- The top 5% fastest strides a patient spontaneously takes in their normal daily environment over a predefined time period

Justification of the endpoint as a clinically meaningful measure of drug effect

- **Formulating the endpoint**

What is being measured?	Steps
What is the time window of observation?	4 weeks
What is the formula for the response in each patient?	Change from week 1 to week 4 in average daily step count

- **Is the endpoint clinically meaningful measurement of drug effect?**
  - **Comparison with existing benchmarks of performance- UPDRS, other Patient reported outcomes, 6MWD**
  - **Input from patients, caregivers, professional societies, disease experts, regulators**

Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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

For questions regarding this draft document contact (CDER) Heather Stone, 301-796-2274, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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

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

Background

- **Medical literature abounds with point-of-care trials, trials with pragmatic elements, large simple trials**
- **All these rely on integration of clinical research with clinical care**
- **These approaches have not been significantly adopted for regulatory submissions**

Context

- **Clinical care and clinical trials are usually not integrated, often involving different locations and different personnel**
- **Unlike trials with decentralized elements, where the goal is to shift trial-related activities to patients homes or other convenient locations, these trials take place at locations where patients go for their care; hospitals, clinics and other care networks, and may include the participation of patients' local healthcare providers (HCPs)**
- **Integrated trials are appealing as they may allow rapid recruitment, convenience for patients, practical efficiencies, broader inclusion of representative populations**

Trials in the clinical practice setting

- **RECOVERY trial the UK for COVID-19**
  - **Reportedly recruited 40,000 COVID patients through the NHS in the UK within 6 weeks**
  - **Were able to show the mortality benefit of steroids, tocilizumab, and baracitinib in treating patients hospitalized with COVID.**
- **Practice settings allow engagement of large numbers of patients in short periods of time**
  - **reflect the effectiveness of treatment in real-world environments,**
  - **accessibility of clinical trials to patients who wouldn't normally participate**

Integrating RCTs into clinical practice

- Goal: to conduct clinical trials where participants get their routine care (sometimes referred to as point-of-care trials)
  - Trial design and activities are streamlined to align with clinical practice
  - Leverage established health care institutions and existing clinical expertise in the medical community to reduce startup times, speed up enrollment and improve accessibility and convenience for patients
  - Real-world data from electronic or other health care records may be used
  - Trial-related activities may be conducted as part of routine practice, with participation of local healthcare providers
  - Dedicated trial staff may participate if needed, to perform activities that require research-specific expertise

Role of Healthcare Institutions

- Sponsors may engage healthcare institutions e.g., health maintenance organizations, hospitals, clinical networks, קופת חולים
- May facilitate rapid enrollment of large numbers of patients by improving accessibility and convenience
- Agreements should document responsibilities of healthcare institutions, their employees and the tasks they will perform, and responsibilities of the sponsor
- Sponsors should ensure that institutions and local HCPs are suitably credentialed

Clinical Investigator Oversight

Clinical investigators:

- **are responsible for ensuring that a trial is conducted according to the signed investigator statement and the investigational plan, and for protecting the rights, safety, and welfare of participants in the trial**
- **must review pertinent trial-related records provided by local HCPs and must ensure the accuracy and completeness of data**

Activities to be Performed by Trial Staff

- Procedures or processes that:
  - Contribute directly and significantly to trial data, and
  - Require study-specific training or detailed knowledge of the protocol

- Examples include:
  - Determining whether a trial candidate satisfies the trial's enrollment criteria
  - Conducting specialized assessments required by the protocol that require trial-specific training and expertise (e.g., evaluating tumor responses using RECIST criteria)
  - Assessing whether a trial-related adverse event is attributable to the investigational product
  - Applying protocol-specified criteria for dose modification or discontinuation of investigational products
  - Confirming that a trial participant has reached a trial endpoint

Conclusions

- **Modern technology has improved our ability to share data, to communicate remotely in real-time and to record data directly from patients.**
- **As a result, there are many opportunities to make clinical trials more convenient for patients, more efficient, and better integrated with clinical practice**

Seminar on Real-World Data and Evidence Generation in Medical Product Development: Past, Present, and Future

December 02, 2024

Non-Interventional (Observational) Studies: FDA perspective

Marie Bradley PhD, MPharm, MScPH
Senior Advisor, Real-World Evidence Analytics
Office of Medical Policy, CDER, FDA

Disclaimer

- This speech reflects the views of the author and should not be construed to represent FDA's views or policies

- I have no conflicts of interest related to this presentation

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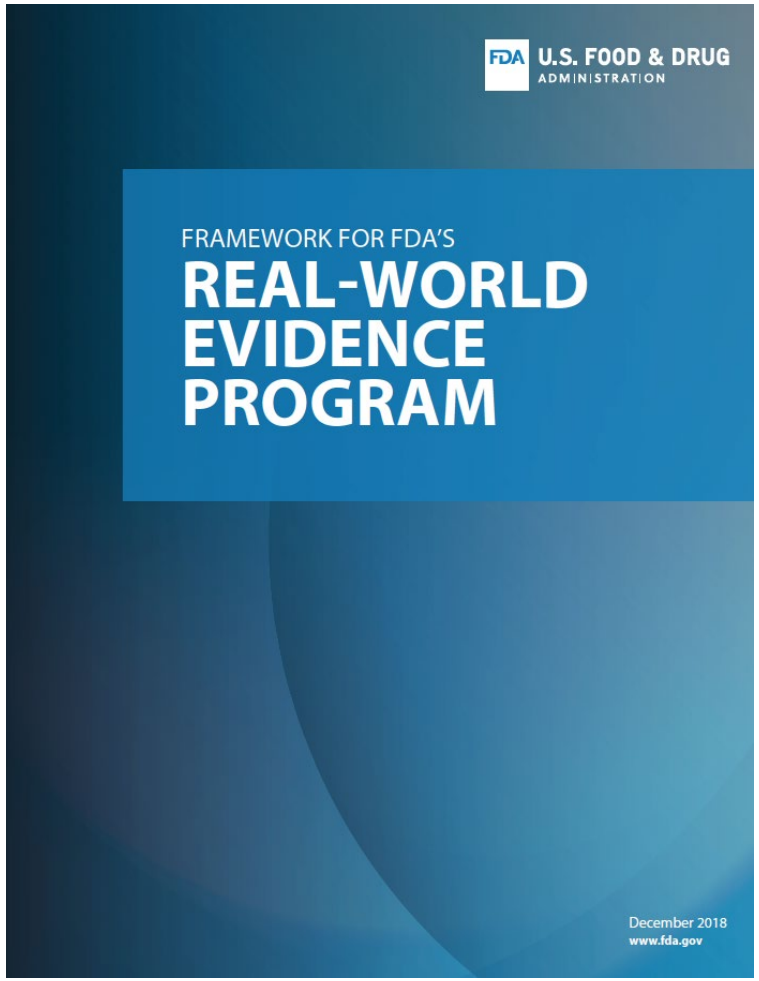
Outline

- FDA RWE Program
- FDA RWE guidance
- FDA approach to evaluating RWE
- Challenges with use of RWE
- Selected RWE demonstration project awards
- Summary

FDA RWE Program

FDA's RWE Framework For Drugs & Biologics (2018)



- Center for Drug Evaluation & Research (CDER)
- Center for Biologics Evaluation & Research (CBER)
- Oncology Center of Excellence (OCE)

- Multifaceted program to implement RWE:
  - internal agency processes
  - external stakeholder engagement
  - demonstration (research) projects
  - guidance development

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

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

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

- electronic health records (EHRs)
- medical claims data
- product and disease registries
- data from digital health technologies in non-research setting
- other data sources that can inform on health status, such as questionnaires

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

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

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

Publication: What is RWD/RWE?

COMMENTARY

WILEY

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

Motiur Rahman[1] | Gerald Dal Pan[2] | Peter Stein[3] | Mark Levenson[4] | Stefanie Kraus[5] | Aloka Chakravarty[6] | Donna R. Rivera[7] | Richard Forshee[8] | John Concato[1,9]

Pharmacoepidemiol Drug Saf 2024 Jan;33(1):e5715

Publication: When Can RWD Generate RWE?

Study design	Is RWE generated? No	Yes
Interventional studies		
Randomized, controlled trials		
Real-world data (RWD) used to develop a study (e.g., to identify potential participants, select trial sites)	✓	
RWD used to assess impact of various enrollment criteria	✓	
Data from trial-provided digital health technology	✓	
Open-label extension studies not using RWD	✓	
RWD used for trial endpoint		✓
Data from digital health technology used in non-research settings		✓
Open-label extension studies including RWD		✓

Study design	Is RWE generated? No	Yes
Interventional studies		
Externally controlled trials		
Single-arm trial with summary level estimate as comparator	✓	
External control arm data* from a clinical trial	✓	
External control arm data* from a RWD source		✓
Non-interventional studies		
Observational cohort study		✓
Case–control study		✓
Case-crossover study		✓
Self-controlled case series		✓

Pharmacoepidemiol Drug Saf 2024 Jan;33(1):e5715

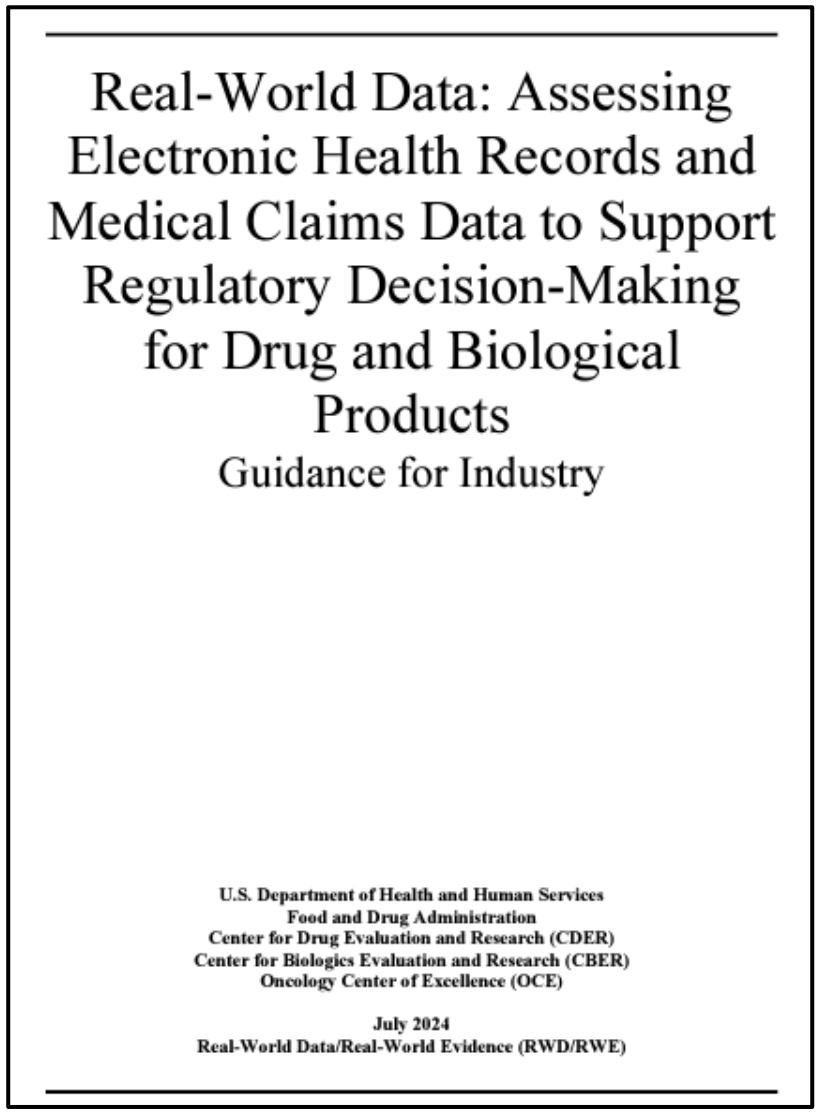
FDA RWE GUIDANCE

FDA RWE Guidance – Drugs & Biologics

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

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

Guidance: EHR and Claims Data (July 2024)



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

Guidance for Industry

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

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

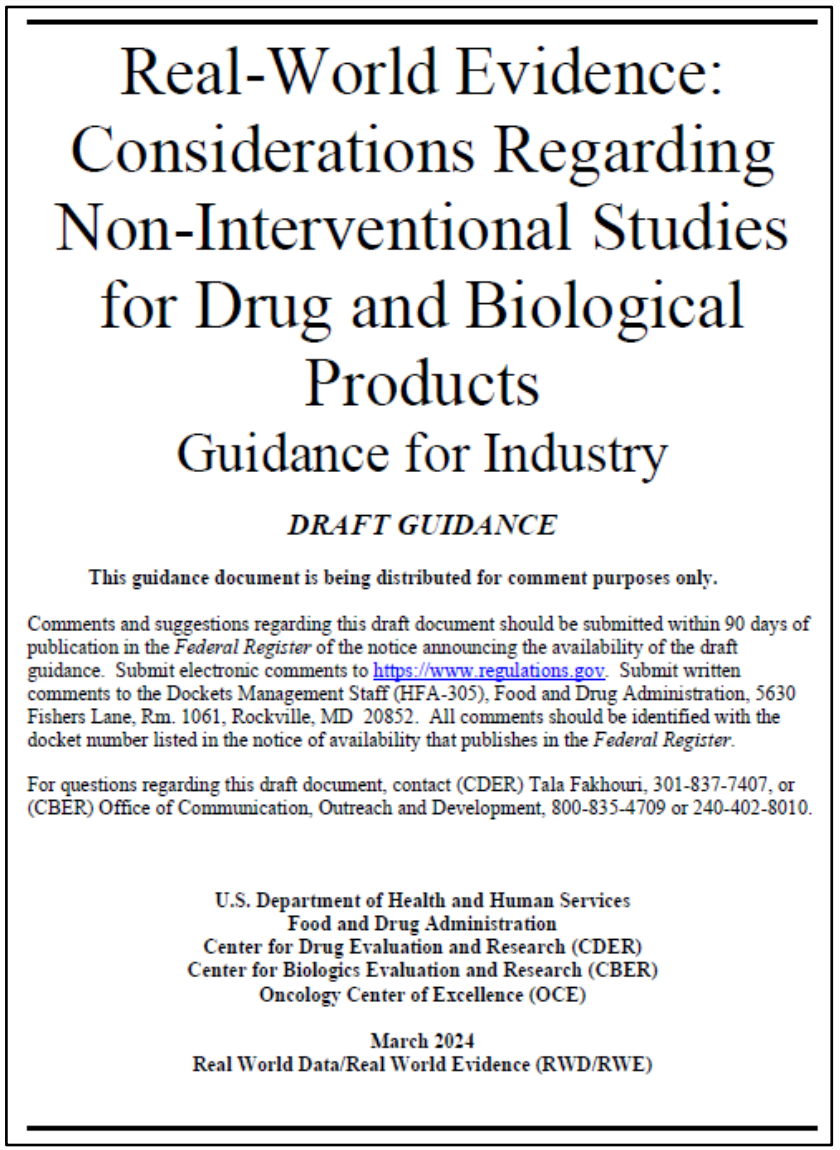
Selection of data source(s) to appropriately address the study question

- **data relevance and reliability**

Development and validation of definitions for exposures, covariates, outcomes

Data traceability & provenance during accrual, curation, and incorporation into the final study-specific dataset.

Guidance: Non-Interventional Studies (Mar 2024)



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

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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

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

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

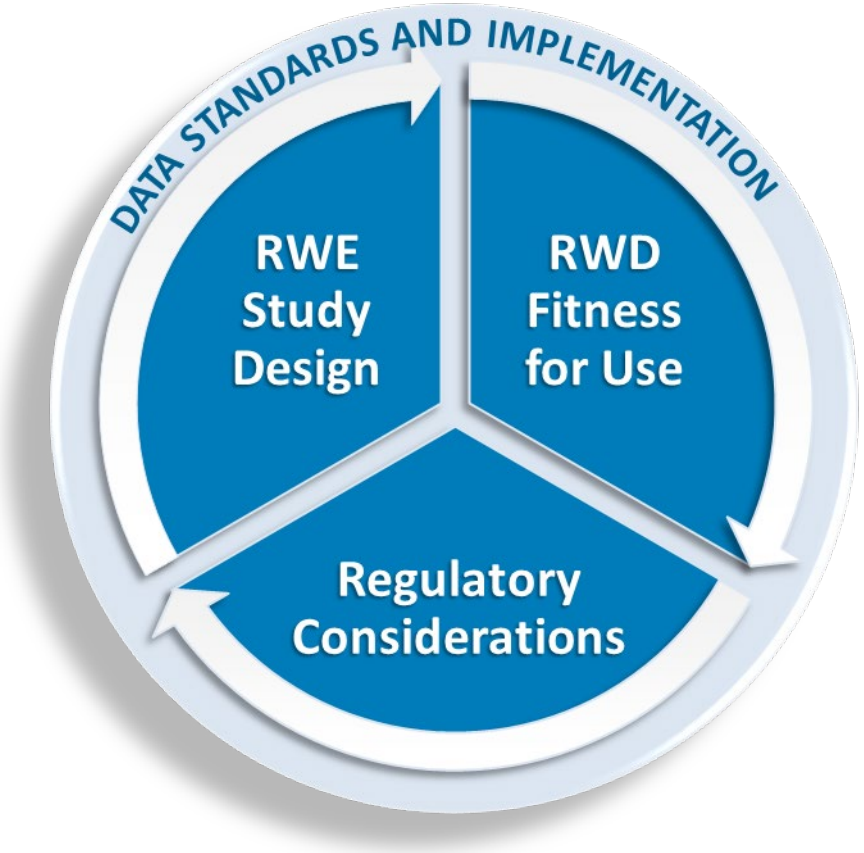
March 2024
Real World Data/Real World Evidence (RWD/RWE)

Focus: Use of a NIS to contribute to a demonstration of substantial evidence of effectiveness and/or evidence of safety of a medical product

- **Impact of and importance of identifying and addressing confounding and other forms of bias on inferences from NIS**
- **Strongly encourages sponsors to engage with Agency in early stages of study design**
- **Sponsors should describe critical study design elements and develop a protocol and prespecified statistical analysis plan (SAP) before initiating study conduct**

FDA Approach to Evaluating RWE

FDA Approach to Evaluating 'RWE' Submissions



Key considerations:

- Whether the RWD are fit for use
- Whether the study design can provide adequate scientific evidence to answer or help answer the regulatory question
- Whether the study conduct meets FDA regulatory requirements

New Indication for Prograf® Based on RWE


FDA approves new use of transplant drug based on real-world evidence

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

‘Adequate and Well-Controlled’ Observational Study

Data source: US Scientific Registry of Transplant Recipients data on all lung transplants in US during 1999–2017; data collected w/ standard analysis files

Design: non-interventional (observational) treatment group, compared to historical controls; analysis plan and patient-level data provided to FDA

Review: FDA determined this non-interventional study to satisfy the “adequate and well-controlled” evidentiary standard. 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.

https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence

Representative Challenges with Use of RWD

Real-world data sources:

- data reliability and clinical relevance
- missing or "mistimed" data
- suitable capture of endpoint data
- need for linkage with other data sources

Design and interpretation of non-randomized studies:

- residual confounding
- problems with index date ("zero time")
- use of inappropriate comparator

Conduct of non-randomized studies:

- protocol and analysis plan not *pre-specified*
- access to patient-level data and ability to inspect RWD sources

Selected Demonstration Project Awards

Demonstration Projects: Overview

FDA supports projects evaluating real-world data to generate real-world evidence in regulatory decision-making, using various funding mechanisms:

- U01 Cooperative Agreements; Broad Agency Announcements (BAAs)
- Centers for Excellence in Regulatory Science and Innovation (CERSIs)
- Interagency Agreements; Sentinel & FDA-Catalyst

CERSI

Sentinel

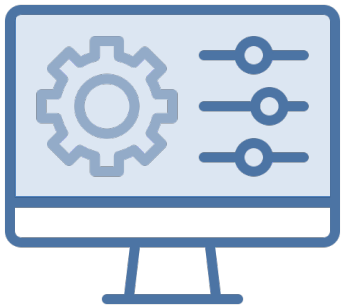
Demonstration Projects: Informal Categories

Data

(e.g., reliability & relevance)

Study Design

(e.g., innovative approaches)



Tools

(e.g., analytic methods)

https://www.fda.gov/science-research/real-world-evidence/rwd-and-rwe-focused-demonstration-projects

‘U01’ Cooperative Agreements: 2023

Title	Awardee	Primary Category
Methods to Improve Efficiency and Robustness of Clinical Trials Using Information from Real-World Data with Hidden Bias	*Duke University and North Carolina State University*	Tools
Generating Reproducible Real-World Evidence with Multi-Source Data to Capture Unstructured Clinical Endpoints for Chronic Diseases	*Harvard-MIT Center for Regulatory Science and Harvard Medical School*	Data
Real-World Data to Generate Real-World Evidence in Regulatory Decision-Making	*ECOG-ACRIN*	Design
Development of Novel Methods to Enable Robust Comparison of Real-World Progression Free Survival (rwPFS) and Clinical Trial PFS in Multiple Myeloma	*Johnson & Johnson*	Tools

https://www.fda.gov/drugs/science-and-research-drugs/fda-grant-awards-projects-supporting-use-real-world-data-generate-real-world-evidence-regulatory

Active Broad Agency Announcements

Title	Awardee	Primary Category
Medicare Advantage for Real-World Evidence in Cardiovascular Disease	*Duke Clinical Research Institute*	Data
*V*alid Real-World *E*vidence and *R*eliable Real-World Data *i*n *F*orming Regulator*y* Decision-Making (VERIFY)	*Verantos, Inc.*	Data
A Benchmark, Expand, and Calibration (Benchexcal) Trial Emulation Approach for Using Real-World Evidence to Support Indication Expansions: Process for an Empirical Evaluation	*Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School*	Study Design

Award to: *Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School*

Real-World Evidence to Support Labeling Expansions for Effectiveness Claims Using a Multi-Stage Trial Emulation Process

PIs: Shirley Wang & Sebastian Schneeweiss

Brigham and Women's Hospital

- **Context: When emulating a trial in an observational study, results can differ based on unmeasured confounding, differences in study design, and differences in the distribution of effect modifiers**
- **Issue: A structured benchmarking process of an initial observational study against RCT evidence—followed by calibration of a subsequent observational study based on differences in results observed—can increase confidence and improve interpretation of the results for a second-stage emulation of a hypothetical trial**
- **Objective: Develop a benchmark, expand, and calibrate (BenchExCal) approach to potentially inform decisions on expanding indications for approved drugs that allows for variation in measurement, follow up, or other design differences between an RCT and a database study that emulates it**

Award to: Johnson & Johnson

Developing Novel Methods to Enable Robust Comparison of Real-World Progression Free Survival (rwPFS) and Clinical Trial PFS in Multiple Myeloma

PIs: Khaled Sarsour & Ashita Batavia

with academic collaborators

Johnson & Johnson – Background

- **Context: RWD has played a limited role in the pre-approval multiple myeloma (MM) setting**
  - **alignment RWD and RCT outcomes remains a challenge**
- **Issue: Bias due to measurement error limits comparison of real-world progression free survival (PFS) and trial PFS**
  - **misclassification bias: discrepancies in progression assessment can result in misclassification of real-world progression events**
  - **surveillance bias: time-to event outcome (e.g., PFS) may differ based on progression assessment frequency and timing.**
- **Objective: Develop novel methods to address misclassification and surveillance biases in RWD, allowing for more robust comparison of rwPFS and trial PFS in MM**

Summary

- FDA's RWE Program is advancing as outlined in our 2018 Framework, including guidance and demonstration projects
- Guidance documents describe FDA's current thinking on topics including RWD sources, types of study design, and regulatory/procedural issues
- Demonstration projects address gaps in approaches for studies using real-world data, providing lessons learned for FDA and the wider community
- Work products include guidance documents, academic publications, and trainings for FDA staff (& others) based on project findings

Acknowledgments

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  - CDER Offices of Medical Policy, New Drugs, Surveillance & Epidemiology, Biostatistics, Regulatory Policy, Scientific Investigations, Strategic Programs, Translational Sciences
  - Center for Biologics Evaluation & Research; Oncology Center of Excellence; Center for Devices & Radiological Health
  - Office of the Commissioner

Thank you

CDER-RWE@fda.hhs.gov

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OSE: Jenni Li, Silvia Perez-Vilar, Hannah Day, Fang Tian, Po-Yin Chang

OCE: Donna Rivera, Catherine Lerro, Paul Kleutz, Bindu Kanapuru

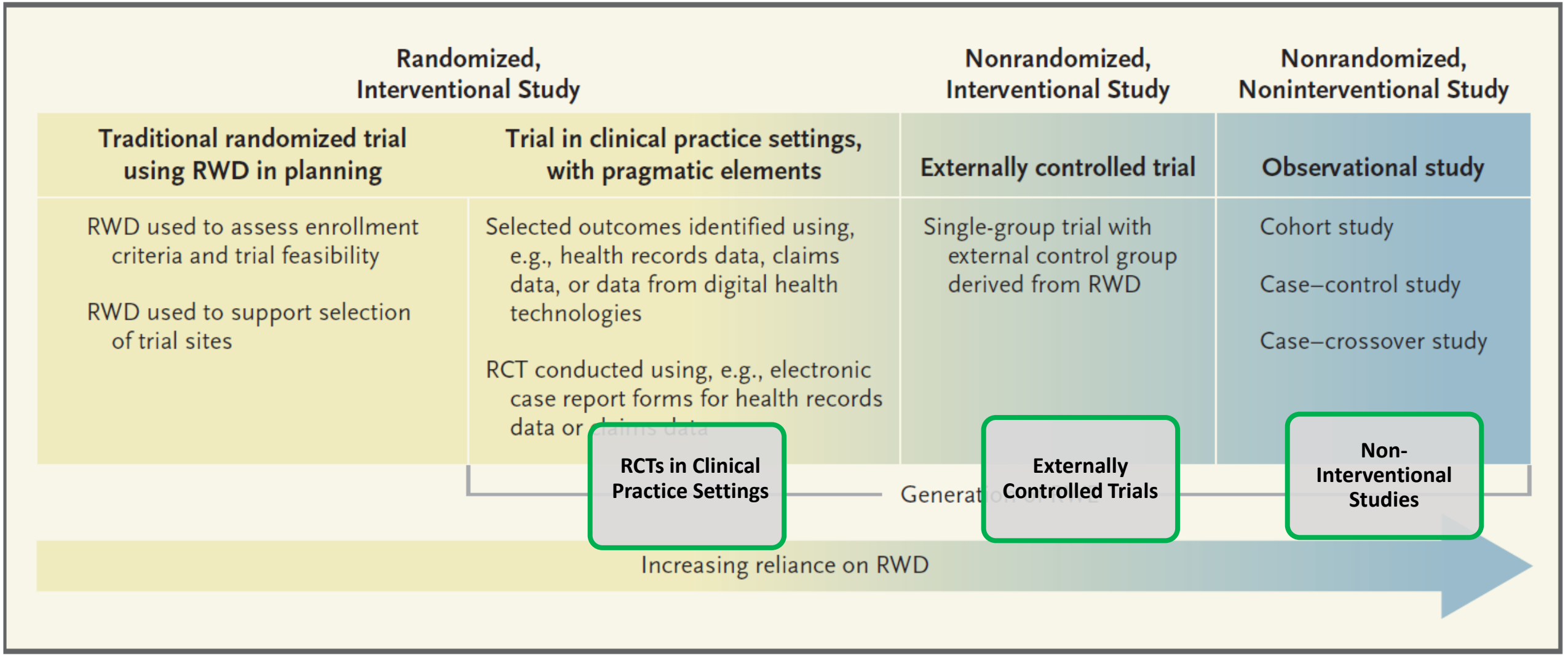
OND: Paul Lee, Laura Baldassari, Austin Anderson, Raj Nair

OB: Mark Levenson, Jiwei He, Jay Zhao

OPT: An Masaro, Melissa Lestini

Real-World Evidence — Where Are We Now?

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



Reliance on RWD in Representative Types of Study Design.

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

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