Reimagining Clinical Research: The Transformation of Trial Design & Conduct

David Burrow, Pharm.D., J.D.
Director, Office of Scientific Investigations
Office of Compliance
CDER | US FDA

Regulatory Education for Industry (REdI) Annual Conference 2024:
Innovation in Medical Product Development – May 30, 2024

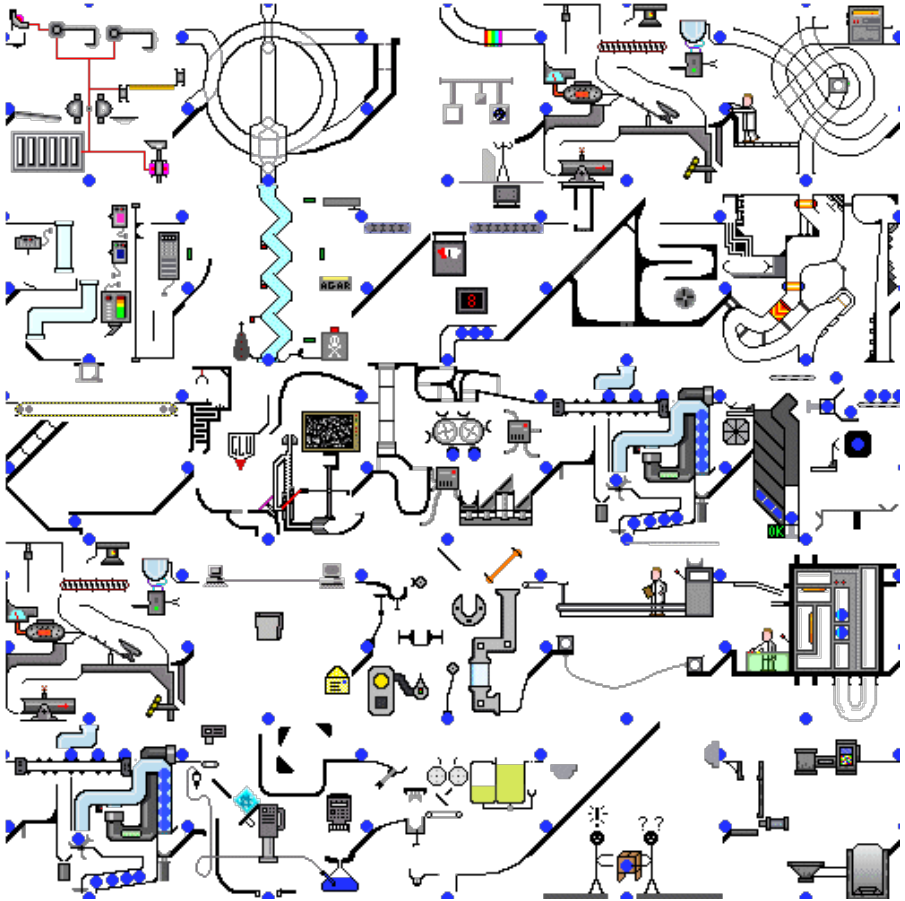
DISCLOSURES

I have no relevant financial relationship(s) in connection with this educational activity.

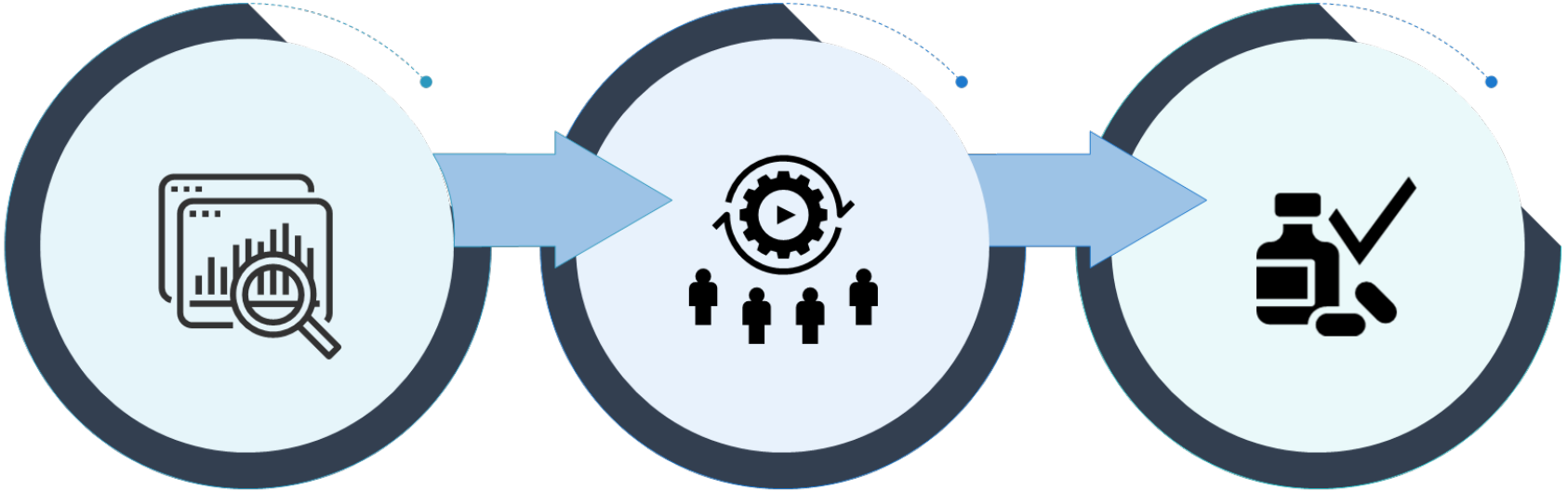
Overview

- Study Design, Execution, Assessment
- Quality by Design
- FDA/CDER Clinical Trial Innovation Programs
- FDA/CDER Center for Clinical Trial Innovation (C3TI)
- The Role of Perspective
- Lightning Round: Debunking FDA Myths

Its Complicated…



Evolving Trial Ecosystem



STUDY DESIGN: Quality by Design; building quality into the design, execution, and assessment

STUDY EXECUTION: Effective operationalization all aspects of trial conduct, and all responsible individuals and entities

STUDY ASSESSMENT: Accurate and consistent assessments aligned with the unique needs of the study/application

Alignment on Terminology

- Pragmatic Trial
- Point of Care Trial
- Decentralized Clinical Trial
- Real World Data/Real World Evidence
- Master Protocols – basket/umbrella/platform

- A spectrum of:
  - Operational approaches
  - Data sources/types
  - Trial designs

Clinical Trial Innovation

Clinical research *IS* innovation – by its very nature

- Novel treatments, growth in clinical practice

Innovation in *HOW* we conduct clinical research. We are talking about innovations in innovation!

- Trial Design (Master Protocols, Pragmatic Trials)
- Data Sources (Real World Data, EHRs)
- Operational Approaches (Decentralized Elements, Vendor/Contractors)

Quality by Design!

- You do not rise to the level of your goals. You fall to the level of your systems.

  - James Clear (Atomic Habits)

Quality by Design

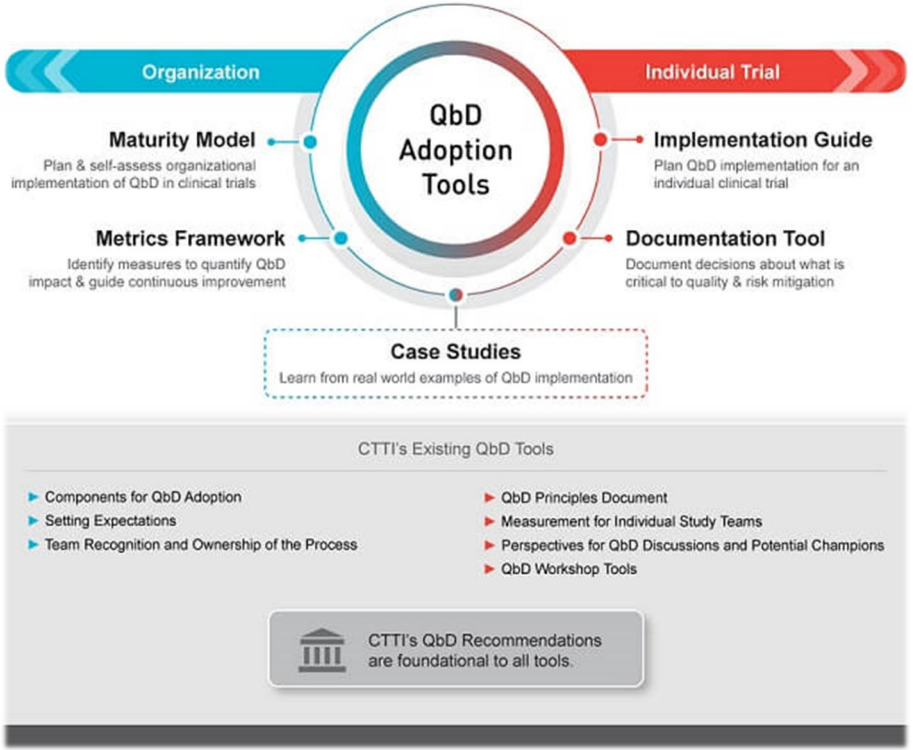
Premise: Quality in clinical trials is defined as the absence of errors that matter.

What do we need to get right to ensure reliability of results and patient protection?

Assumption: Likelihood of a successful, quality trial can be improved through prospective attention to preventing important errors that could undermine our ability to obtain meaningful information from a trial.

Quality by Design (QbD) Project

Identified best practices and develops methods and tools to apply principles of QbD to the scientific and operational design of clinical trials.



Quality by Design (QbD) Project Principles Document

- Describes CTQ factors generally relevant to most clinical trials
- Emphasizes that the criticality of different CTQ factors is based on the type and design of trial being conducted
- Emphasizes the importance of not falling into check list mentality, but use of interactive discussion when consider CTQ factors
- Provides considerations and example questions for each CTQ factor to spur cross-functional group discussion
- Emphasizes the importance of engaging all stakeholders in study development

Engage All Stakeholders in Study Development

- Share critical information and assess risk/impact
  - Use that information to inform choices!
- Sponsors, CROs, Vendors
- Sites: as a group, as individual sites
- People: CIs, study staff. All roles, all people
- Patients and research participants
- Understand the operational realities
  - Network of systems/commitments
  - People: Human factors


YER PACKIN' TOO HEAVY, LEON. ROOKIE MISTAKE.
©2012 T. BLACKMAN
crotchetycomics.blogspot.com

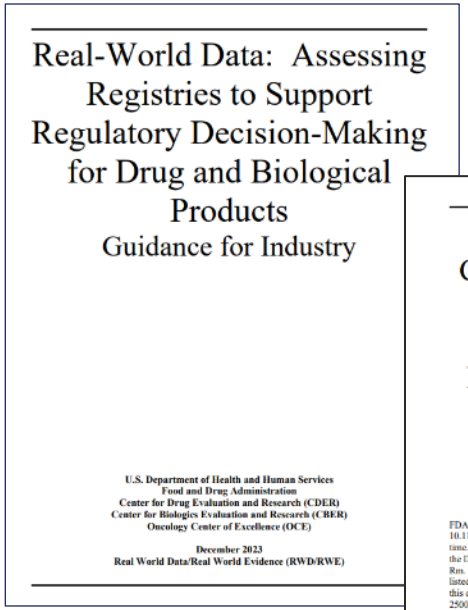
CDER's Clinical Trial Innovation Programs

Examples of FDA's Center for Drug Evaluation and Research efforts related to clinical trial innovation efforts include (but are not limited to):

Key Programs	Key Activities
Complex Innovative Trial Designs (CID)	• Developing efforts to enhance use of simpler trials that could more easily be integrated into clinical practice (often called "point-of-care trials")
Model-Informed Drug Development (MIDD)	• Guidance on implementing decentralized clinical trial (DCT) designs
Real-World Evidence (RWE)	• Artificial intelligence and machine learning in the drug development lifecycle
Rare Disease Endpoint Advancement (RDEA)	• Efforts to improve enrollment of participants from underrepresented populations, including racial and ethnic groups, through innovative clinical trials
Patient-Focused Drug Development (PFDD)	• International harmonization efforts related to innovative clinical trial design and conduct
Digital Health Technologies (DHTs)	• Public-private partnerships and other external collaborations
Drug Development Tool Qualification	

FDA Guidance Supporting Innovation

(more) FDA Guidance Supporting Innovation

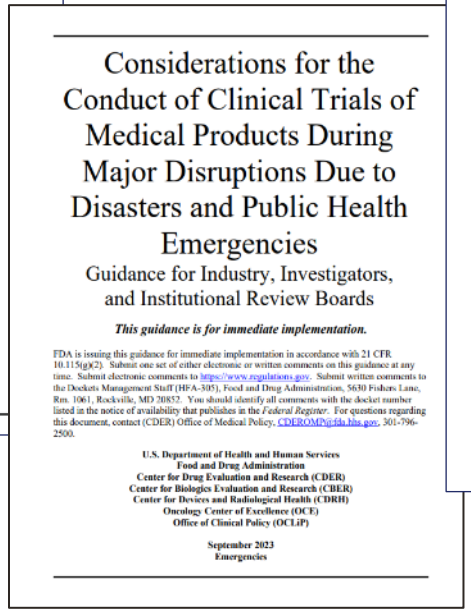


Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

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)

December 2023
Real World Data/Real World Evidence (RWD/RWE)



Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies

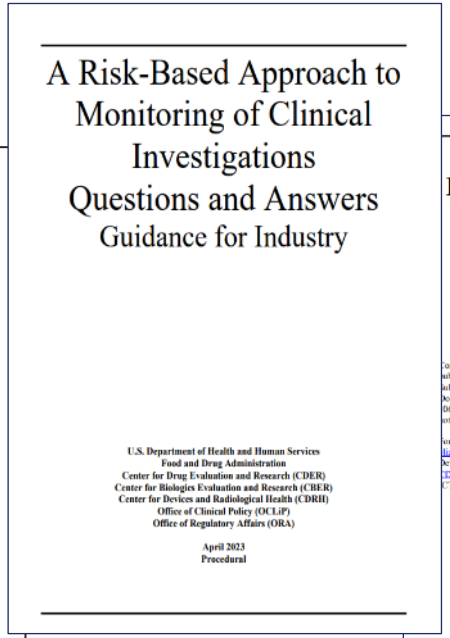
Guidance for Industry, Investigators, and Institutional Review Boards

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Submit one set of either electronic or written comments on this guidance at any time. 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. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. For questions regarding this document, contact (CDER) Office of Medical Policy, CDEROMP@fda.hhs.gov, 301-796-2500.

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 Clinical Policy (OCLiP)

September 2023
Emergencies

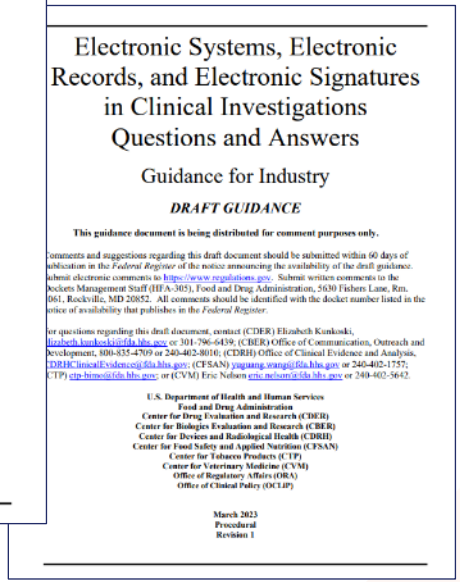


A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers

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)
Center for Devices and Radiological Health (CDRH)
Office of Clinical Policy (OCLiP)
Office of Regulatory Affairs (ORA)

April 2023
Procedural



Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers

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 60 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, elizabeth.kunkoski@fda.hhs.gov or 301-796-6439; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; (CDRH) Office of Clinical Evidence and Analysis, CDRHClinicalEvidence@fda.hhs.gov; (CFSAN) yuguang.wang@fda.hhs.gov or 240-402-1757; (CTP) ctp-hrmo@fda.hhs.gov; or (CVM) Eric Nelson eric.nelson@fda.hhs.gov or 240-402-5642.

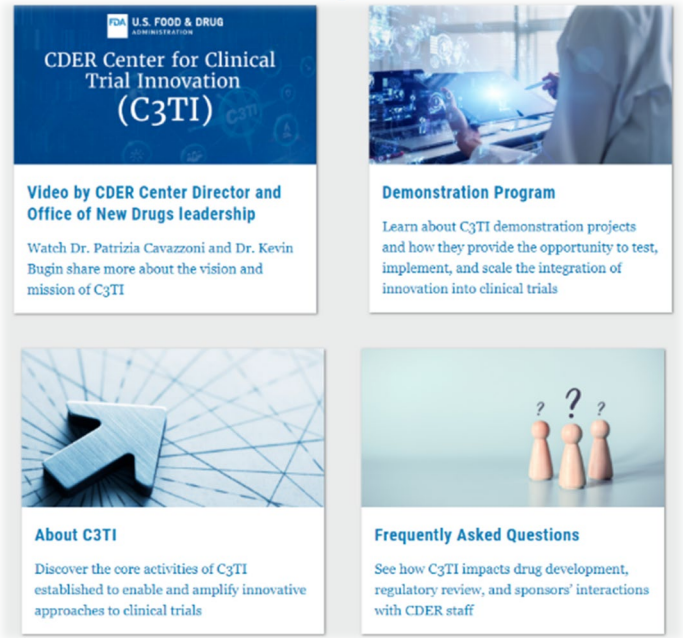
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Tobacco Products (CTP)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)
Office of Clinical Policy (OCLiP)

March 2023
Procedural
Revision 1

fda.gov/cdersbia

https://sleepinggc.com/team/angry-looking-little-owl-athene-noctua-perched-on-a-branch/
https://www.pinterest.com/pin/537265430523060862/
https://wallpapers.com/picture/funny-owl-pictures-cqs5b0p8uxmlxtsj.html

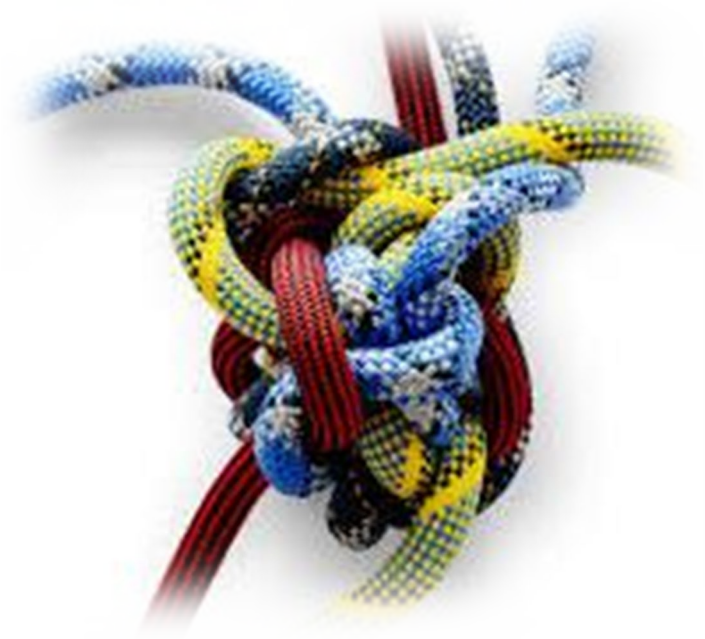
CDER Center for Clinical Trial Innovation (C3TI)



1. **Facilitate** the sharing of lessons learned across CDER's existing and new clinical trial innovation programs.
2. **Communicate and collaborate** with external parties about innovative clinical trials.
3. **Manage a C3TI Demonstration Program** that will expand opportunities for sponsors of drug development programs to work with CDER experts in enhanced ways to illustrate the value and impact of innovative approaches to the design and conduct of clinical trials.

fda.gov/cdersbia

Regulation of Clinical Research



- The **delicate balance** of providing structure and direction in a highly regulated global industry where the stakes are high and reasonable minds may differ
- Maintaining **a baseline standard** for quality
- **Flexible** to allow for a wide degree of autonomy/choice
- **Agile** to allow for growth and evolution over time
- **Aligned** with global regulators and industry at large
- **Focused on critical interests**: subject safety, products that work, optimal efficiency
- **Aware** of the time-space continuum (hindsight // knowledge management)
- **Communication** with FDA is critical – before, during, and after

The Role of Perspective

- Fluid and dynamic environment
- Explanation versus Excuse
- Response versus Reaction
- Clinical Research Workforce Crisis
- Impact of people on people
- Remember your/our why
- Acknowledge blind spots

Lightning Round: Debunk FDA Myths

1. Normalize the inspection process: who knows what, and when?
2. What does it mean to “pass” an inspection?
3. What is an FDA 483, and what does it mean?
4. How do inspections inform the review of an application?
5. How does OSI’s recommendation impact the review?
6. How do I avoid a poor outcome? And how does that make communication/collaboration even MORE critical?

Reimagining Clinical Research

- What does innovation mean
- The next evolution of quality by design
- How might we integrate clinical research into clinical care
- The delicate balance of regulation in a dynamic system
- The role of perspective, and how to maintain it
- One day….
- Day one!

Resources

- Consolidated Appropriations Act, 2023
- Public Meeting: Mitigating Clinical Study Disruptions During Disasters and Public Health Emergencies
- ICH Harmonized Guideline Good Clinical Practice (GCP) E6(R3), Draft
- Digital Health Technologies for Remote Data Acquisition in Clinical Investigations
- Decentralized Clinical Trials for Drugs, Biological Products, and Devices
- Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities
- Conducting Remote Regulatory Assessments Questions and Answers
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
- Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies
- A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers
- Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers
- CDER Docket and Public Workshop: *Enhancing Adoption of Innovative Clinical Trial Approaches*
- CDER Complex Innovative Trial Design Meeting Program
- Model-Informed Drug Development Paired Meeting Program
- Advancing Real-World Evidence Program
- Rare Disease Endpoint Advancement Pilot Program
- CDER Patient-Focused Drug Development
- Digital Health Technologies (DHTs) for Drug Development
- Drug Development Tool (DDT) Qualification Programs

fda.gov/cdersbia