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

The public meeting will begin shortly

Real-World Evidence Guidance Webinar Series

November 22, 2024, from 1-1:45 pm ET

REAGAN-UDALL FOUNDATION FOR THE FDA

This webinar is part of a series hosted by the Reagan-Udall Foundation for the FDA, in collaboration with the U.S. Food and Drug Administration (FDA). This series is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an award of $75,417 in federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit FDA.gov.

Housekeeping

REAGAN-UDALL FOUNDATION FOR THE FDA

Due to the meeting size, your microphone and video will remain off during the meeting.

This public meeting is being recorded. The slides, transcript, and video recording will be available on the FDA Foundation website after the meeting.

Please share your questions and comments for the speakers using the Zoom Q&A function.

Agenda

REAGAN-UDALL FOUNDATION FOR THE FDA

1 pm	Welcome
1:05 pm	Opening Remarks
1:10 pm	Overview of Draft Guidance
1:25 pm	Questions and Answer
1:40 pm	Closing Remarks
1:45 pm	Adjourn

RWD/RWE Guidance Webinar Series

REAGAN-UDALL FOUNDATION FOR THE FDA

1. Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products (November 4, 2021)
2. Data Standards for Drug and Biological Product Submissions Containing Real-World Data (December 3, 2021)
3. Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products (January 28, 2022)
4. Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (February 11, 2022)
5. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (April 13, 2023)
6. Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products (May 30, 2024)
7. **Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice (November 22, 2024)**

If you are interested in viewing the recording of the webinars about the guidances listed on the screen, please visit the FDA Foundation website at reaganudall.org

Why Are We Here Today?

REAGAN-UDALL FOUNDATION FOR THE FDA

Provide an overview and address questions from the public about the draft guidance titled *Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice.*

Submit comments on the draft guidance by December 17, 2024, to https://www.regulations.gov/docket/FDA-2024-D-2052 to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance

REAGAN-UDALL FOUNDATION FOR THE FDA

Opening Remarks

John Concato, MD, MS, MPH
Associate Director for Real-World Evidence Analytics, Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

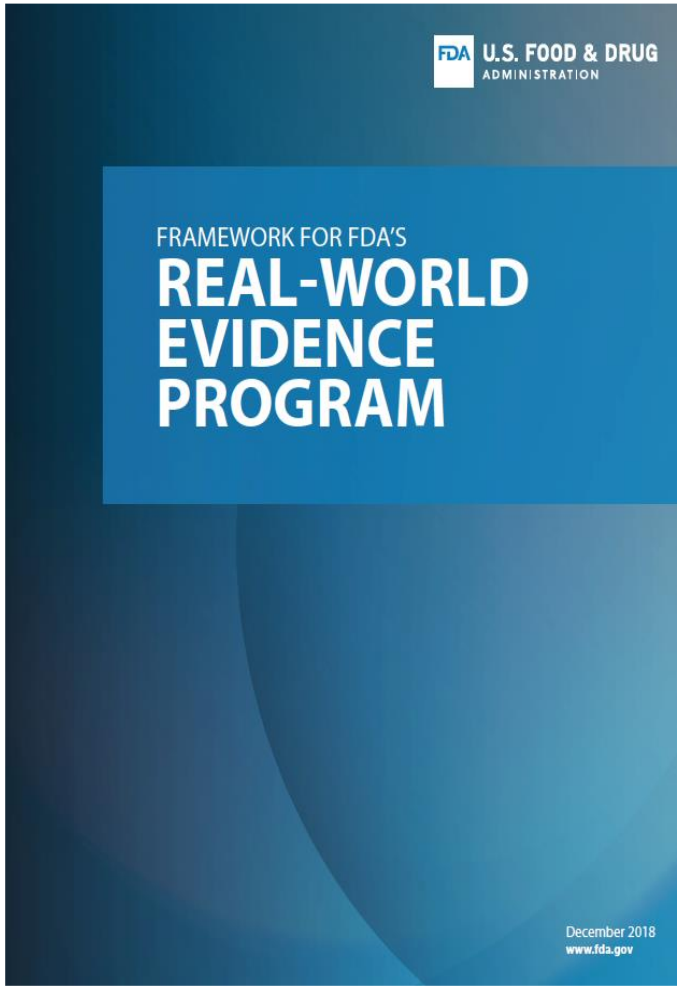
Public Webinar

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

22 Nov 2024

John Concato, MD, MS, MPH
Associate Director for Real-World Evidence Analytics
Office of Medical Policy, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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)
- Center for Devices & Radiological Health (CDRH) has separate regulations and RWE program
- Multifaceted program to implement RWE:
  - internal agency processes (e.g., consults)
  - external engagement (e.g., "listening sessions")
  - demonstration projects (e.g., U01 awards)
  - guidance development (e.g., *today's topic*)

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

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

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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, externally controlled trials, and observational studies

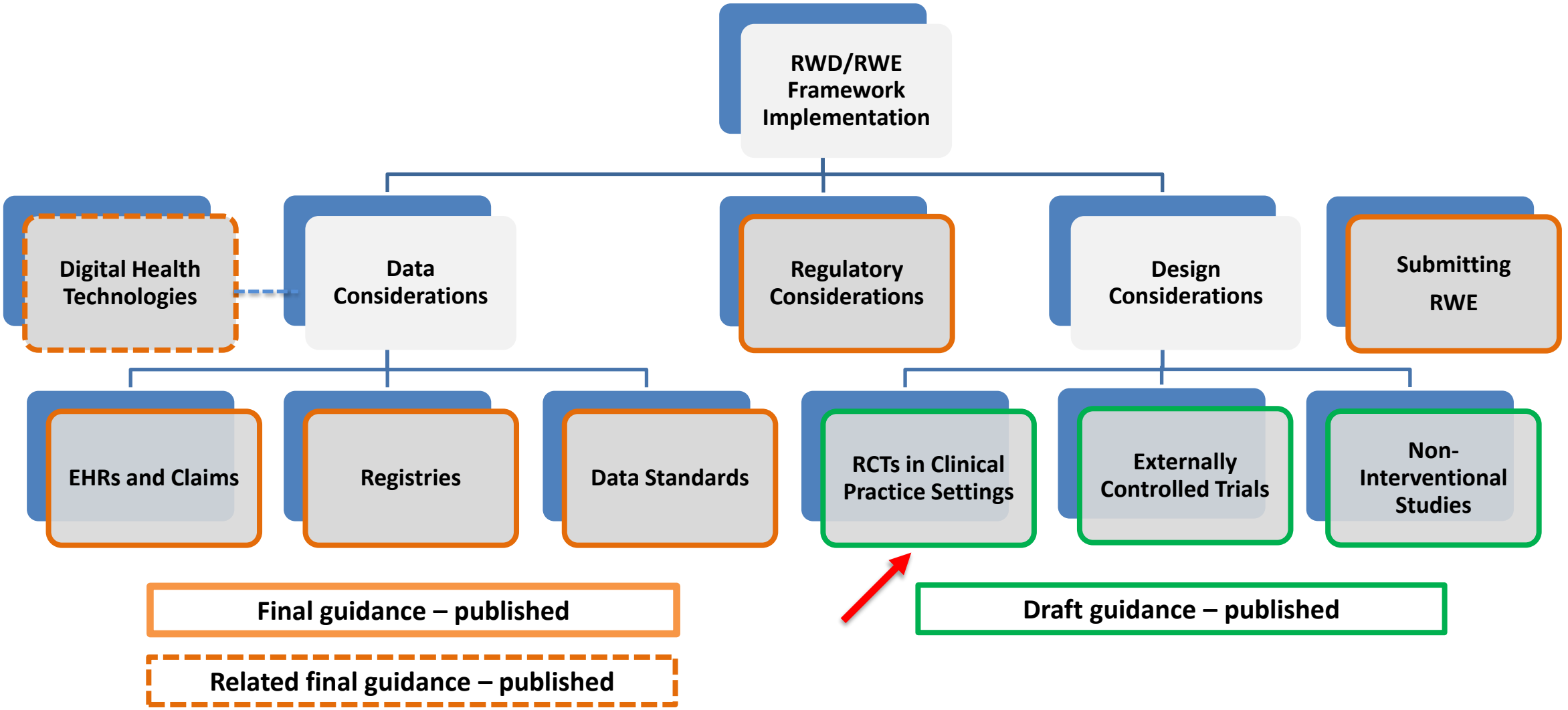
https://www.fda.gov/media/120060/download

FDA RWE Guidance – Drugs & Biologics (as of 2024)

Topic	Category	Status
EHRs and claims data	Data considerations	final issued
Registry data	Data considerations	final issued
Data standards	Data submission	final issued
Regulatory considerations	Applicability of regulations	final issued
Submitting RWE	Procedural	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

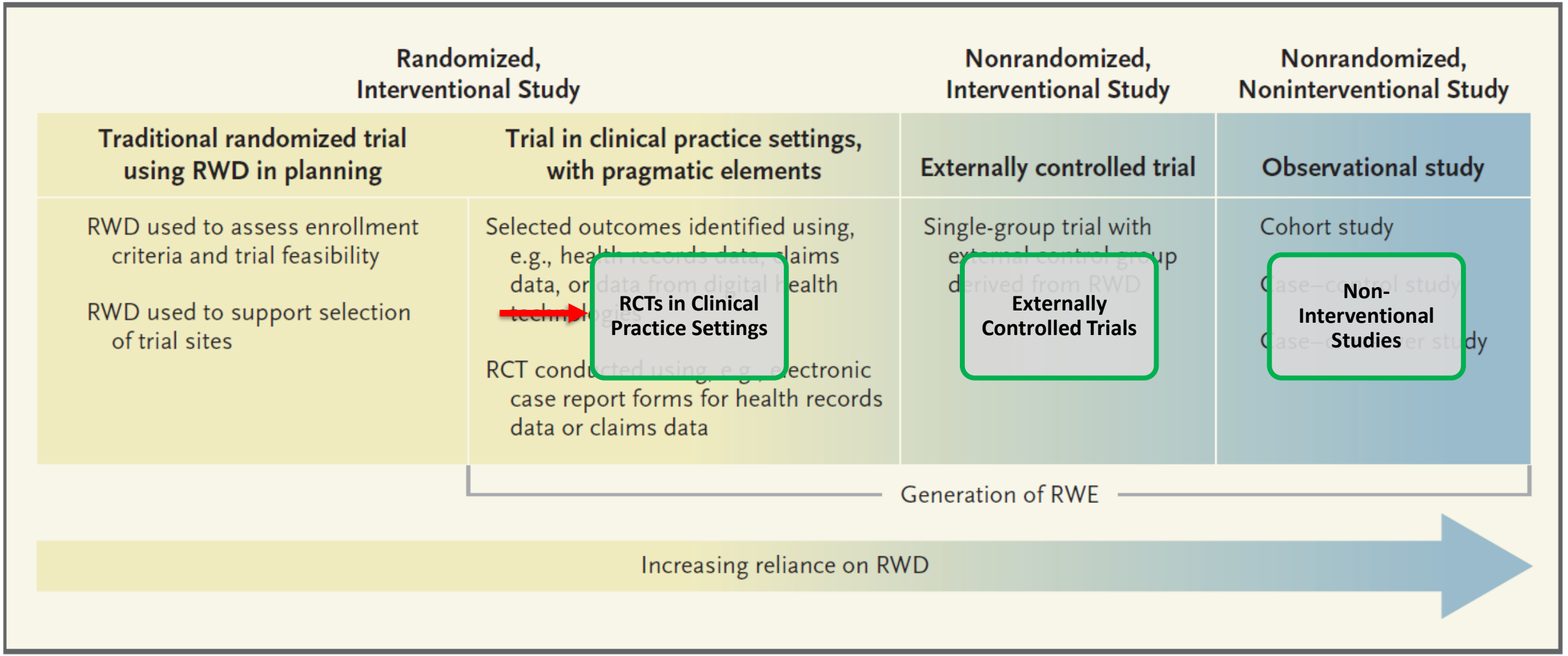
https://www.fda.gov/science-research/real-world-evidence/center-biologics-evaluation-and-research-center-drug-evaluation-and-research-real-world-evidence

FDA RWD/RWE Guidance (as of 2024)



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

Leonard Sacks, MBBCh
Associate Director
Clinical Methodologies, Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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Overview of Draft Guidance

Heather Stone, MPH
Health Science Policy Analyst
Clinical Methodologies, Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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

Draft Guidance for Industry

Leonard Sacks, MD and Heather Stone, MPH
Office of Medical Policy, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Background

- Medical literature includes many examples of point-of-care trials, trials with pragmatic elements, large simple trials
- All these designs rely on integration of clinical research with clinical care
- These approaches have not been significantly adopted by drug developers
- Draft guidance we will be discussing today is aimed at supporting such “integrated” trials

Context

- Clinical care and clinical trials are usually not integrated, often involving different locations and different personnel
- Technological advances provide new opportunities for integrating trials with routine clinical practice:
  - interactive communication technology
  - sharing of data/images/documents
- 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

Opportunities

- There is a wealth of expertise in the clinical care environment that may be applied to clinical research, but is currently largely untapped
- The clinical care environment—including healthcare institutions, treatment networks and health systems—is an additional resource for clinical research
- Simplifying trials, as appropriate, is an important strategy to improve efficiency while maintaining data quality
- Reliance on existing data reduces burden on sites and participants, and may allow the development of trials that are rapidly responsive to evolving needs
- These trials allow patients living far from trial sites, including those with rare diseases to access research opportunities and to participate

Trial Modernization

Integrated trials take advantage of:

- Widespread use of technology
- Interoperative EHRs
- Engagement w/ clinical practice

Goal of Integrating RCTs into Clinical Practice

To conduct clinical trials where participants get their routine care:

- **Trial design and activities are streamlined to align with clinical practice**
- **RWD from health care records may be used**
- **Trial-related activities may be conducted as part of routine practice, with participation of local HCPs**
- **Dedicated trial staff may participate to perform research-specific activities, if needed**

Role of Healthcare Institutions

- Sponsors may engage healthcare institutions (e.g., health maintenance organizations, hospitals, clinical networks)
- This 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**

Role of Local Healthcare Providers

- **Local HCPs, working as part of health care institutions or individual practices, may be engaged to perform trial-related tasks (see examples on next slide)**
- **These activities should not require trial-specific knowledge, trial-specific training, or research expertise**
- **Local HCPs may need limited instructions to ensure that these activities are performed as required**

Examples of Activities by Local HCPs

- **Performing routine medical procedures (e.g., blood draws, radiographs, vital signs, clinical examinations) as specified in the protocol**
- **Collecting routine clinical data for the trial using a template**
- **Following prompts in the EHR to document specified clinical events (e.g., death, myocardial infarction, stroke, seizure)**

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**

Trials Potentially Suitable to Integrate into Practice

- **Trials of FDA approved drugs (e.g., new indications, new populations, new routes of administration or doses)**
- **It may be possible to study unapproved drugs with well-understood safety profiles in clinical practice environments (e.g., members of an existing class, those where safety is already well characterized from prior trials)**

Quality-by-Design Considerations

Focus on factors that are critical for quality, including:

- **Appropriate flexibility in trial protocols to align with clinical practice (e.g., timing of trial visits)**
- **Eligibility criteria should be minimal and straightforward**
- **Informed consent documents may be embedded in EHRs**
- **Randomization and blinding are recommended whenever possible**
- **Flags in EHRs may alert local HCPs to comorbidities or concomitant medications that are not allowed**
- **Real-time monitoring of EHRs and/or calls to participants can be included to capture adverse events**

What is Novel in this Guidance?

- Addresses trial settings that are convenient for participants and may support rapid recruitment of broad populations
- Focuses on efficiencies, using existing healthcare institutions and staff, RWD, and streamlined trial designs
- Supports the engagement of large healthcare institutions, healthcare networks, and community healthcare facilities that have historically been less involved in FDA-regulated clinical trials

What is Novel in this Guidance? (cont'd)

- **Describes the roles that local HCPs can play in conducting trial-related activities**
- **Supports use of data collected during routine clinical practice to avoid duplication of data entry and reduce the need for dedicated trial sites**
- **Supports a spectrum of trials, ranging from those that rely completely on data generated during routine clinical practice to those that require supplemental activities by dedicated trial staff**

Regulatory Requirements Must be Satisfied

- Clinical investigators are responsible for ensuring the trial is conducted according to the signed investigator statement, investigational plan, applicable regulations, and for protecting the rights, safety and welfare of participants
- Activities that contribute directly and significantly to trial data and require study-specific training or a detailed knowledge of the protocol must be performed by trial staff (e.g., obtaining informed consent)
- Sponsors remain responsible for ensuring that the institutions and individual local HCPs they engage are suitably credentialed and qualified to participate in the research
- Sponsors must ensure that source records (or certified copies of source records) to support clinical trial data submitted to FDA are available for review by FDA upon request
- Integration of RCTs into clinical practice should not interfere with appropriate delivery of patient care

Acknowledgments

- **FDA Center for Drug Evaluation and Research**
  - Office of Medical Policy
  - Office of New Drugs
  - Office of Regulatory Policy
  - Office of Scientific Investigations
  - Office of Strategic Programs
  - Office of Surveillance and Epidemiology
  - Office of Translational Science
- **FDA Center for Biologics Evaluation and Research**
- **FDA Oncology Center of Excellence**


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Question and Answer

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Moderated by

Susan C. Winckler, RPh, Esq.

Panelists

John Concato, MD, MS, MPH

Leonard Sacks, MBBCh

Heather Stone, MPH

Next Steps

Submit comments on the draft guidance by December 17, 2024, to https://www.regulations.gov/docket/FDA-2024-D-2052 to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance

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Thank you!