Medicines & Healthcare products Regulatory Agency

Good Clinical Practice Workshop Opening Remarks

Presented by Donald D Ashley, J.D.
Director, Office of Compliance, CDER, FDA

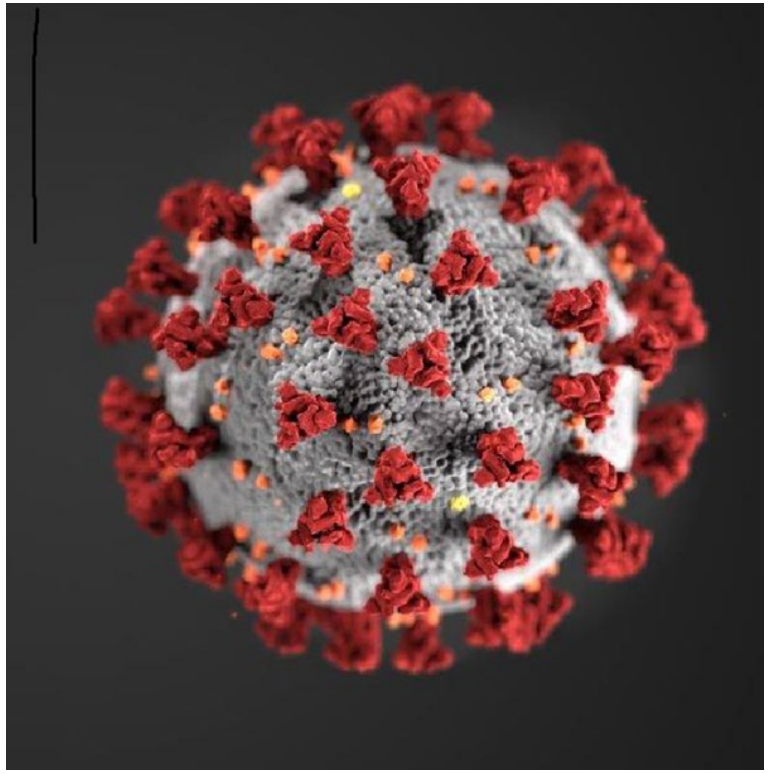
7 March 2022

In partnership with:

FDA U.S. FOOD & DRUG ADMINISTRATION

Health Canada Santé Canada

COVID-19 Impact

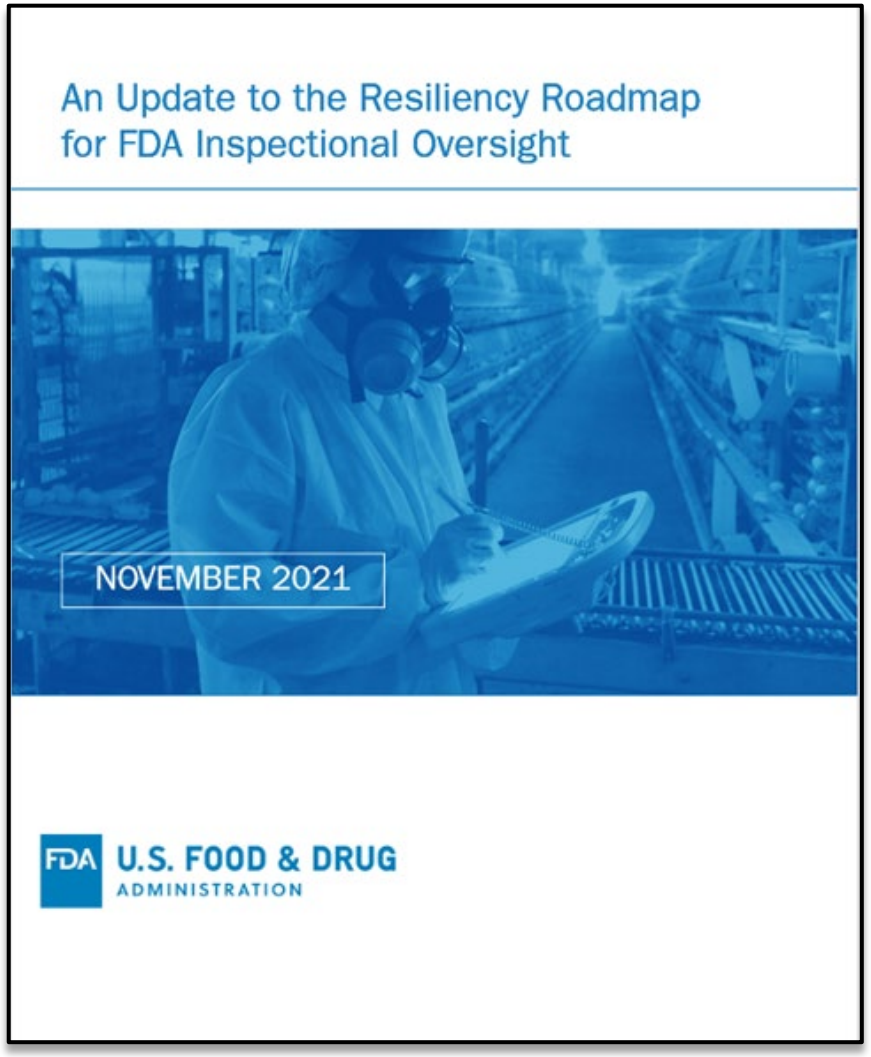


- Quarantines, site closures, travel limitations
- Supply chain interruptions
- Unproven drugs with fraudulent claims

FDA Pandemic Response

- Facilitating efforts to diagnose, treat and prevent COVID-19
  - Guidances
  - Coronavirus Treatment Acceleration Program
  - Emergency Use Authorizations
- Surveillance of medical product supply chain
  - Outreach
  - Enforcement discretion
- Leveraging tools to help oversee safety and quality of FDA regulated products and to protect consumers
  - Continued on-site inspections
  - International collaboration, Remote Interactive Evaluations
  - Addressing fraud and unsafe products

FDA Inspection Activity and COVID



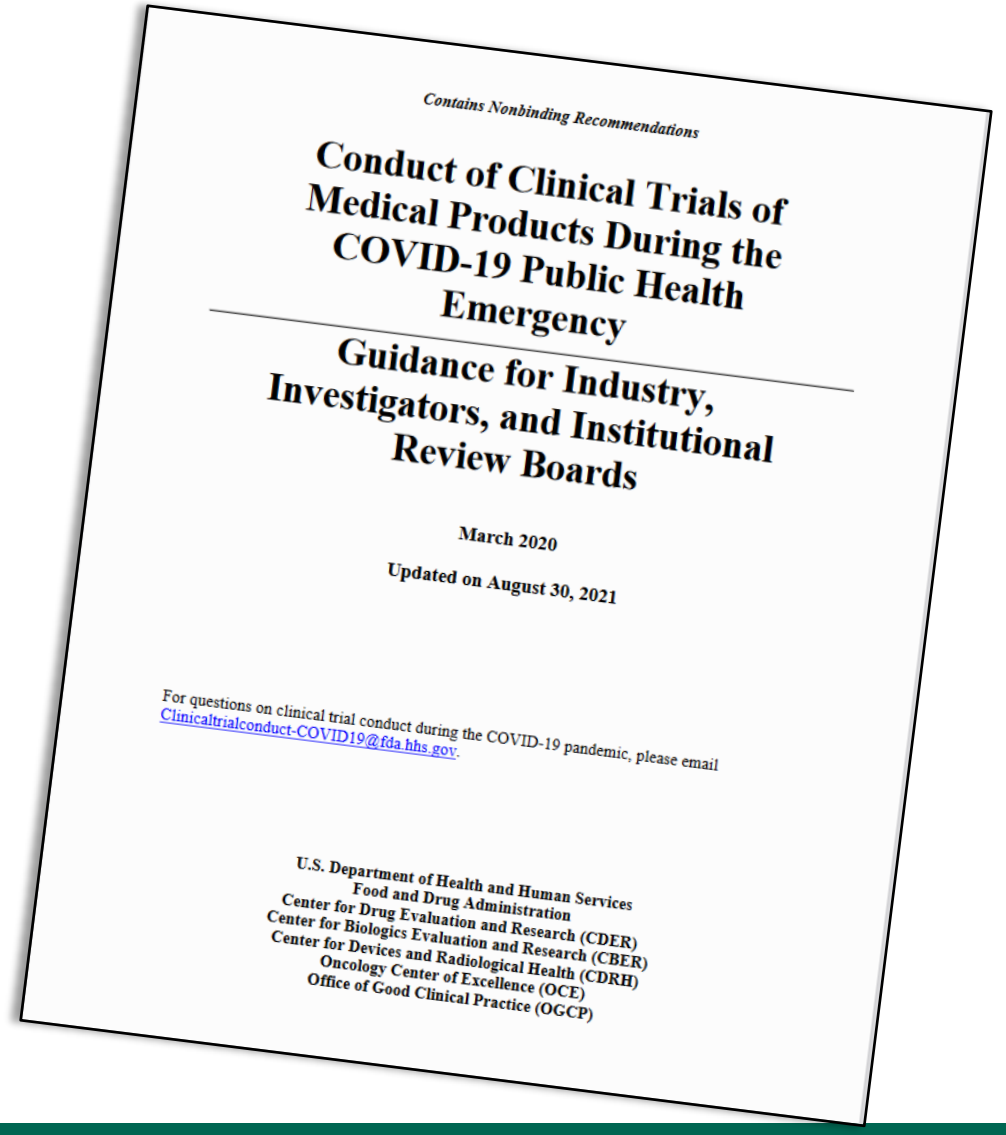
- +800 onsite BIMO inspections since the start of the public health emergency
- Approximately100 Remote Interactive Evaluations (RIEs) since the start of the public health emergency
- Numerous information sharing engagements with our foreign regulatory counterparts

Clinical Trial Conduct and COVID-19

- Remote consenting
- Electronic data capture
- Remote outcome assessments
- Virtual visits
- Home delivery of investigational product
- Risk-based monitoring
- Remote and central monitoring

GCP Compliance and COVID-19

- Ensuring the safety of trial participants is paramount
- Engaging with IRBs as early as possible when changes to the protocol or ICD anticipated.
- Documentation is key
- Optimize use of central and remote monitoring programs to maintain oversight of clinical sites



Contains Nonbinding Recommendations

Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on August 30, 2021

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

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

https://www.fda.gov/media/136238/download

Looking Forward at the FDA

- Clinical Trial Design and Conduct: CDER Guidance Agenda (January 2022)
  - Real-World Data and Real-World Evidence Guidances
  - Decentralized Clinical Trials
  - Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21CFR Part 11 – Questions and Answers

- GCP Oversight:
  - Maximize on-site inspections as feasible
  - Remote Interactive Evaluations / Remote Regulatory Assessments
  - Read only access to electronic systems
  - Information and Inspections from Regulatory Partners

Quality by Design in Clinical Trials

Presented by Miah Jung,
Supervisory Pharmacologist, FDA

Disclaimer

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

Importance of Quality in Clinical Research

<u>Clinical Trials of Quality</u>

- Importance of clinical trial quality is to ensure reliable clinical trial evidence to inform decision making on use of a preventive, diagnostic, or therapeutic intervention
  - Clinical trials should be adequately designed and well-conducted
  - Data produced are sufficiently accurate, reliable, and fit for purpose (e.g., quality and amount of information generated is sufficient to support good decision making)
  - The rights, safety, and welfare of trial participants have been adequately protected

Quality Management in Clinical Trials

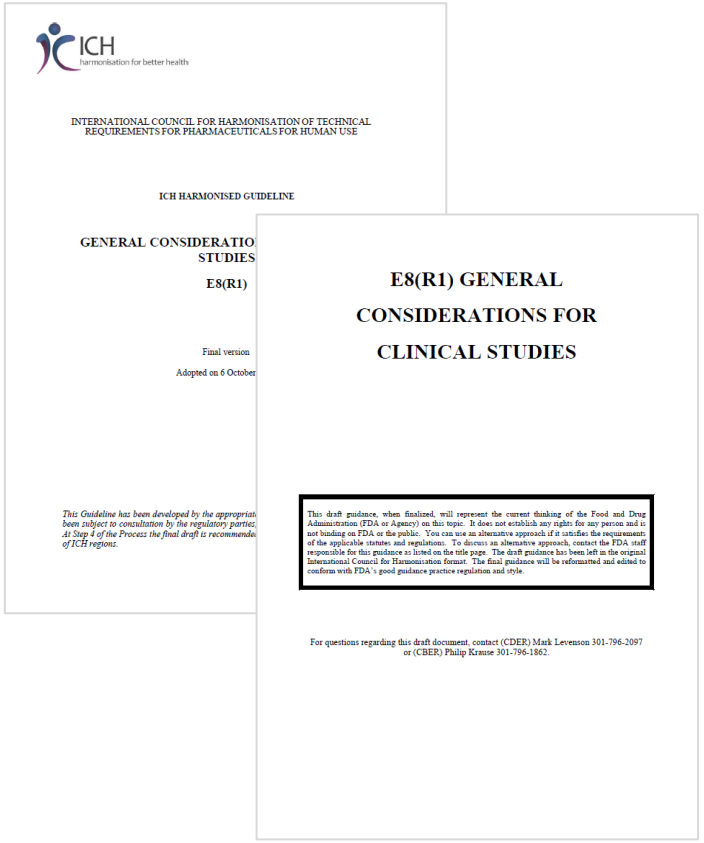
- Systematic, prioritized, risk-based approach to quality management of clinical trials, to support the principles of Good Clinical Practice (GCP) and to complement existing quality practices, requirements, regulations, and standards
- Implementing and maintaining **quality assurance and control** systems **with written procedures** to secure clinical trial quality, to provide assurance of protection of trial participants, data are reliable, and results of the trials are credible

https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-risk-based-quality-management-clinical-trials_en.pdf

ICH E8(R1)

Quality by Design (QbD) Approach

- Quality of a clinical study considered fitness for purpose
- Proactively designing quality into the study protocol and processes
- Focusing on factors critical to study quality
- NOT one size fits all approach



FDA/ICH E8(R1): https://www.fda.gov/media/129527/download
ICH E8(R1) Step 4: https://database.ich.org/sites/default/files/E8-R1_Guideline_Step4_2021_1006.pdf

Approach to Identifying the Critical to Quality Factors

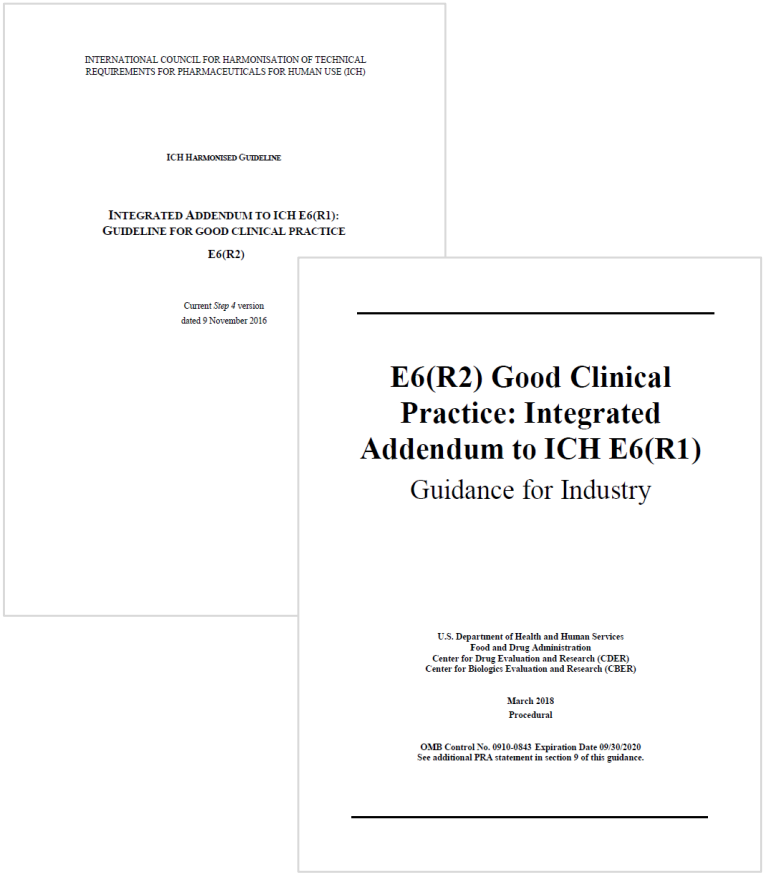
1. Creating a culture that values and rewards critical thinking and open dialogue
2. Focusing efforts on activities essential to the study
3. Engaging stakeholders in study design
4. Periodically reviewing critical to quality factors
5. Assessing feasibility to ensure study design and protocol are both scientifically sound and operationally viable

ICH E8(R1) Step 4: https://database.ich.org/sites/default/files/E8-R1_Guideline_Step4_2021_1006.pdf

ICH E6(R2)

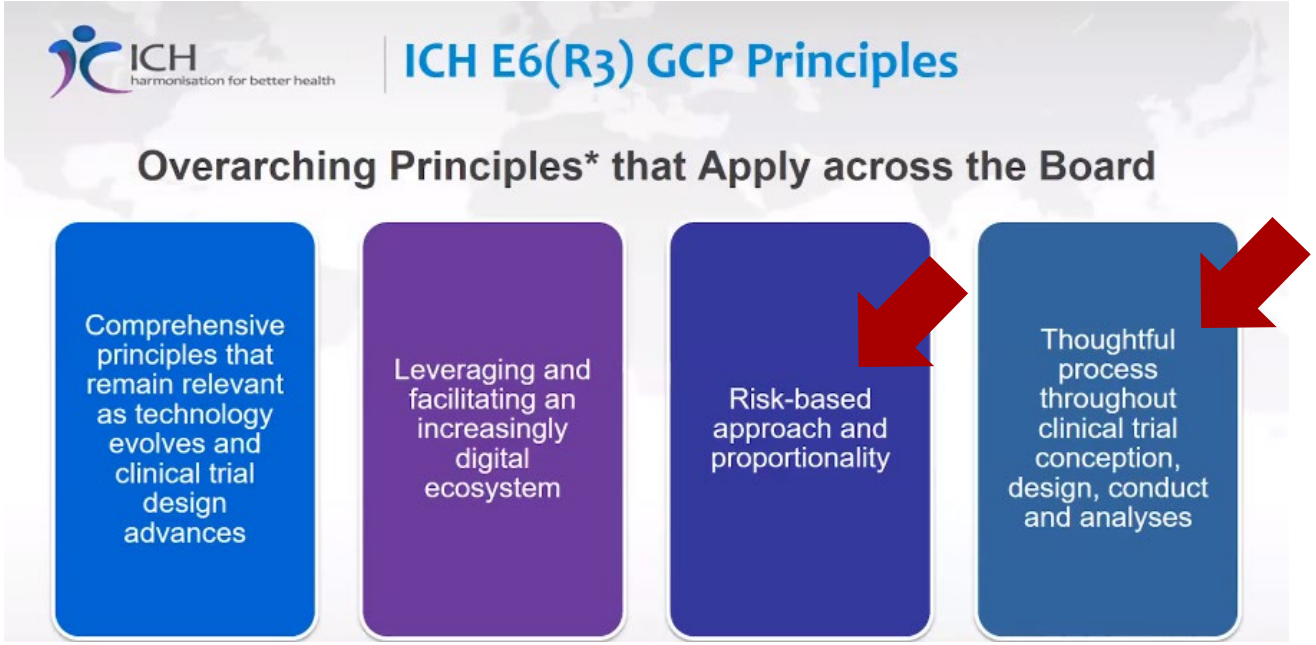
Section 5.0 Quality Management

- Focus on trial activities essential to ensuring human subject protection and the reliability of trial results
- Methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected.
- Sponsors should ensure oversight of any trial-related duties and functions carried out on their behalf, including trial-related duties and functions that are subcontracted to another party
- Systematic, prioritized, risk-based approaches to monitoring clinical trials



FDA/ICH E6(R2): https://www.fda.gov/media/93884/download
ICH E6(R2): https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

ICH E6(R3)



ICH Reflection on "GCP Renovation": Modernization of ICH E8 and Subsequent Renovation of ICH E6

January 2017

Introduction

This paper outlines an approach to potential renovation of the ICH Guidelines related to clinical trial design, planning, management, and conduct. The scope of the renovation would include the current *E8 General Considerations for Clinical Trials* and the *E6 Guideline for Good Clinical Practice*. The goal is to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of clinical trial designs and data sources that are being employed to support regulatory and other health policy decisions. The underlying principles of human subject protection and data quality would remain.

ICH believes that the proposal outlined in th
expressed by some research organizations ar
February 2016 letter to ICH, these stakeholde
to sufficiently recognize variations in the leve
corresponding flexibility in managing the risks
was felt that a guideline entitled "good clinica
conduct of clinical trials.

The proposed renovation would address thes
made to two current ICH guidelines.

- First, ICH would propose to address the
planning for an appropriate level of da
Considerations for Clinical Trials. This is
depends on the quality of the study that
affect the reliability of the study conclusi
and fairly comprehensive review of the
quality. This may include "critical to qu
planning a study. Among the ICH Efficacy g
an updated comprehensive guide or cro
sponsors should refer to when planning ar
- Subsequently, ICH would propose to add
Good Clinical Practices to anticipate and
while retaining the current E6 focus on go

This reflection paper begins with a backgroun
the range of regulatory and other health resea
addition to traditional interventional trials th
how E8 might be revised to enhance its uti

[1] Updated open Letter to EMA & ICH: From 5 resea
researchers in 22 countries, 26th February, 2016: Cl
Council for Harmonisation (ICH) on its proposed E6
Clinical Practice".

ICH Reflection on "GCP Renovation" January 2

ICH
harmonisation for better health

19 April 2021

ICH-E6 Good Clinical Practice (GCP)

Explanatory Note

The International Council for Harmonisation (ICH) is committed to developing timely technical requirements for pharmaceuticals for human use in a manner that is responsive to the needs of the global community. ICH is committed to stakeholder engagement and transparency in the development of its guidelines.

ICH E6 Good Clinical Practice (GCP) Guideline is widely used by clinical trial researchers beyond the membership and regional representation of ICH itself and has a significant impact on trial participants and patients. Acknowledging the wide and substantial impact of ICH E6, the ICH Management Committee is making available a draft, work-in-progress version of the updated principles that are currently under development by the ICH E6(R3) Expert Working Group (EWG). The principles are interdependent and should be considered in their totality to assure ethical trial conduct, participant safety, and reliable results of clinical trials.

The renovation of ICH E6(R2) will set out principles which will be aligned with the principles in ICH E8(R1) Revision of General Considerations for Clinical Studies. ICH E8(R1) includes a framework for designing quality into clinical trials, stakeholder engagement, trial design, proportionate trial management and focus on factors critical to the quality of trials. When complete, ICH E6(R3) will be composed of an overarching principles document (the document of which a draft is now made public), Annex 1 (addressing interventional clinical trials), and Annex 2 (providing any needed additional considerations for non-traditional interventional clinical trials). The overarching principles document and Annex 1 will replace the current ICH E6(R2).

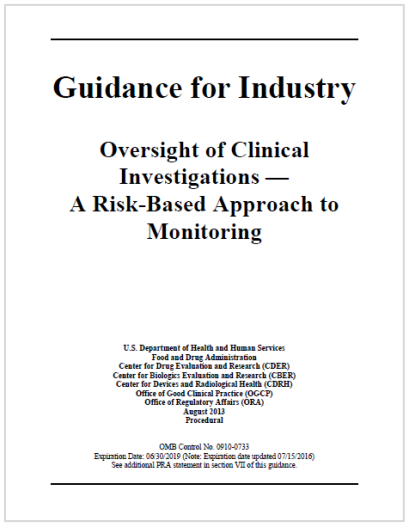
Although the EWG's work is continuing and the group is still progressing towards *Step 2* of the ICH guidance development process (https://ich.org/page/formal-ich-procedure), the ICH Management Committee decided that sharing the draft version of the principles would facilitate transparency and common understanding. Although public comments are not requested at this time, once the updated ICH E6 Guideline achieves *Step 2* of the ICH guidance development process, public input will be invited and considered. *Step 2* will involve simultaneous publication of both the draft principles and Annex 1, along with an introduction and a glossary. Public comment will be invited at that point since the principles need to be seen and commented on alongside the details in Annex 1.

The ICH E6(R3) EWG is organizing a web conference to present the current draft of the GCP principles as a work in progress. Additionally, the general ICH process will be presented with a focus on the ICH E6(R3) development process.

1

Source: https://database.ich.org/sites/default/files/ICH_E6R3_WebConference_Report_Final_2021_1011.pdf
ICH E6(R3) Draft Principles: https://database.ich.org/sites/default/files/ICH_E6-R3_GCP-Principles_Draft_2021_0419.pdf
ICH Reflection Paper on GCP Renovation: https://www.ich.org/page/reflection-papers#5-1

Guidances

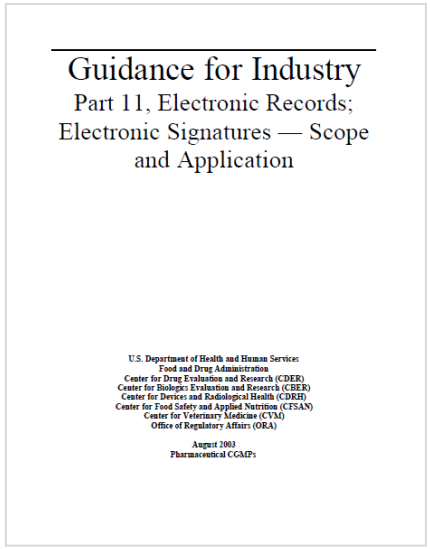


Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

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 Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)
August 2013
Procedural

OMB Control No. 0910-0733
Expiration Date: 06/30/2019 (Note: Expiration date updated 07/15/2016)
See additional PRA statement in section VII of this guidance.

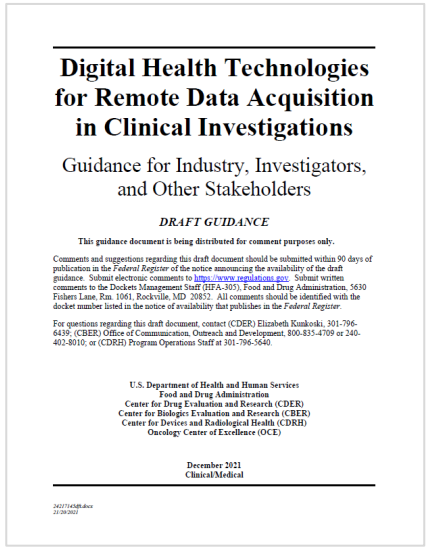


Guidance for Industry

Part 11, Electronic Records; Electronic Signatures — Scope and Application

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 Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

August 2003
Pharmaceutical CGMPs



Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Guidance for Industry, Investigators, and Other Stakeholders

DRAFT GUIDANCE

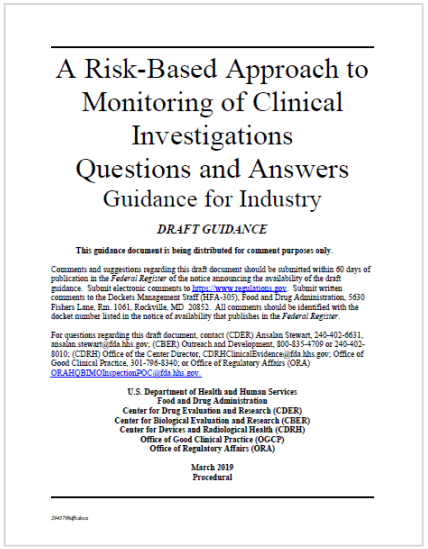
This guidance document is being distributed for comment purposes only.

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



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

DRAFT GUIDANCE

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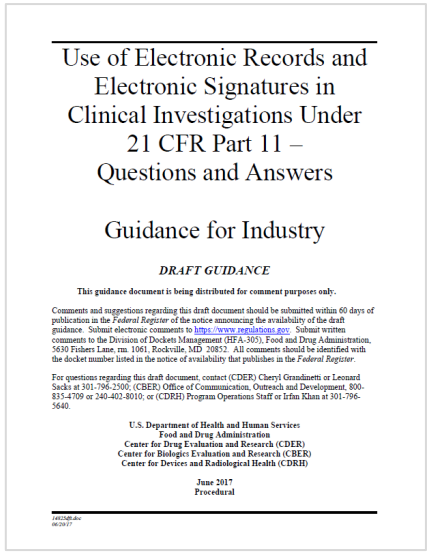
For questions regarding this draft document, contact (CDER) Ansalan Stewart, 240-402-6631, ansalan.stewart@fda.hhs.gov; (CBER) Outreach and Development, 800-835-4709 or 240-402-8010; (CDRH) Office of the Center Director, CDRHClinicalEvidence@fda.hhs.gov; Office of Good Clinical Practice, 301-796-8340; or Office of Regulatory Affairs (ORA) ORAHQBIMOInspectionPOC@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biological Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)

March 2019
Procedural



Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers

Guidance for Industry

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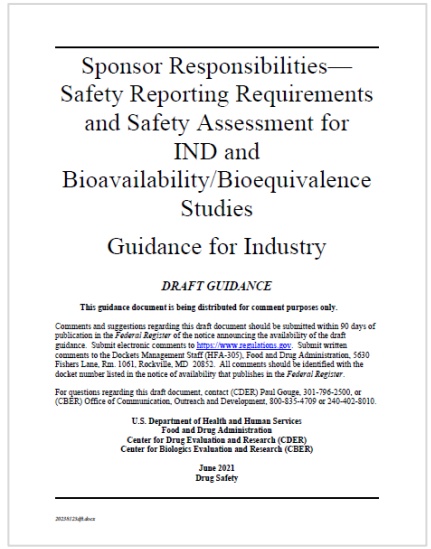
For questions regarding this draft document, contact (CDER) Cheryl Grandinetti or Leonard Sacks at 301-796-2500; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Program Operations Staff or Irfan Khan at 301-796-5640.

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)

June 2017
Procedural



Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies

Guidance for Industry

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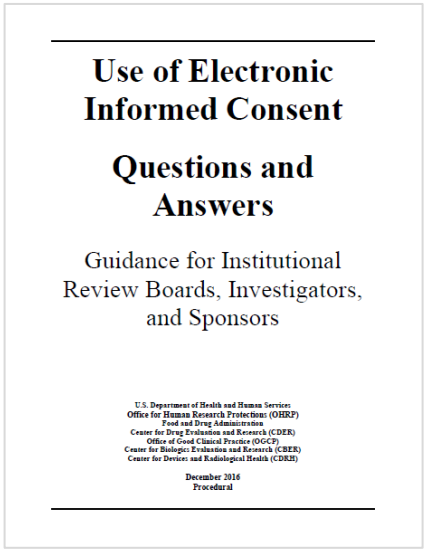
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2021
Drug Safety



Use of Electronic Informed Consent Questions and Answers

Guidance for Institutional Review Boards, Investigators, and Sponsors

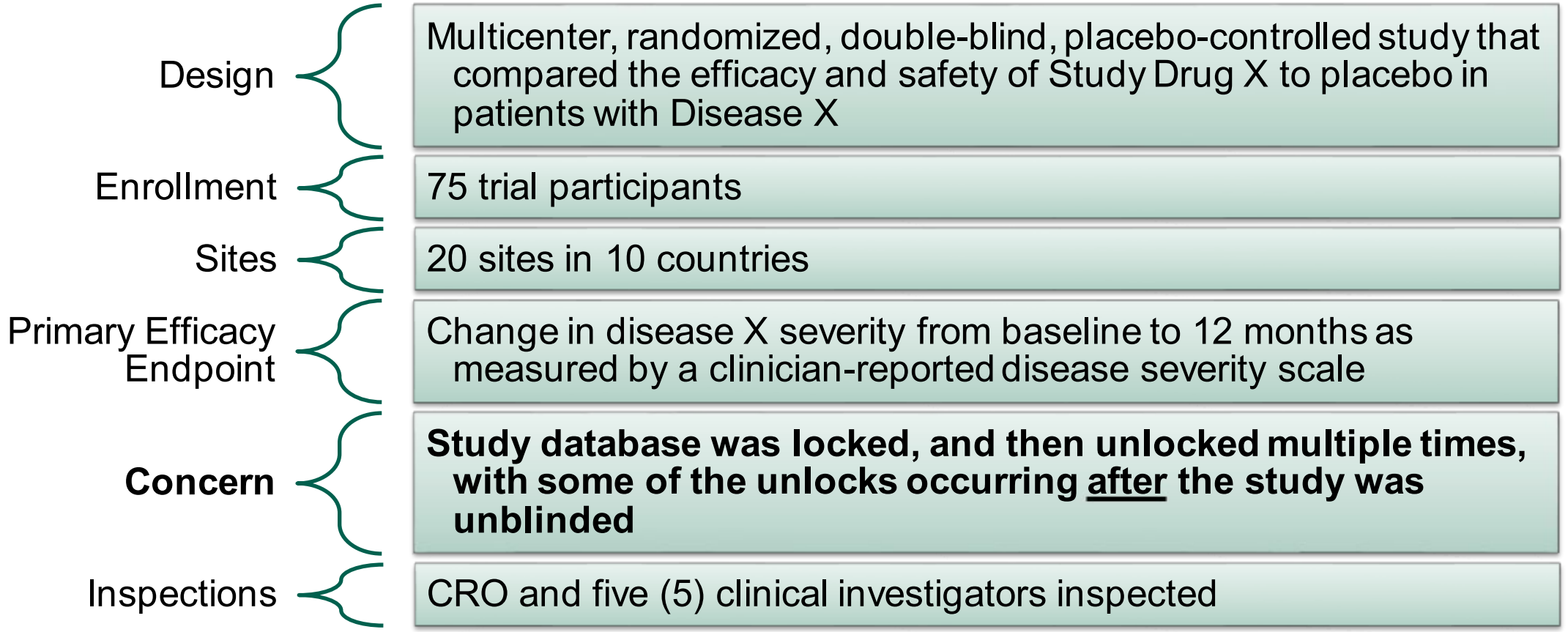
U.S. Department of Health and Human Services
Office for Human Research Protections (OHRP)
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Good Clinical Practice (OGCP)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2016
Procedural

General Concepts of QbD in Clinical Trials

- Proactive, prospective, multidisciplinary approach
- Built into scientific and operational design and conduct of the trial
- Factors critical to the quality of each trial identified and reviewed at study design and planning, and throughout conduct, analysis and reporting
  - Develop and implement quality management plan with risk assessment and management strategies
  - Assess and monitor risk utilizing a prospective, risk-based approach
  - Systematically implement training and improve procedures

Case Example: Ensuring eCRFs are Fit for Purpose and Designed According to the Protocol



Inspectional Observations

Database Lock and Data Changes:

- Format and content of eCRF's audit trails hindered the regulatory agency's review to determine what changes were made, by whom, and when, and if the changes were authorized
- The CRO's statistical programmers had hardcoded a subset of the primary efficacy data in the dataset extracted from the eCRFs

Discrepancies & Scoring Errors:

- Errors were noted in disease severity scales on the paper template source worksheets used for calculating and documenting the disease severity scores
- Score calculation errors
- Discrepancies were noted between source worksheets and sponsor's data line listings

Database Lock and Data Changes

Insufficient processes and procedures for data reconciliation/data validation

Insufficient processes and procedures for locking and unlocking the study database

Lack of sufficient documentation throughout the data lock process to document the decisions made

Discrepancies and Score Calculation Errors

Inconsistent processes and procedures were used for the collection of primary efficacy endpoint data

No quality checks on the site-generated templates

Inadequate training of site personnel

Implications to Data Integrity and Reliability

- Poorly designed eCRFs and inconsistent data collection and handling methods resulted in poor study data quality
- Potential for bias to be introduced to the study results because data queries were sent to the sites after unblinding of the treatment assignments and the sponsor/CRO had reviewed the study results

Take-Home Message

- Need for RBQM in Clinical Development

Medicines & Healthcare products Regulatory Agency

Bioresearch Monitoring (BIMO) Inspections to Evaluate Data Reliability in Studies Using RWD/RWE

Presented by Cheryl Grandinetti, Pharm.D.,
FDA, CDER, OC, OSI

7 March 2022

In partnership with:

FDA U.S. FOOD & DRUG ADMINISTRATION

Health Canada Santé Canada

Disclaimer Slide

- This presentation reflects the views of the author and should not be construed to represent the Food and Drug Administration's views or policies

Overview of Today's Presentation

- Background on the use of RWD/RWE for regulatory decision-making by FDA
- Important considerations and challenges when conducting BIMO inspections and data audits to evaluate RWD reliability
- Highlights from FDA guidances on RWD/RWE (i.e., related to BIMO inspections, study conduct, and data reliability assessments)
- RWE Hypothetical Inspection Case Example

Background

- 21st Century Cures Act, signed into law in December 2016
- Is intended to accelerate medical product development and bring innovations faster and more efficiently to the patients who need them
- FDA established a program to evaluate the potential use of RWE in regulatory decision making to help:
  - Support the approval of a new indication for a previously approved drug
  - Support or satisfy post-approval study requirements

FDA Recommendations on RWE/RWD

Final Guidance, "Guidance: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices"

(Aug 2017)

Final Guidance, "Use of Electronic Health Records Data in Clinical Investigations"

(July 2018)

Framework for FDA's Real-World Evidence Program

(Dec 2018)

Draft Guidance, "Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics Guidance for Industry"

(May 2019)

Draft Guidance, "Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products"

(Sep 2021)

Draft Guidance, "Data Standards for Drug and Biological Product Submissions Containing Real-World Data"

(Oct 2021)

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

(Nov 2021)

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

(Dec 2021)

Background: FDA Definitions

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, which are data derived from sources other than traditional clinical trials

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

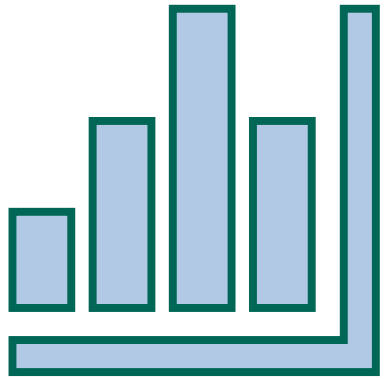
Examples of RWD

- Data derived from electronic health records (EHRs)
- Medical claims and billing data
- Data from product and disease registries
- Patient-generated data, including from in-home-use settings, and data gathered from other sources that can inform on health status, such as digital health technologies

Recent Examples of RWE Submitted to Support FDA Approval

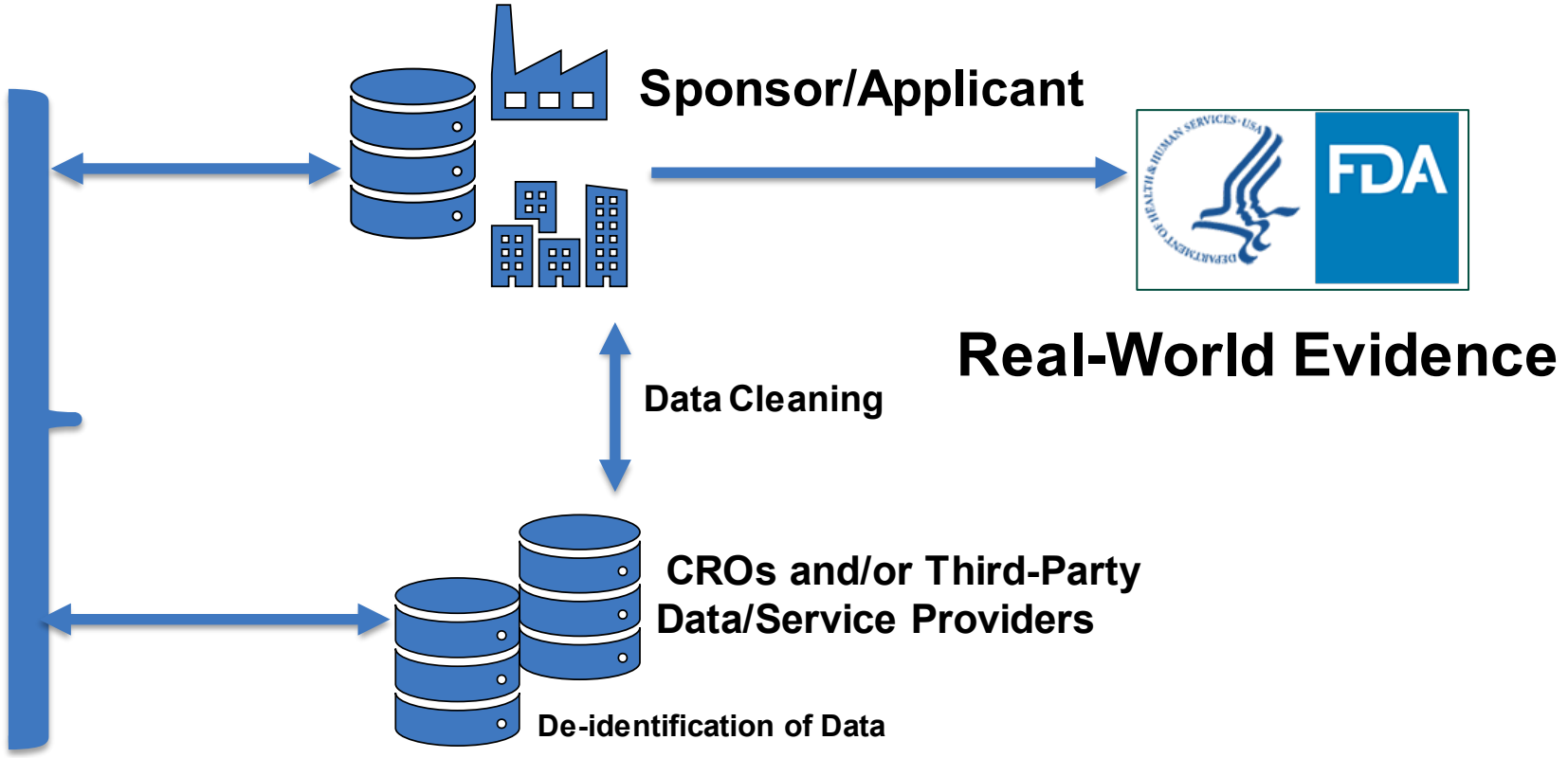
Product	Year	Indication	Types of Studies
Tacrolimus	2021	In combination with other immunosuppressant drugs to prevent organ rejection in adult and pediatric patients receiving lung transplantation	Non-interventional (observational) study; RWD from the U.S. Scientific Registry of Transplant Recipients (SRTR)
Palbociclib	2019	Advanced or metastatic breast cancer in males	Retrospective Claims Data, Electronic Health Records Analysis and a Safety Database
Blinatumomab	2019	Refractory/relapsed acute lymphoblastic leukemia	Single arm open label trial compared with historical control based on chart review
Lutetium Lu 177 dotatate	2018	Gastroenteropancreatic neuroendocrine tumours	Randomized open-label, active-controlled multicenter trial and retrospective study
Ivacaftor	2017	Expanded the indication from the treatment of 10 cystic fibrosis mutations to 33	Post-marketing registry data and mechanistic information from lab studies
Thiotepa	2017	Pediatric beta-thalassemia	Retrospective observational study
Cerliponase alfa	2017	Neuronal Ceroid Lipofuscinosis 2	Single-arm clinical study compared with natural historical cohort (Natural History Database DEM-CHILD)
Avelumab	2017	Merkel cell carcinoma	Open-label single-arm multicenter trial and RWD-generated historical control as benchmark

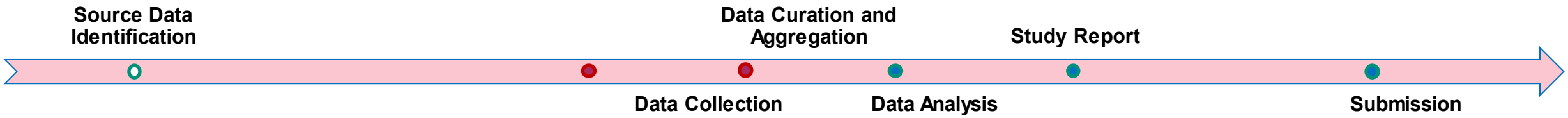
Important Considerations for BIMO Inspections and Data Audits Evaluating RWD



Schematic of the Data-Flow For Studies Using RWE

Real-World Data





Where Do BIMO Inspections and Data Audits Occur?

RWD Sources

Data Review and Verification

Sponsor, CRO, and/or Third-Party Data and Service Provider

- Curated/Aggregated data

Review processes and procedures for processing of data

- Application (CSR, Data Tables, SDTM and ADaM datasets, Line Listings)

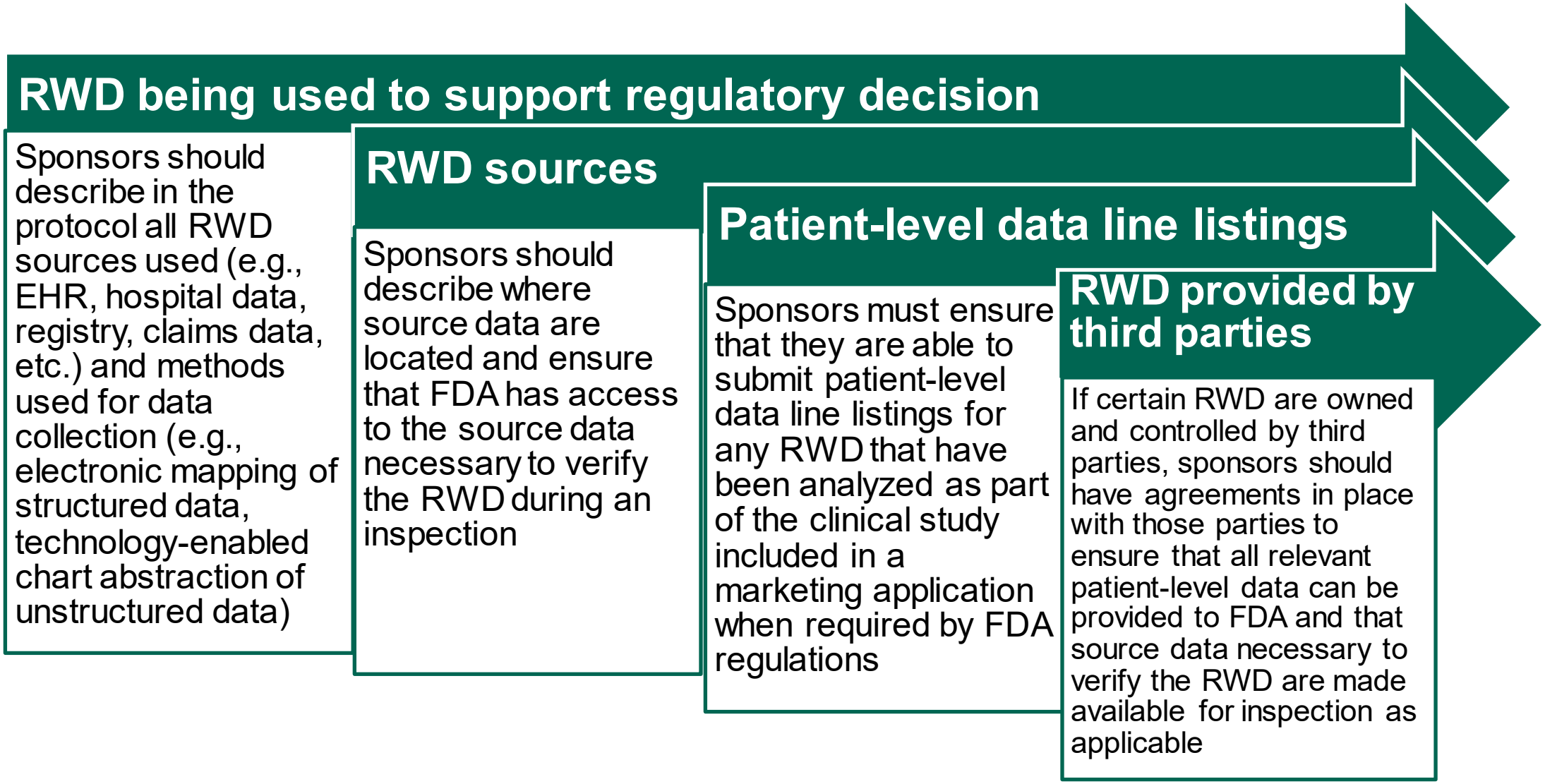
FDA Submission

The primary focus of RWE/RWD BIMO inspections is to assess data reliability and not compliance with any regulations (except 21 CRF parts 50 and 56, if applicable)

BIMO Inspection Challenges

- Submission of only aggregate datasets does not permit data verification
- Review and copying of source records may require approval from various IRBs/Ethics Committees; redaction of personal identifiers, which can be a time-consuming process, may delay the FDA audit and verification of the RWD
- Multiple locations of source data may complicate and prolong data review and verification
- Access to and review of Sponsor, CRO and/or Data/Service provider records, which document the quality control procedures and processes performed by them, is necessary
- Information on the quality of the source (e.g., EHRs, registries, claims database) of the RWD used is often not available

Highlights From FDA Guidances on RWD/RWE



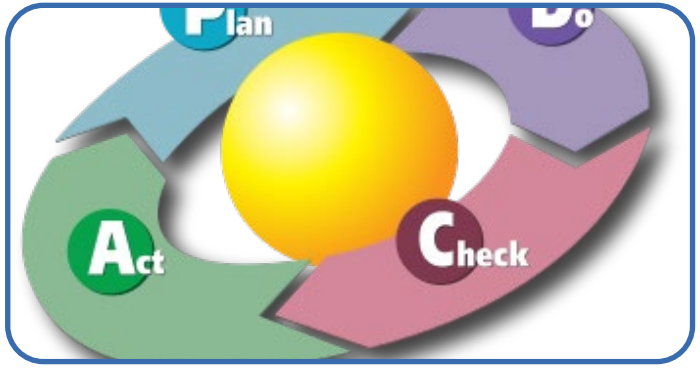
Highlights From FDA Guidances on RWD/RWE

Sponsors should take responsibility for all activities related to the design, conduct, and oversight of the studies, including the following:

- Ensuring that the study is conducted according to the final protocol and statistical analysis plan and documenting any deviations
- Maintaining and retaining adequate study records
- Selecting researchers qualified by training and experience to perform their assigned/delegated study-related activities
- Documenting the roles and responsibilities of the third parties performing study related activities and making these documents available to FDA upon request

Highlights From FDA Guidances on RWD/RWE

Sponsors should ensure that there are adequate processes in place for data collection, management, curation, transformation, and analysis to increase confidence in the resultant data

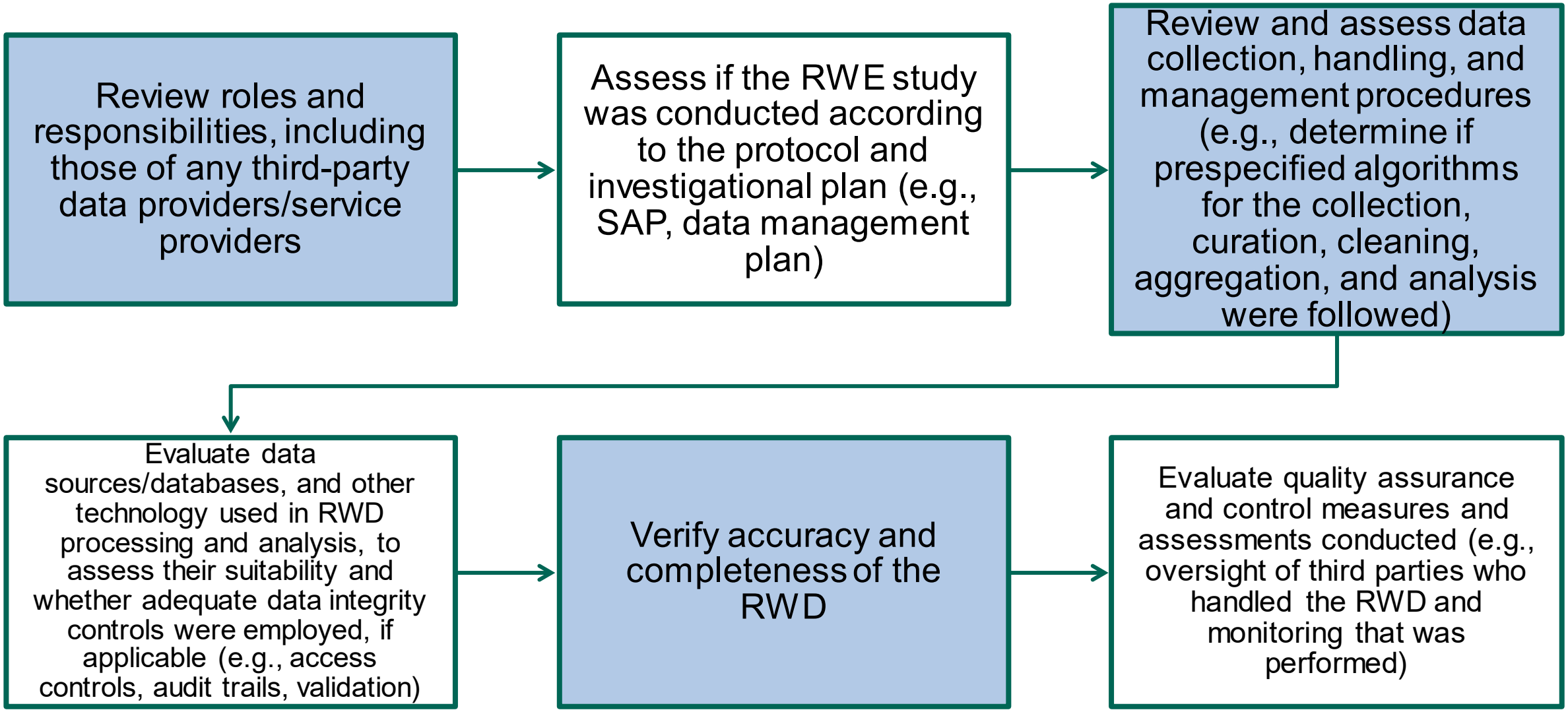


Sponsors should ensure appropriate monitoring of the study

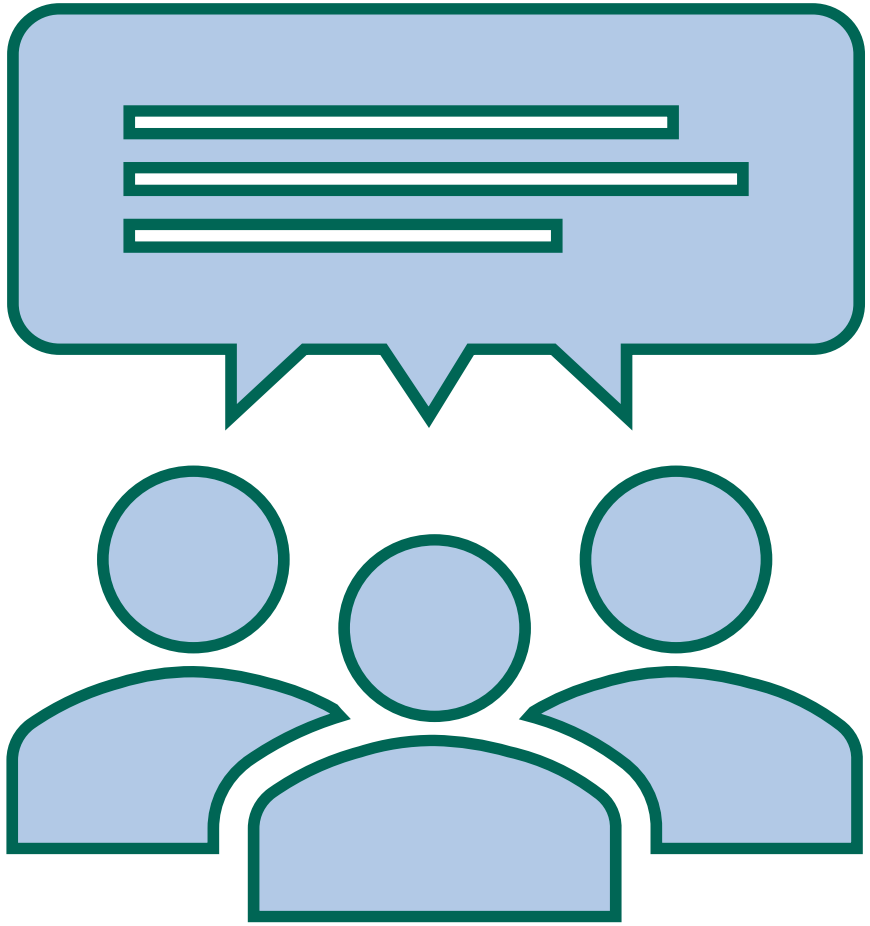
FDA encourages sponsors to use a risk-proportionate quality management approach to RWE study oversight

In general, monitoring should focus on maintaining data integrity and reliability of RWD beginning with extraction of the data from its source (data collection) through data curation, transformation, and reporting of results

BIMO Inspections and Data Audits of Studies Using RWD/RWE



RWE Inspection Case Example



Case Example Background

- RWE submitted to support a new indication
- The sponsor submitted two “traditional” RCTs to support the efficacy and safety of Study Drug X:
  - Study 1 was a double-blind, randomized, placebo-controlled 24- week study in patients with a rare disease
  - Study 2 was an open-label, 3-year extension study for subjects who completed Study 1
- The primary efficacy endpoint was a clinician-reported measure of functional status

Case Example Background

- The placebo-controlled study (Study 1) failed to demonstrate statistically significant differences between the investigational treatment arm and the placebo arm on the primary efficacy endpoint.
- The sponsor subsequently proposed to evaluate the long-term efficacy (i.e., over a 3-year period) in the open-label extension study against a group of historical controls receiving standard of care identified from a natural history database
- The sponsor identified historical control patients who could be matched with subjects from Study 2 on specific characteristics
- The sponsor reported that the mean change in functional status was worse in the historical control group compared to the active study group at the 3-year timepoint

Data Audits to Review and Verify the Historical Control Data

- Focus of the historical control data audit:
  - To verify the primary efficacy endpoint data of the historical control group
  - To verify data regarding therapeutic interventions given to the historical control patients during their participation in the registry
- FDA record review required IRB/Ethics Committee approval and subject informed consent (or waiver) before FDA could review records
- Source data for the natural history control patients were located at 10 different locations in 3 countries
- Reviewed all historical control patients
- Interviewed all researchers (including the coordinating researcher) who participated in the natural history study

Data Audit Findings

- Review of the Natural History Database:
  - Data were entered on excel spreadsheets at the 10 sites and these spreadsheets were emailed to coordinating center for data entry into the natural history database
  - There were no standard reporting procedures in place, and no audit trails were employed or available to track the collection of data, including changes made to the data
- Significant discrepancies in the primary efficacy endpoint data between the source data, natural history database, and the sponsor's data line listings were noted in all historical control subjects
- 20% of the historical control patients were enrolled in another clinical trial and had received active treatment
- Significant inconsistencies in how the clinicians performed the efficacy assessments were noted in 30% of the historical control subjects

Data Reliability Assessment

Primary efficacy assessments in at least 50% of the subjects who were part of the historical controls could not be considered part of the natural history course of the rare disease

- Outcomes were not assessed and recorded consistently within the historical controls and as compared to the active treatment group in 30% of the subjects
- The effect of intercurrent events on the outcome of interest were not considered (i.e., 20% of the historical control patients were enrolled in other RCTs and receiving active drug during the time period of interest)

Overall, historical control data were deemed not reliable and not fit for regulatory purposes

- Significant discrepancies in the primary efficacy endpoint data between the source data, natural history database, and the sponsor's data line listings were noted in all historical control subjects
- There was a lack of data collection and reporting procedures at the site-level and there were no audit trails that documented the data changes made, including the any reasons for the change

Final Notes

RWD/RWE

- Is a valuable contribution in drug development and its use to complement RCT data is paramount, especially in conditions where it may be difficult to conduct RCTs (e.g., rare disease, oncology)

Early discussion

- Between the sponsor and the relevant OND review division is critical if a sponsor intends to use data from a real-world setting to support a regulatory submission

Applicants/Sponsors

- Should submit patient-level data line listings for any RWD that have been analyzed as part of the clinical study
- Should ensure that FDA has access to the source records
- Should ensure that signed informed consent is obtained from patients or an IRB waiver prior to data collection in order to allow FDA inspectors to review study related source records

Medicines & Healthcare products Regulatory Agency

Have Regulatory Expectations Changed as a Result of the Pandemic?

Barbara Wright (FDA)

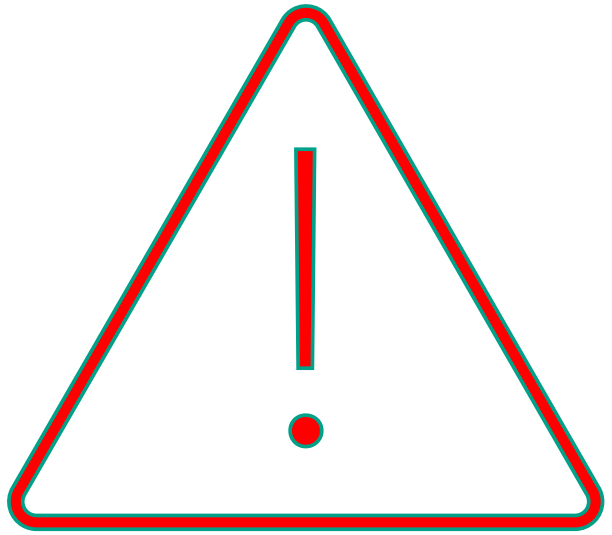
In partnership with:

FDA U.S. FOOD & DRUG ADMINISTRATION

Health Canada Santé Canada

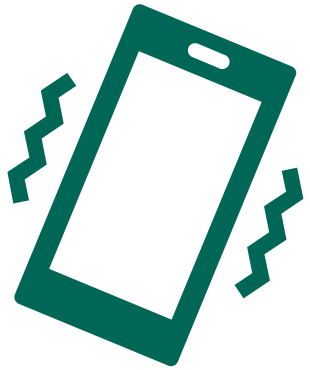
Barbara Wright, Supervisory Investigator Foreign Inspection Cadre, FDA

Challenges in clinical research during the pandemic



- Inability of clinical staff and study subjects to visit research site for study visits.
  - Missed protocol treatments, tests and assessments.
  - Dosing interruptions.
  - Subjects Lost to Follow-up.
- Investigational Product (IP) shipping interruptions.
- Planned and unplanned changes to the investigational plan.
- Inability of sponsors and monitors to visit the research site for qualification, training or monitoring.
- Risk-mitigation strategies – social distancing, masking, testing.

Changes in clinical research during the pandemic



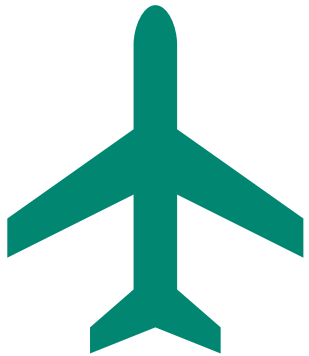
- Increased use of technology and remote assessments and monitoring.
  - Telehealth visits
  - mobile/home health care providers
  - Electronic Informed Consent
  - Digital Health Technologies – ePRO devices (phone/tablet) and wearables
  - Remote monitoring visits
- Direct-to-Subject Investigational Product shipments.
- Expanded use of vendors and local health care providers.

Changes in GCP inspections during the pandemic

Remote Regulatory Assessments

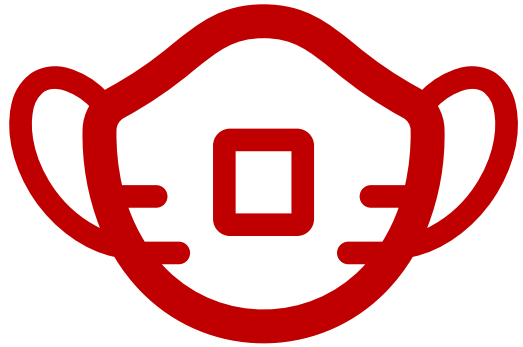
- Voluntary remote interactive evaluations of Sponsors, Clinical Investigators and Contract Research Organizations.
- Risk-based Site Selection.
- Feasibility Assessment – ability to access key documents remotely, including, legal, ethical and logistical challenges (e.g., time zones, languages, technology).
- Conducted as a series of video conferences with shared documents and interviews of study staff.
- Document sharing - accomplished via read-only access to data systems and/or redacted document uploads to an FDA remote file-sharing account.

Changes in GCP inspections during the pandemic



Risk mitigation strategies for on-site inspections

- Social distancing
  - Record reviews in conference rooms outside of patient care areas.
  - Limited number of attendees in face-to-face meetings and interviews.
  - Adjustments to in-person observations of clinical facilities.
  - Increased use of technology (video projectors, teleconferencing, electronic data transfers).
- Masking
- Health monitoring prior to arrival



Expectations for research conducted during the pandemic

Subject safety is paramount

- Each study, each subject is unique. Decisions must be made to:
  - Continue or Discontinue Enrollment and/or Dosing?
  - Continue or Modify Assessments per Protocol?
  - Suspend or Alter Procedures, Methods, Schedules?
- Communication and consultation with Ethics Committee
  - Changes to the investigational plan.
  - Changes to informed consent.
  - Approval for the use of remote tools and remote access and handling of subject data.

Expectations for research conducted during the pandemic

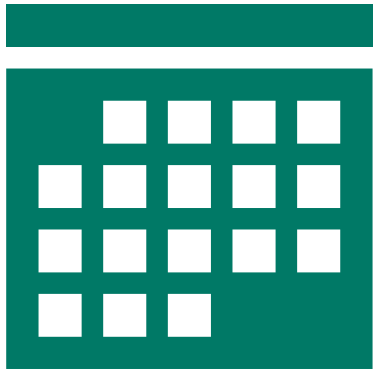
Control of changes to the Investigational Plan

- Alternative methods for safety or efficacy assessments (e.g., virtual visits, phone contacts, local labs/imaging) should be evaluated for their ability to:
  - protect the study subject
  - meet the objectives of the trial
- Impact on the quality and reliability of data collected by alternate means must be assessed.

Expectations for research conducted during the pandemic

Deviation management

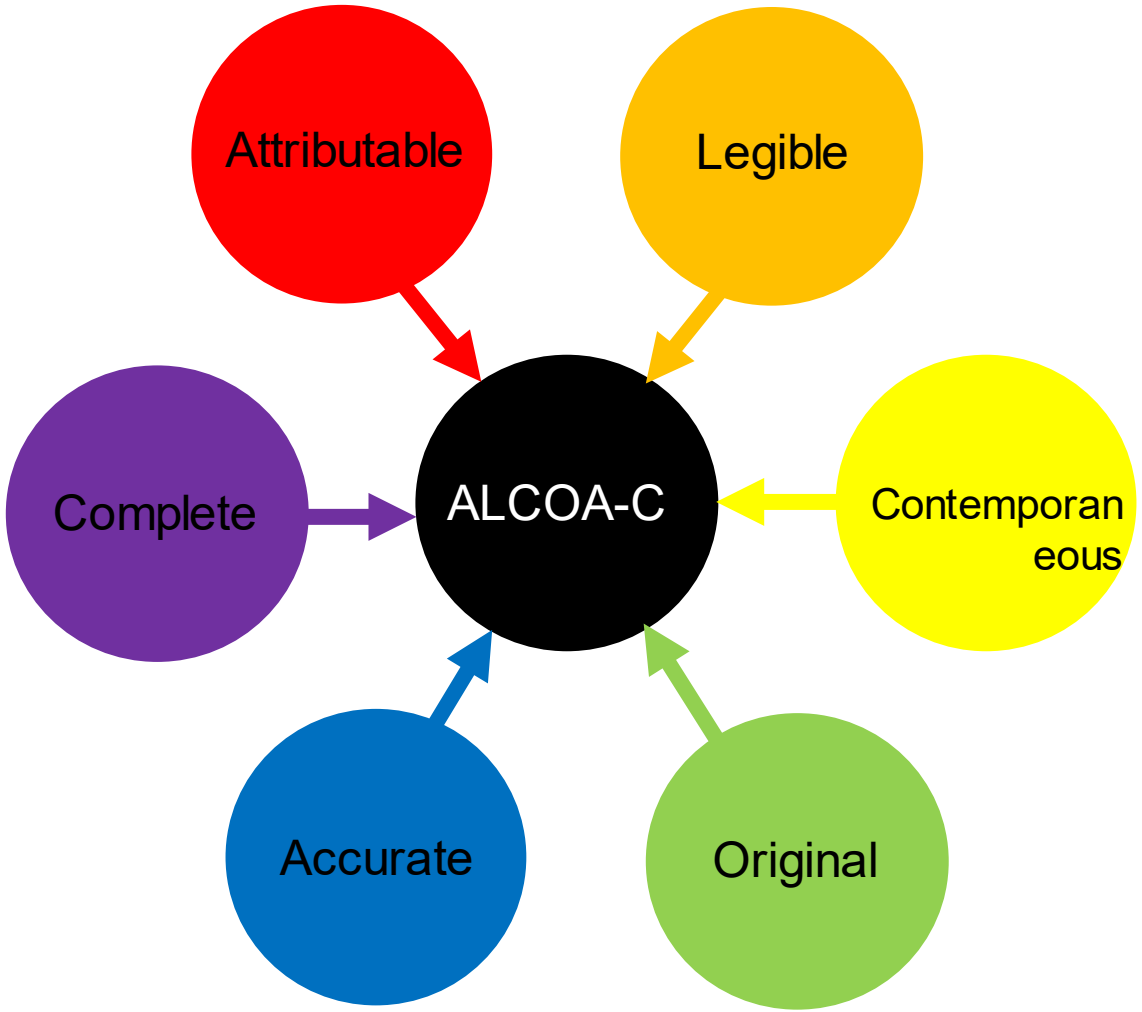
- Planned and unplanned changes must be adequately documented, assessed for impact on the quality and integrity of the data, and reported.
- Protocol Amendments, except where necessary to protect human subjects.
- Ethics Committees should be informed of deviations, particularly those which may increase risks to study subjects.



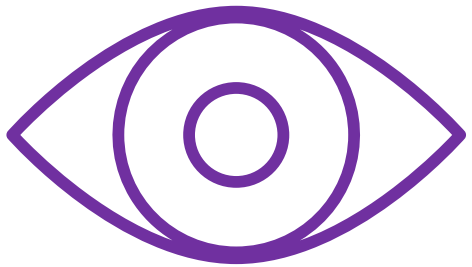
Expectations for research conducted during the pandemic

Assurance of Data Integrity

- Data gathered through alternative methods must meet the same standards for accuracy and reliability.
- Documentation should be ALCOA-C.
- Electronic Data should be preserved and accessible for verification, with all metadata, audit trails, and remote transmission details, as applicable.
- Data, including third party data, must be verifiable as an original or certified copy.



Expectations for research conducted during the pandemic

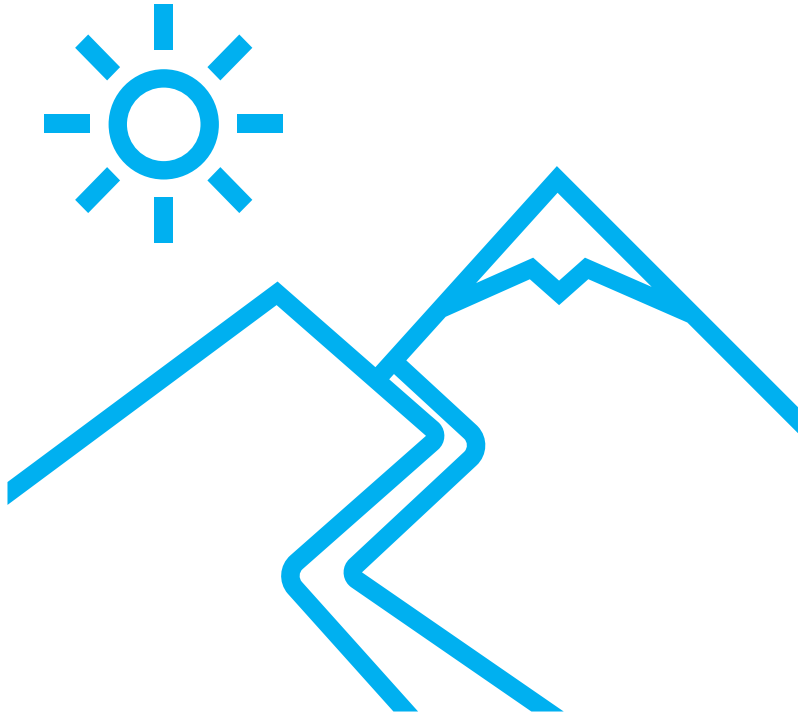


Sponsor and Investigator Oversight

- Whether conducted during a pandemic or not, Investigators are responsible for all compliance with the protocol. Training and oversight of those performing protocol tests, assessments, or providing subject care during the trial is the responsibility of the Principal Investigator.
- The Principal Investigator is responsible for maintaining subject case histories, whether collected at the research site, via DHTs or through vendors.
- Sponsors are responsible for monitoring the investigation even when unable to visit the clinical site.

Changes to research and regulatory oversight moving forward

- Increased use of Decentralized Clinical Trial designs.
- Increased use of technology at Clinical Investigator sites for:
  - obtaining informed consent
  - collection of subject case histories (DHT for safety and efficacy assessments & virtual study visits)



Changes to research and regulatory oversight moving forward

- Increased use of technology by sponsors for:
  - Site qualification & training
  - Remote monitoring

- Increased use of technology by FDA for:
  - Remote Regulatory Assessments
  - Electronic data review and collection of records during onsite inspections.

Guidance documents

FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency | FDA

COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders | FDA

Protecting Participants in Bioequivalence Studies for Abbreviated New Drug Applications During the COVID-19 Public Health Emergency | FDA

Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency Guidance for Industry | FDA

Medicines & Healthcare products Regulatory Agency

Potential Uses of Artificial Intelligence (AI) and Machine Learning (ML) in Clinical Trials (CTs)

Presented by Dr. Mathew T. Thomas, Senior Policy Advisor, U.S. FDA-CDER-OC-OSI

In partnership with:

U.S. FOOD & DRUG ADMINISTRATION

Health Canada Santé Canada

The opinions expressed in this presentation are those of the presenter, and do not represent the views of the U.S. Food and Drug Administration, U.S. Government, or any other entity.

I do not have any conflicts of interest to disclose

Objectives

- Brief overview of Artificial Intelligence (AI) and Machine Learning (ML)
- Potential uses and challenges of applying artificial intelligence and machine learning in clinical trials
- Considerations for ensuring GCP compliance

Overview of AI

- AI is the theory and development of systems able to perform tasks that normally require human intelligence and cognitive abilities

- A discipline that draws from and integrates other disciplines such as computer science, information engineering, statistics, and other disciplines

- A 60 to 70 years old discipline - experiencing an expansion since 2010 due to advances in computer sciences and access to massive quantities of data

Overview of AI (continued)

- The terms Artificial Intelligence (AI) & Machine Learning (ML) are often used interchangeably but are distinctly different

- ML is a subset of AI that allows computer algorithms to learn and improve automatically through data without being explicitly programmed to perform a task.

- ML techniques include

  - Deep Learning (DL) through artificial neural networks
  - Natural Language Processing (NLP)
  - Optical Character Recognition (OCR) – pattern recognitions, computational vision
  - Other applications driven by sophisticated analytical algorithms and mathematical models

Some Familiar AI Applications

- In 2011 – IBM's Watson beat 2 Jeopardy champions
- iPhone technology - text and speech recognition, and translations
- Autonomously operating vehicles (cars, airplanes, rockets)
- Military simulations
- Financial and Banking industry applications

Potential Uses of AI In Health Care Domains

- Early disease prediction
- Outcome prediction
- Personalized treatment
- Drug discovery & development
- Clinical trial research
- Smart electronic health records
- Diagnosis and treatment
- Prognosis evaluation
- Behavior modification
- Drug manufacturing
- Radiology and radiotherapy
- Epidemic & outbreak prediction

Potential Uses of AI in Drug Discovery and Development

- Drug screening for prediction of physicochemical properties, bioactivity, toxicity, target protein structure, drug-protein interactions
- Modernizing pharmaceutical manufacturing systems
- Pharmaceutical Product Management: product market positioning, market prediction and analysis, assessing product costs
- Advancing pharmaceutical product development: e.g., formulation development, dosage forms, delivery characteristics
- Data quality control and quality assurance by regulation of in-line manufacturing processes to achieve standards
- Advanced Applications: use in delivery of nanomedicine, combination medical products, and prediction of synergism/antagonism

Potential Uses of AI In Clinical Trials

- Linking big and diverse datasets
  - Electronic medical records (EMRs)
  - Published medical literature
  - Clinical trial databases (CTDs)

- Analyzing EMRs and CTDs and matching them to trial announcements, social media, or registries for
  - Identifying potential study subjects
  - Informing potential study subjects

Potential Uses of AI In Clinical Trials (continued)

- Patient selection
  - Reducing population heterogeneity – filtering inclusion/exclusion, patient inclusion based on specific genome and exposome profile analysis
  - Prognostic enrichment – selecting patients with higher probability of having a measurable clinical endpoint
  - Predictive enrichment: predicting responsiveness to interventions

- Personalized dosage administration
  - to maximize efficiency, minimize adverse effects

Potential Uses of AI In Clinical Trials (continued)

- Monitoring participants using wearable technology
  - Improves compliance with protocol requirements, monitoring medicine intake
  - Increases reliability of assessments of endpoints
  - Generates patient-specific disease diaries

- AE signal detection and drug-drug interactions

- Software as a Medical Device (SaMD) – These don't have to be SaMD
  - Devices using AI/ML to detect and diagnose diseases, and image-based end-point detection – radiology, dermatology, ophthalmology

Challenges of AI

- Gaining access to electronic medical records (EMRs)
  - Privacy and access issues

- Data mining across multiple settings, institutions and geographies for data from
  - Past clinical studies
  - Journal articles
  - Real-world data

Challenges of AI (continued)

- Maintaining Data integrity
  - Difficulty in harmonization of processes
  - Interoperability of diverse formats
  - Assessing the variability in standard of care
  - Detecting and preventing adversarial data that may impact outcomes

- End user acceptability
  - Understandability
  - Replicability & Scalability

Challenges of AI (continued)

- Personnel issues
  - Requires skilled personnel – medical data scientists, software engineers and technologists, etc.
  - Fear of job losses for current personnel
  - Skepticism – As good as humans?

- General overarching concerns
  - Addressing legal and ethical issues related to data privacy
  - Validation of clinical, analytical, technical, and monitoring processes

- Budgetary expansions

Considerations for GCP Compliance

- Data integrity in AI & ML
  - Accounting for missing data
  - Identifying and filtering adversarial data
- Hiring skilled personnel – medical data scientists, software engineers, data forensics experts
- Developing regulations and guidance
- Addressing ethical considerations

FDA Digital Health Center of Excellence: https://www.fda.gov/medical-devices/digital-health-center-excellence

References

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- Perspectives in Clinical Research, 2021 Jan-Mar; 12(1);: 1-3)
- Application of ML in Drug Development and Regulation: Current Status and Future Potential, Clinical Pharmacology & Therapeutics, Vol. 107, No. 4, April 2020.
- A comprehensive study on AI and ML in Drug Discovery and Development; Accepted 11 October 2021 – Intelligent Medicine
- Digital Health Center of Excellence: https://www.fda.gov/medical-devices/digital-health-center-excellence

Laurie Muldowney, MD,
Deputy Director, Office of Scientific Investigations
Center for Drug Evaluation and Research,
U.S. Food and Drug Administration

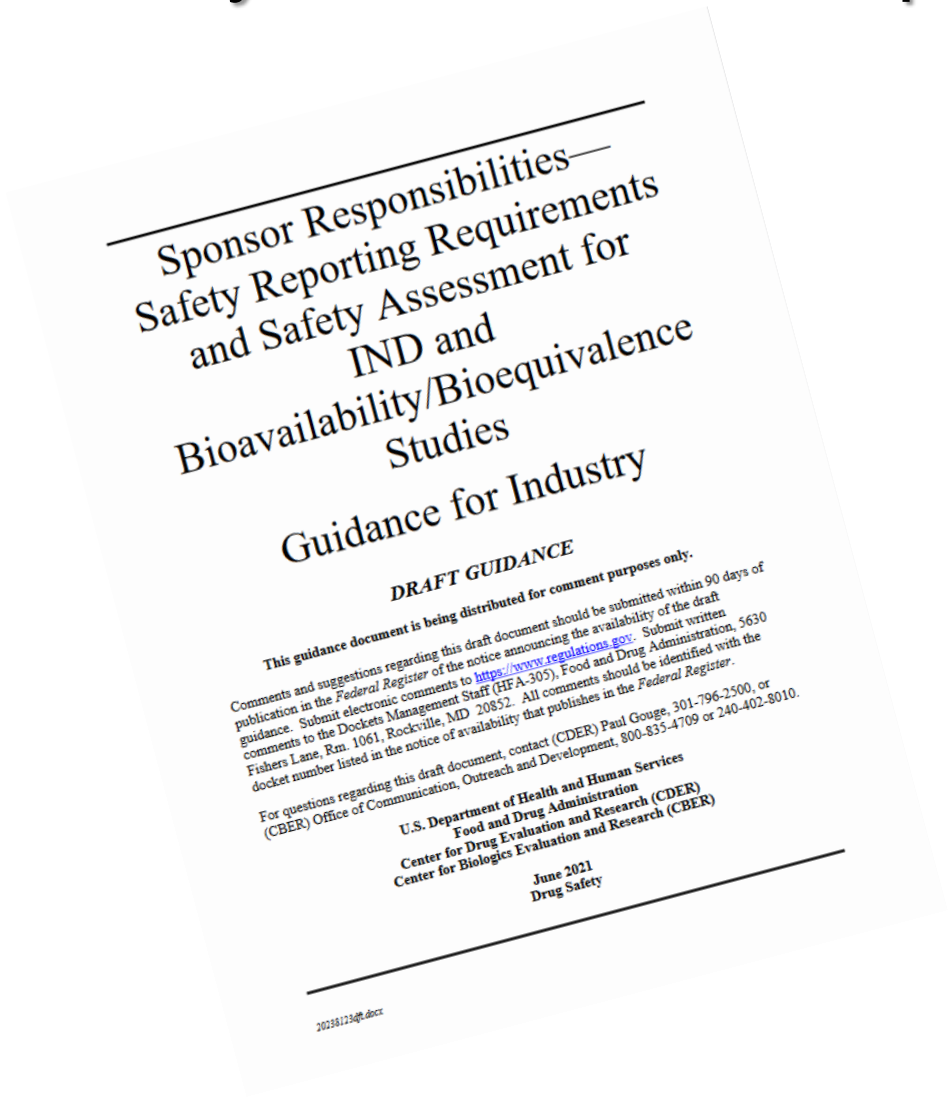
2021 FDA Guidance Development: Clinical Trial Conduct and Reporting

- FDA issued ~150 draft and final guidances in 2021
  - 80+ from CDER

- Many guidances included recommendations and FDA's current thinking on aspects of clinical trial conduct and reporting

https://www.fda.gov/regulatory-information/search-fda-guidance-documents

IND Safety Guidance Development



Sponsor Responsibilities—
Safety Reporting Requirements
and Safety Assessment for
IND and
Bioavailability/Bioequivalence
Studies

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) Paul Gouge, 301-796-2500, 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)

June 2021
Drug Safety

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Investigator Responsibilities —
Safety Reporting for Investigational
Drugs and Devices

Guidance for Industry

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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)
Center for Devices and Radiological Health (CDRH)

September 2021
Drug Safety

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https://www.fda.gov/regulatory-information/search-fda-guidance-documents

Timeline of IND Safety Reporting Policy and Guidance Development

2021 Draft Guidance: Sponsor Responsibilities – Safety Reporting Requirements and Safety Assessment

- IND safety reports to FDA:
  - it is **serious**; and
  - it is **unexpected**, i.e., not listed in the investigator's brochure; and
  - there is evidence to suggest a **causal relationship** between the drug and the adverse event

This standard (serious and unexpected suspected adverse reaction) referred to as **SUSAR**

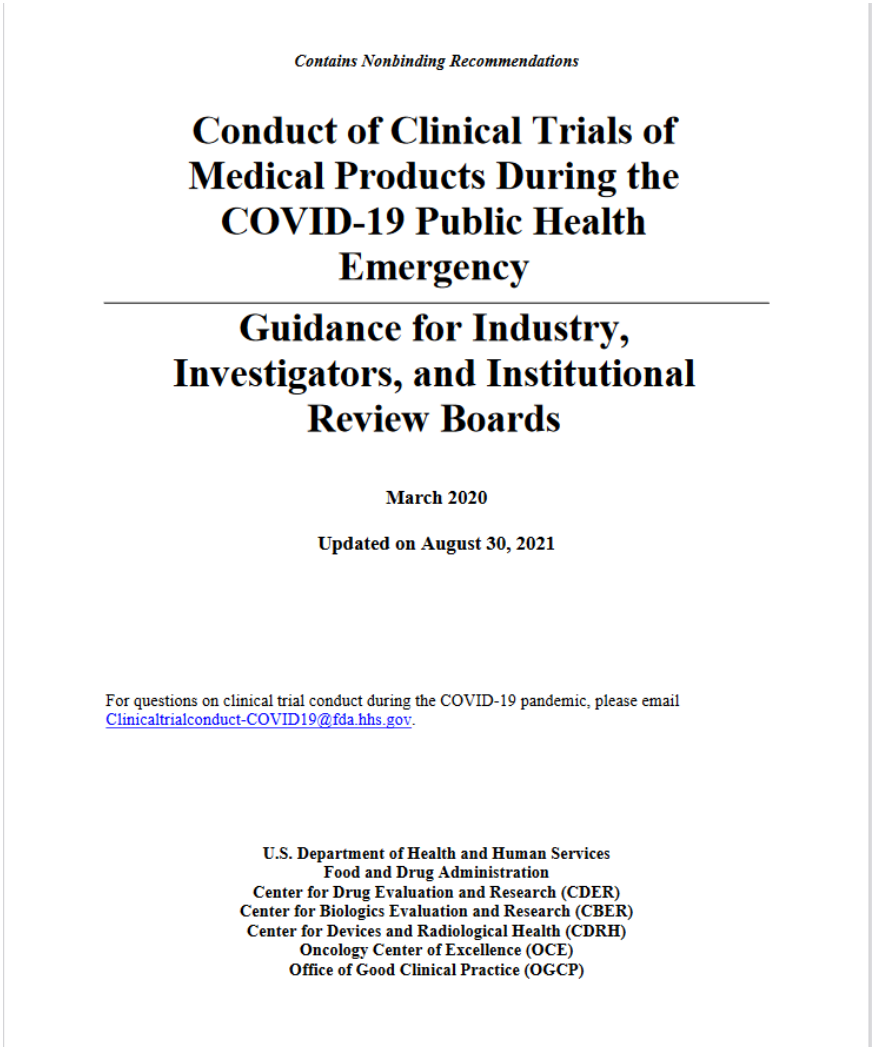
- Aggregate Analyses
  - Needed to detect an imbalance of AEs across treatment arms: Most useful in evaluating an increased rate of relatively common events
  - Draft Guidance discusses considerations, methods, and approaches to conducting aggregate analyses: Tailor approach for implementing aggregate analysis based on the disease and type of events

2021 Draft Guidance: Investigator Responsibilities – Safety Reporting for Investigational Drugs

- Investigator reporting to Sponsors:
  - Determine if AE is serious
    - SAEs must be immediately reported to the sponsor regardless of whether the investigator believes the SAEs are related to the drug (§ 312.64(b))
    - Nonserious AEs must be recorded and reported to the sponsor according to the protocol
    - Study endpoints that are SAEs must be reported as endpoints in accordance with the protocol **unless** there is evidence suggesting a causal relationship between the drug and the event (§ 312.64(b))
  - Assessment of Causality
    - Sponsor is ultimately responsible for determining causality; however, the investigator must include an assessment of whether there is a reasonable possibility
- Investigator reporting to IRBs
  - Review IND safety reports and report any unanticipated problems involving risk to human subjects or others to the IRB (FDA considers all IND safety reports to be unanticipated problems)

Clinical Trial Conduct and COVID-19

- Ensuring the safety of trial participants is paramount
- Engage with IRBs as early as possible when changes to the protocol or ICD anticipated.
- Documentation is key
- Optimize use of central and remote monitoring programs to maintain oversight of clinical sites



Contains Nonbinding Recommendations

Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

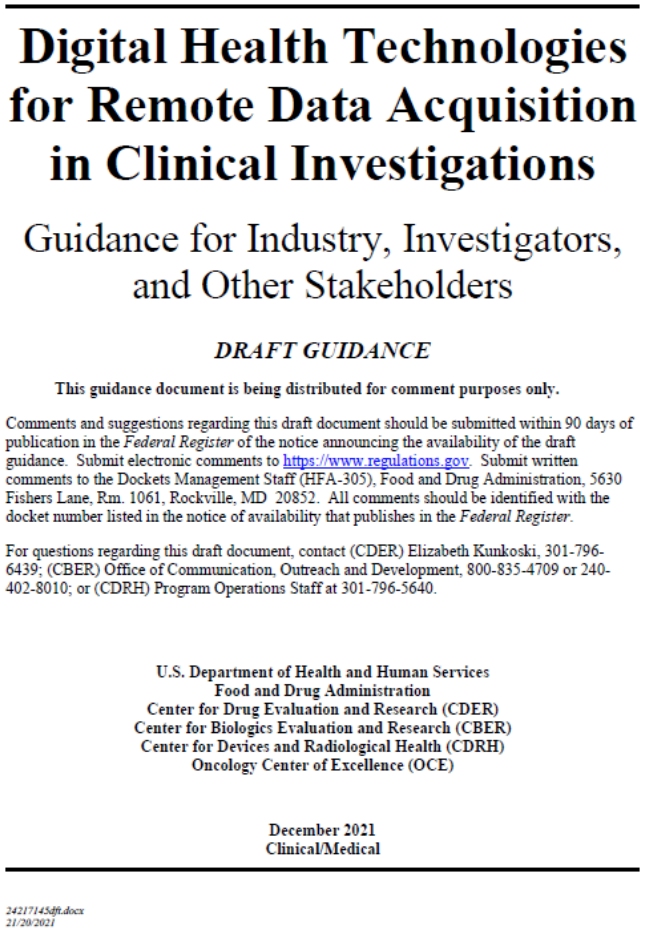
March 2020

Updated on August 30, 2021

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

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

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations



Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Guidance for Industry, Investigators, and Other Stakeholders

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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

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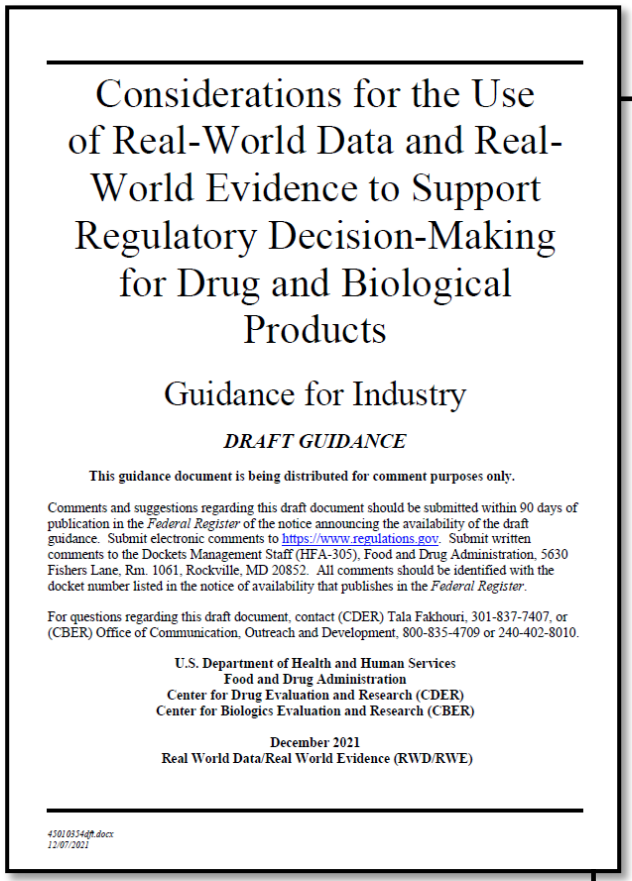
21/20/2021

Recommendations addressing DHTs in clinical investigations including:

- Selection of DHTs suitable for use
- Verification and validation of DHTs for use
- DHTs to collect data for trial endpoints
- Identification of risks associated with the use of DHTs
- Management of risks related to the use of DHTs

Real World Data/Real World Evidence



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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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)

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

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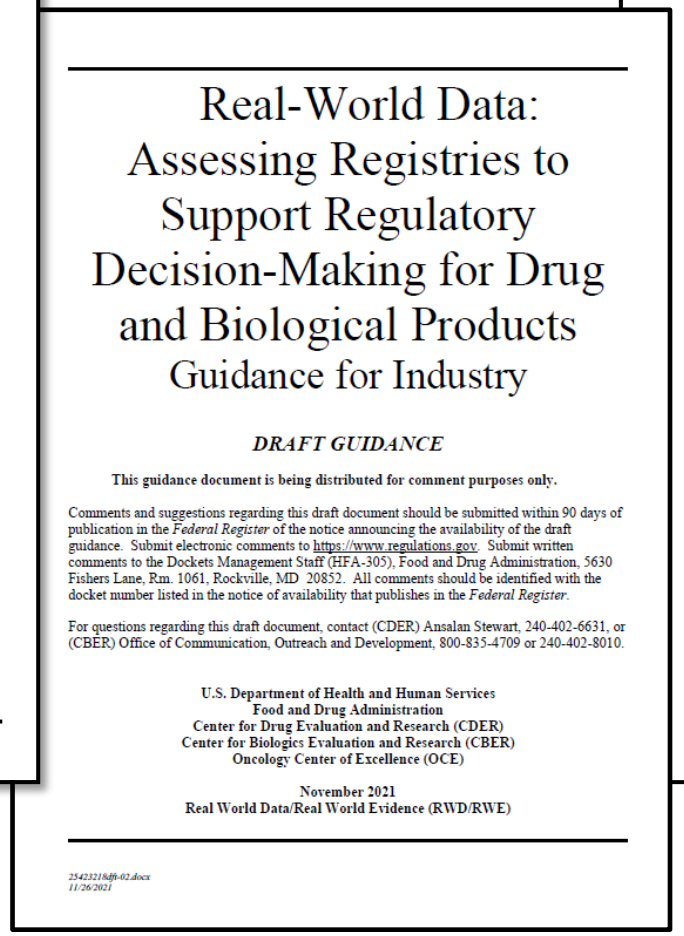

Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Ansalan Stewart, 240-402-6631, 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
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Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

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

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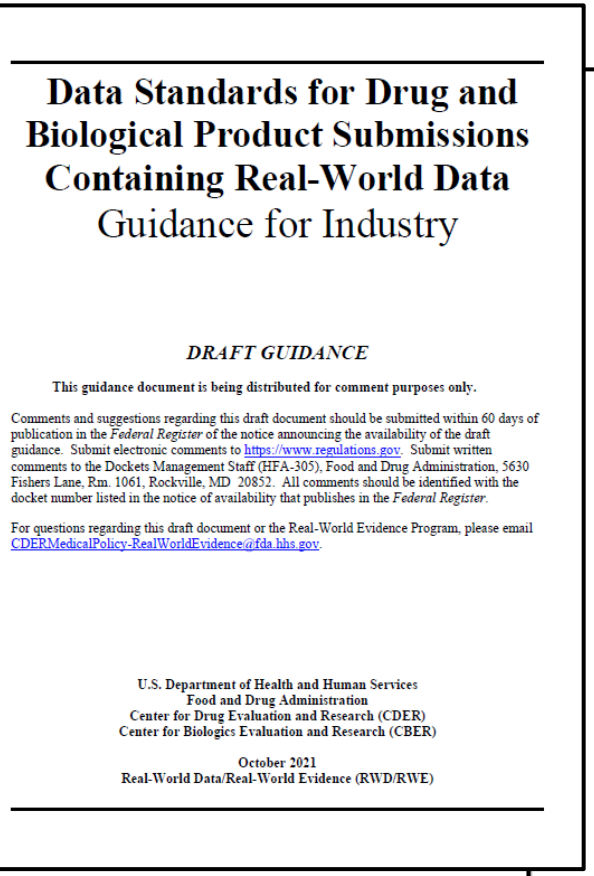
11/26/2021



Data Standards for Drug and Biological Product Submissions Containing Real-World Data

Guidance for Industry

DRAFT GUIDANCE

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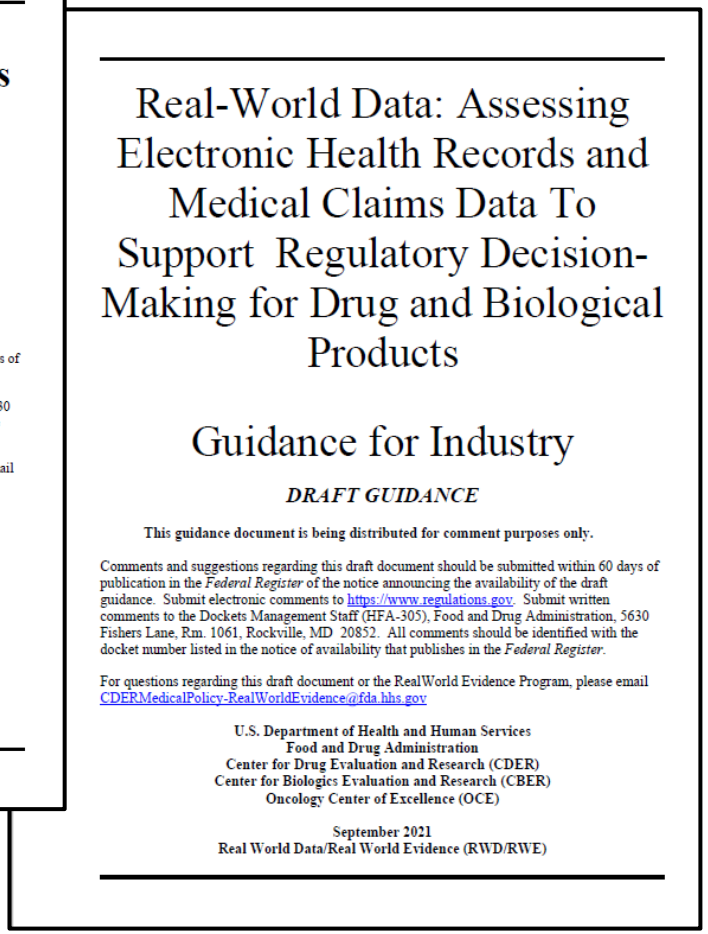
For questions regarding this draft document or the Real-World Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov.

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)

October 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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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)

Clinical Trial Reporting: Submitting Standardized Study Data

Looking Forward: CDER

- Clinical Trial Design and Conduct: CDER Guidance Agenda (January 2022)
  - Protocol Deviations
  - Decentralized Clinical Trials
  - Use of Data Monitoring Committees in Controlled Clinical Trials
  - Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21CFR Part 11 – Questions and Answers

- 21CFR 10.115(5) Once a year, FDA will publish, both in the Federal Register and on the Internet, a list of possible topics for future guidance document development or revision during the next year. You can comment on this list (e.g., by suggesting alternatives or making recommendations on the topics that FDA is considering).

https://www.fda.gov/media/134778/download

Medicines & Healthcare products Regulatory Agency

An update on FDA's inspections and use of Remote Regulatory Assessments for Bioavailability and Bioequivalence studies

Presented by Sean Kassim, PhD,
Director, Office of Study Integrity and Surveillance

In partnership with:

U.S. FOOD & DRUG ADMINISTRATION

Health Canada Santé Canada

Disclaimer

This presentation reflects the views of the author. It should not be construed to represent FDA's views or policies.

Outline

- Overview of the Office of Study Integrity and Surveillance
- Inspections and the Pandemic
- Looking forward

Office of Study Integrity and Surveillance

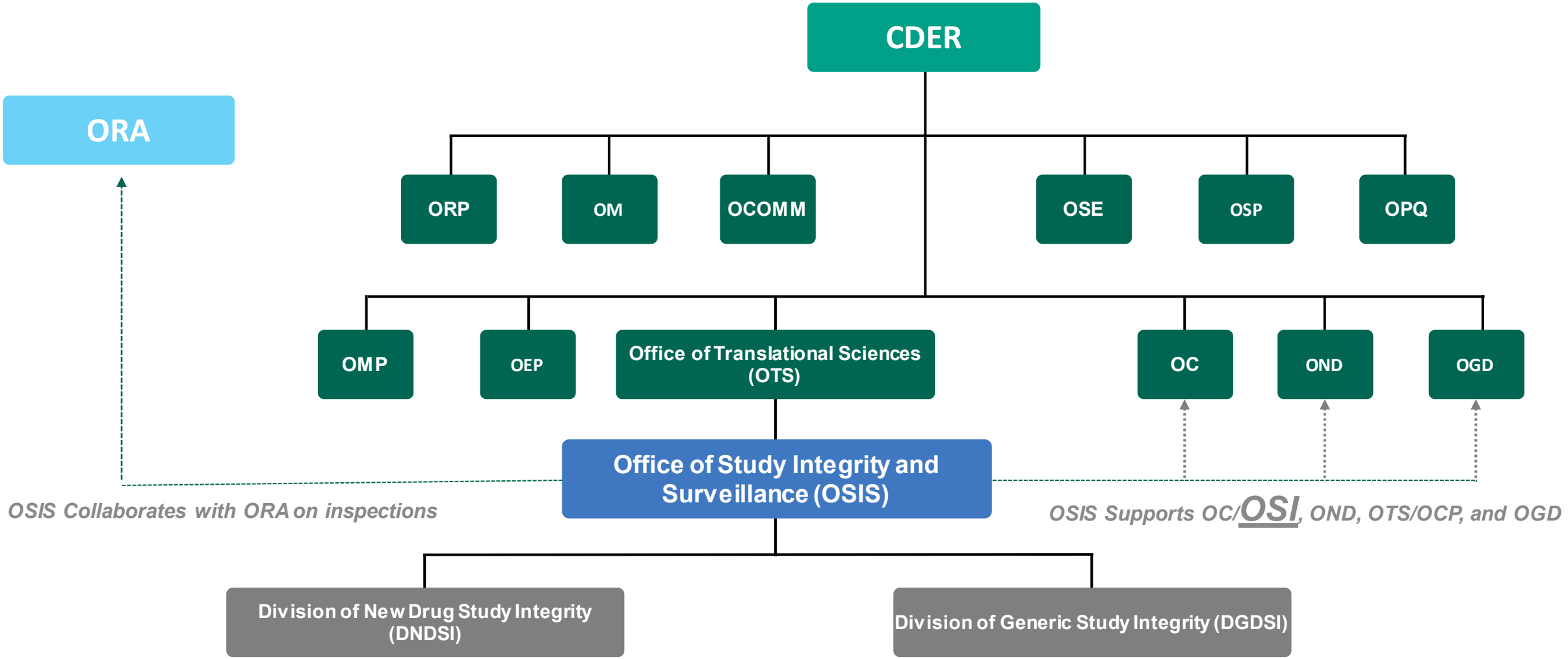
OSIS Vision

OSIS improves the public health by protecting study subjects and promoting properly conducted studies.

OSIS Mission

OSIS promotes the public health by ensuring the welfare of study subjects and by verifying the quality, study integrity and regulatory compliance of bioavailability/bioequivalence (BA/BE), nonclinical (GLP), and animal rule (AR) studies.

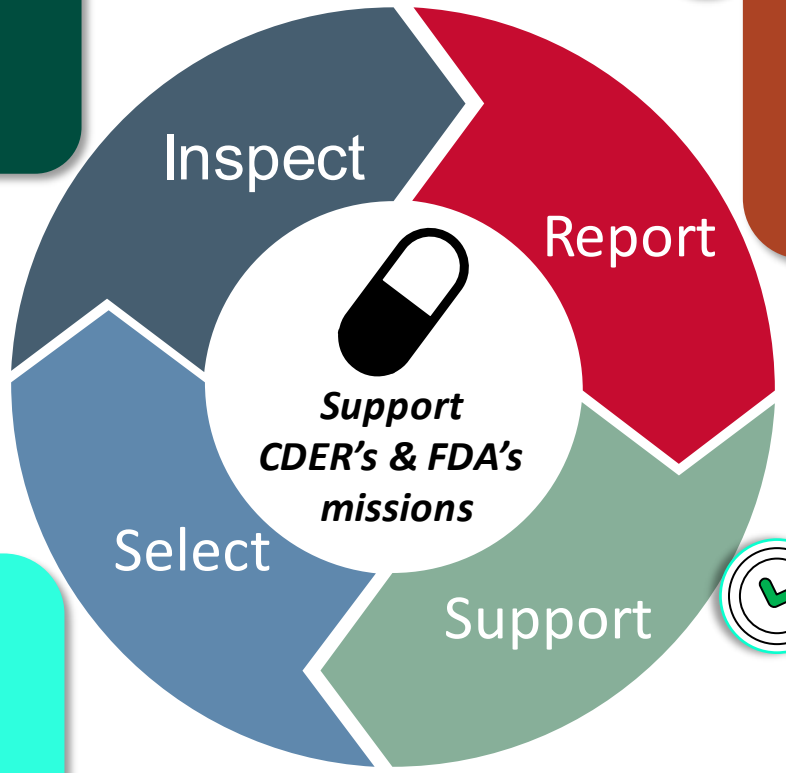
Organization Chart



OSIS Mission: **Select, Inspect, Report, Support**

Inspect sites to ensure quality and integrity of studies

Report on inspections by writing Establishment Inspection Reports and EIR Reviews



Select sites for inspection through surveillance evaluation and site assessment

Support CDER with data reliability recommendations and compliance evaluations

OSIS Mi : Select, Inspect, Report, Support

Remote Regulatory Assessment

Insp
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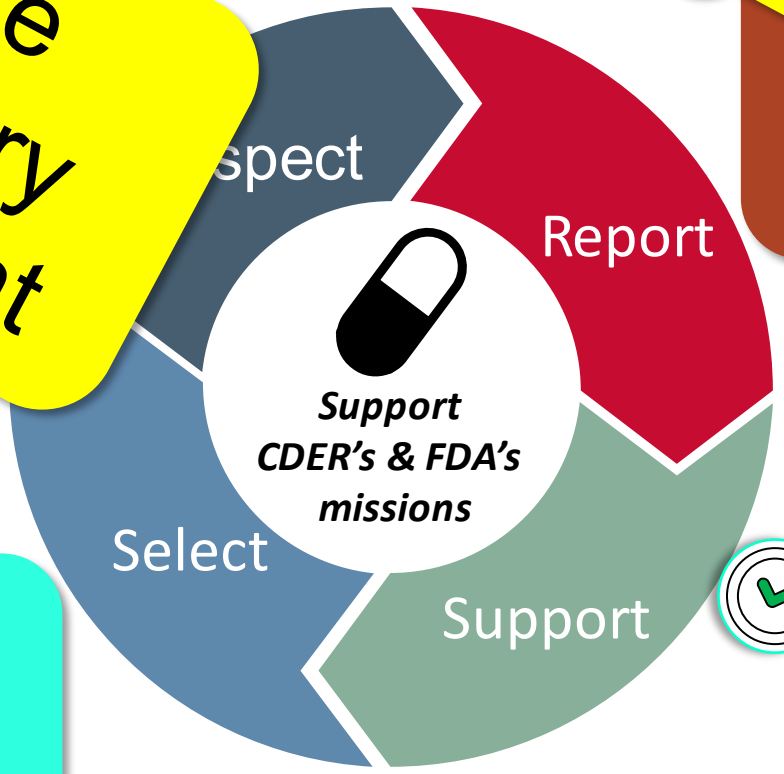


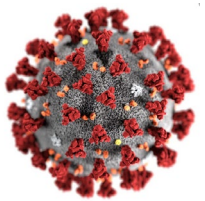
RRA Report

on inspections by
lishment
Inspec ts and
EIR Review

Select sites for inspection through surveillance evaluation and site assessment

Support CDER with data reliability recommendations and compliance evaluations

Definitions
Remote Regulatory Assessment (RRA)



- Remote Regulatory Assessment (RRA) – Umbrella term for remote approaches used across the agency
- Remote Interactive Evaluation (RIE) guidance published in April 2021 (a type of RRA)
- OSIS and ORA/OBIMO conducted RRAs for BIMO site evaluations

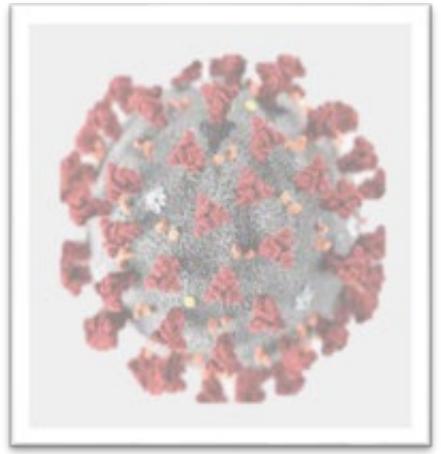
Evolution of Terminology

RRA-Remote Regulatory Assessment

RIE-Remote Interactive Evaluation

- RRR-Remote Record Review

Inspections And the Pandemic

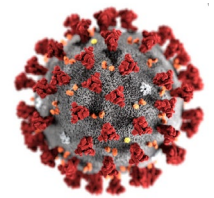


COVID-19 global pandemic – routine travel stopped

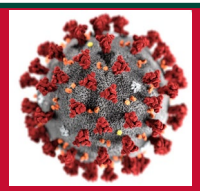
All inspection travel was cancelled as of March 2020

OSIS Responded – Started developing Remote Record Review (March 10, 2020)

Remote Approaches



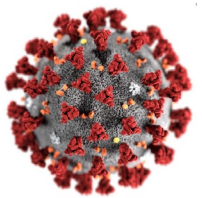
- OSIS developed a type of RRA (Mar/Apr), piloted (May)
- Started using in June 2020 to support CDER application assessments
- Voluntary interaction with a site of interest
- Review of bioavailability, bioequivalence, and GLP studies supporting NDAs, ANDAs, BLAs, and INDs and sites' study conduct.



RRA Process in OSIS

Request Participation	Send Communication Letter 1 seeking willingness for voluntary participation.
Document Request	Send Communication Letter 2 announcing studies and requesting specific documents to upload in secure document sharing system for FDA
Preparation	Review submitted and uploaded documents and plan.
Opening	Schedule & conduct an opening meeting with the site.
Virtual Facility Tour	Includes sample receipt & storage areas, laboratories, clinical facilities, archives, equipment, server room, etc.
Discussions with Site	Daily meetings to discuss any questions or concerns about the requested data; request additional documents
Close out	Conduct a close out meeting with the site. Issue observations via email prior to closing. No Form FDA 483

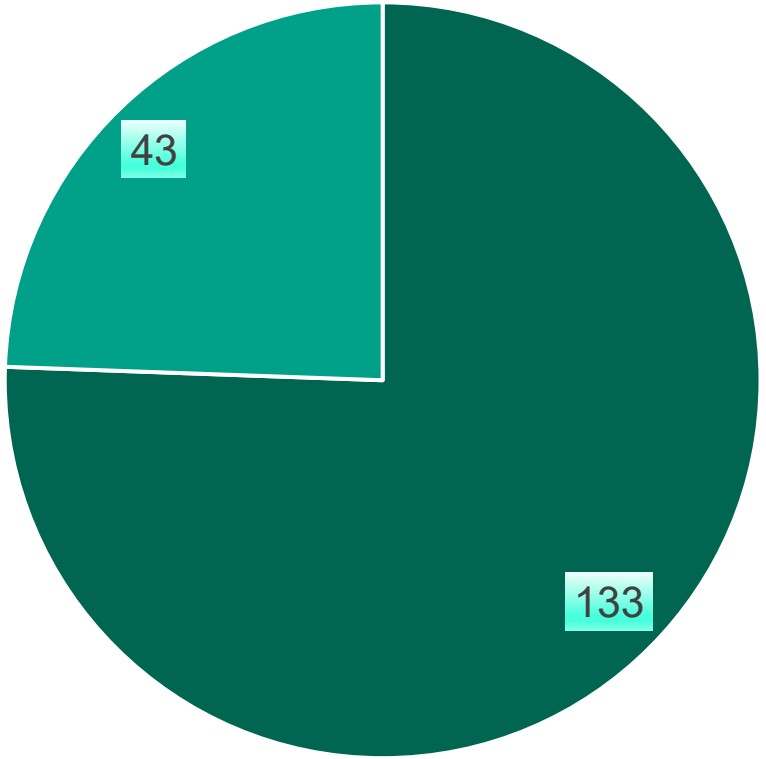
Scope of OSIS RRA

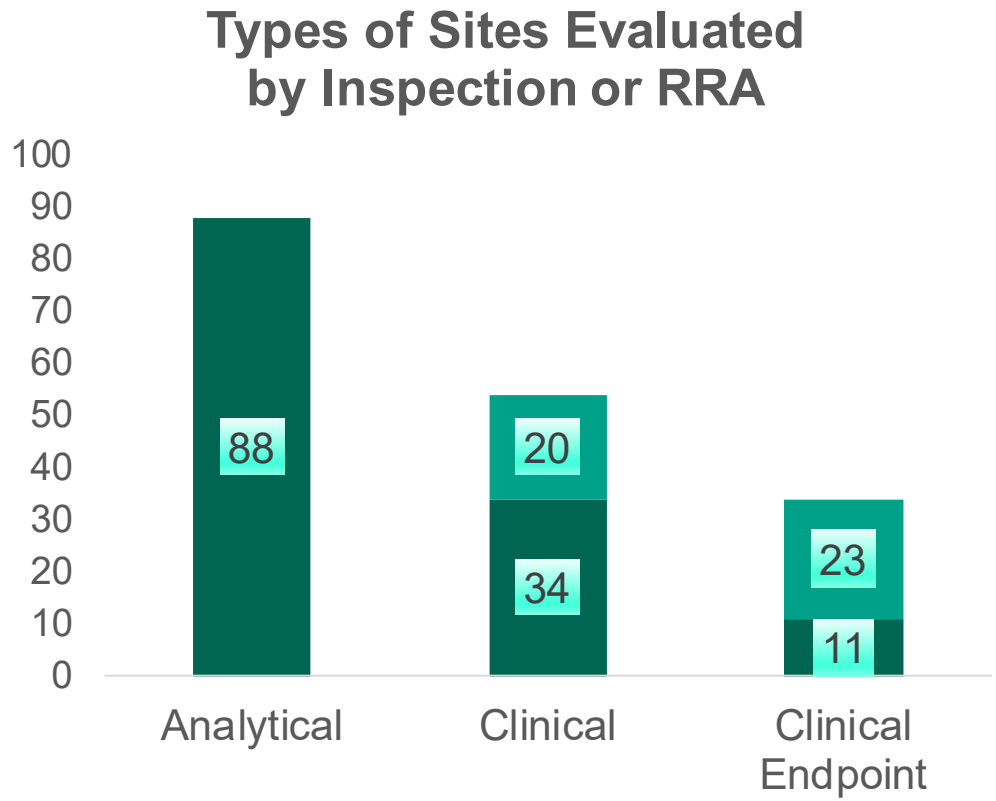


- Facilities & Site Operations
- Drug Product & Subject Sample Accountability (storage, handling & processing)
- Reserve Samples
- SOPs, Protocols & Protocol Deviations
- Training Records
- Method Validations & Sample Analysis
- Method Performance
- Audit Trails & Data Security
- Instrument Calibration & Maintenance
- Documentation
- AE reporting, Monitor Reports & IRB/IEC oversight (clinical)

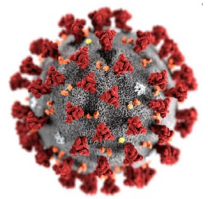
OSIS Inspections and RRAs

March 2020 – December 2021

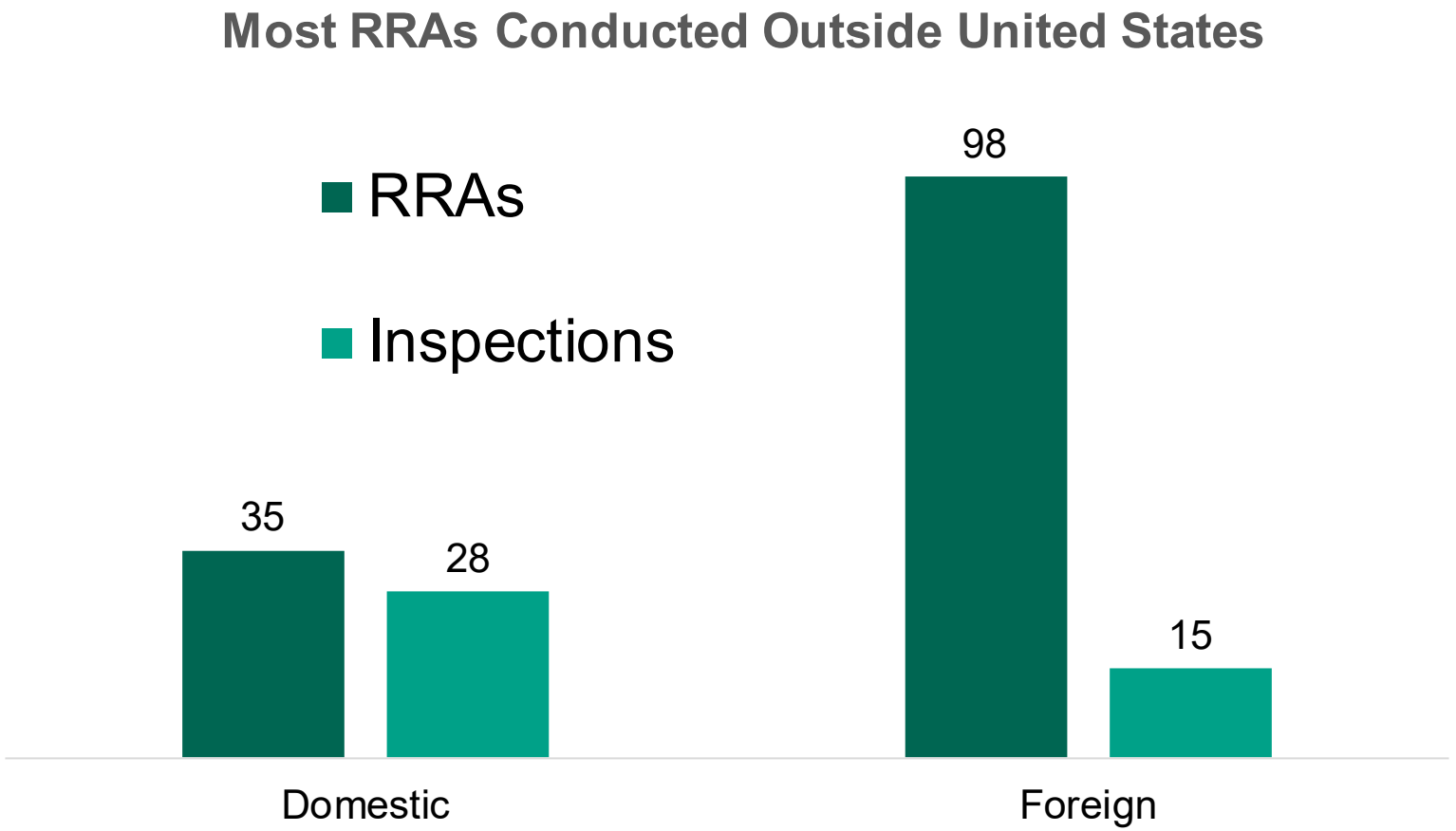




Locations of RRAs and Inspections

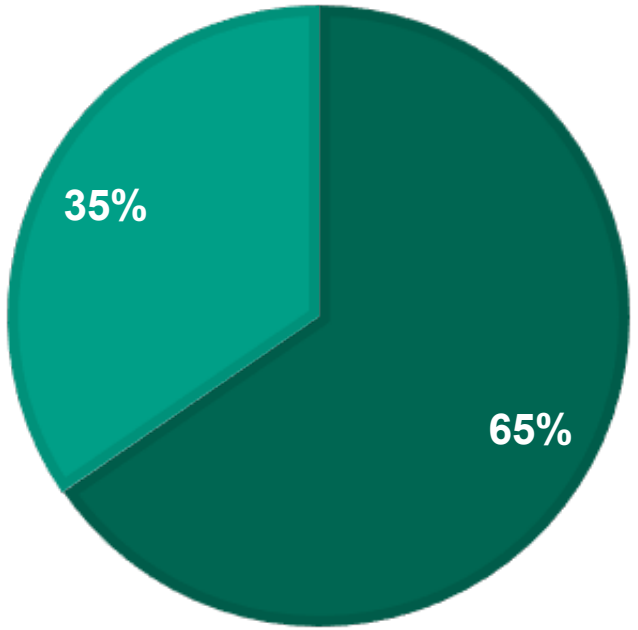


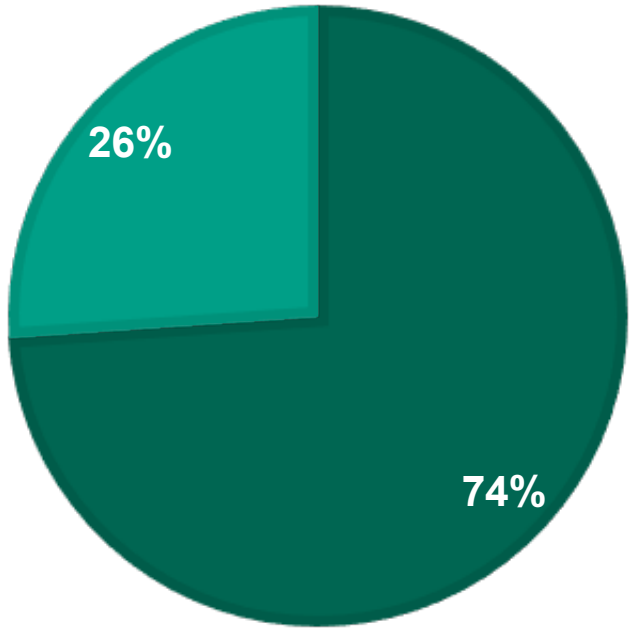
March 2020 – December 2021

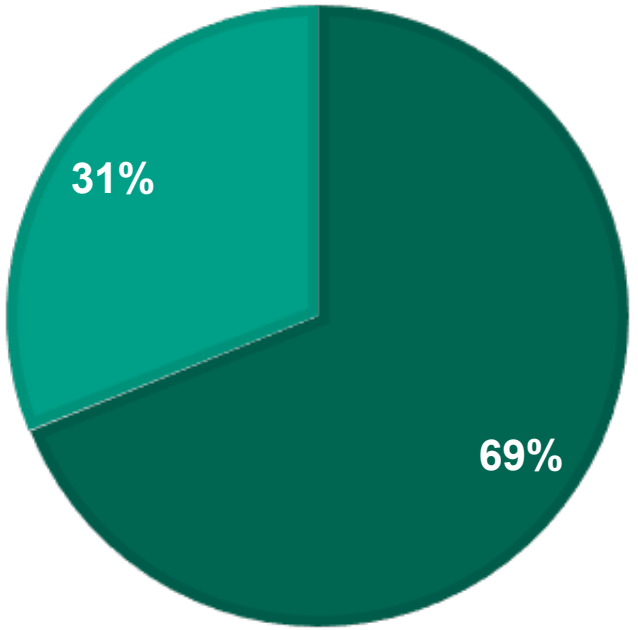


BA/BE Inspections/RRAs– Outcomes

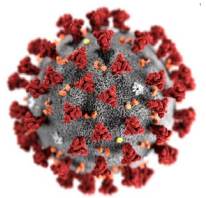
March 2020 – December 2021



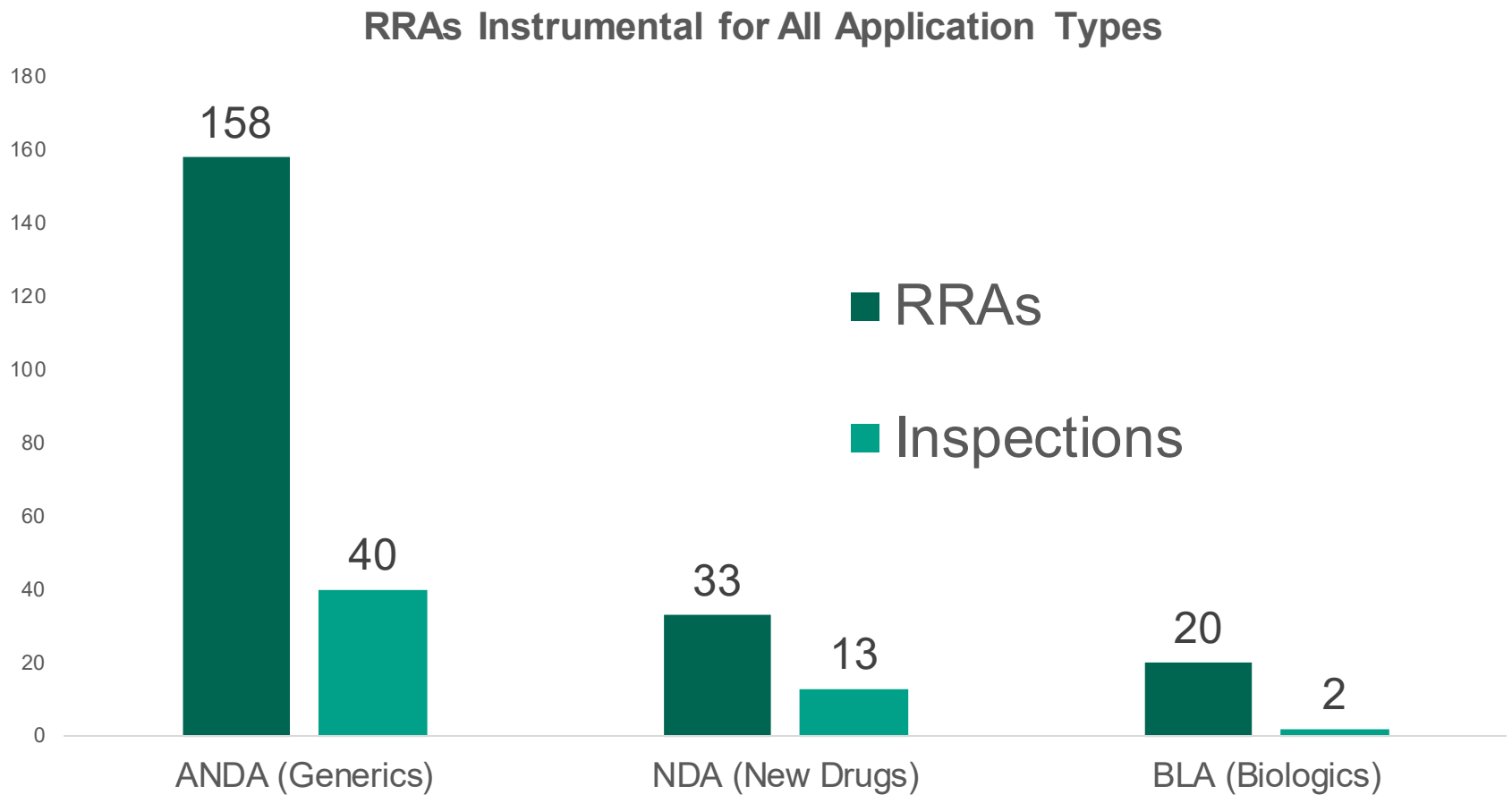




BA/BE Application coverage



March 2020 – December 2021



Looking Forward

- RRA is a critical tool
- Continued refinements to RRAs will help ensure public health missions are achieved
- Return to travel is proceeding as possible and Agency will use its tools to best fit the needs and circumstances
- Industry and Regulatory staff flexibility makes innovation possible

Submitting Questions on Interrupted Studies During the COVID-19 Pandemic

- For ANDAs that have already been submitted to FDA, ANDA applicants should direct questions to the Regulatory Project Manager for their ANDA.
- Prospective applicants may use OGD's genericdrugs@fda.hhs.gov mailbox to submit general questions related to the impact of COVID-19 on BE studies or to notify FDA of BE studies that have been interrupted.
- For ANDAs that have not yet been submitted to FDA, prospective applicants should submit specific questions related to their impacted BE studies via the controlled correspondence process, or if applicable, the pre-ANDA meeting request pathway.

Acknowledgments

Brian Folian, OSIS Deputy Director
Nicola Fenty-Stewart, OSIS Chief Project Manager
Charles Bonapace, OSIS Division Director
Julia Cho, OSIS Division Director
Arindam Dasgupta, OSIS Division Deputy Director
Kim Benson, OSIS Division Deputy Director
OTS, OGD, OND, OSI and ORA/OBIMO
Entire OSIS office

THANK YOU!

References

4/14/2021 - FDA issued a guidance for industry on Remote Interactive Evaluations

- Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency
- Describes various interactive and virtual tools and FDA's use of any combination of these tools as a remote interactive evaluation

5/5/2021 - Resiliency Roadmap for FDA Inspectional Oversight

- Agency's inspectional activities during the COVID-19 pandemic and its plan toward a more consistent state of operations

11/22/2021 - An Update to the Resiliency Roadmap