Overview of Sponsor-Investigator Roles and Responsibilities in Clinical Investigations for Drugs and Biologics Orphan Products Grantees

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Outline

Sections:

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DISCLAIMER

This presentation is not intended to be used as a substitute for formal training in Good Clinical Practice.

This presentation is an overview of the requirements and recommendations for Orphan Drug Grantees who conduct clinical investigations with an orphan drug or biologic product. The information is meant to serve as an introduction to the roles and responsibilities of personnel involved in conducting a clinical trial with Orphan drugs. This overview is not intended to be all-inclusive or a substitute for formal training in Good Clinical Practice.

For additional information, contact orphan@fda.hhs.gov

SECTION I
INTRODUCTION AND PURPOSE OF THIS PRESENTATION

ORPHAN PRODUCTS GRANTS PROGRAM

OPD Clinical Research Grants (R01) for Orphan Diseases

- The goal of the Orphan Products Research Grants Program is to encourage **clinical** development of products, including drugs, biologics, medical devices, or medical foods, for use in rare diseases
- Supports research that is conducted within the U.S.A. or outside the USA, funded by public, private or for-profit sources, and both academic and industry sponsored research
- Request for Application (RFA) available at https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/orphan-products-grants-program under Orphan Products Grant Program; then click detailed RFA link under Funding Opportunities

SOME TERMINOLOGY

What is a Rare Disease?

- Defined by the Orphan Drug Act (ODA) as a disease or condition that affects less than 200,000 people in the US.

What is the Orphan Drug Act (ODA)?

- A law passed in 1983 that incentivizes the development of drugs to treat rare diseases (orphan designated) by offering . . .
  - Tax credits for qualified clinical (in humans) testing
  - Waiver of the Prescription Drug User Fee (currently about $3 million for a new drug)
  - Potential 7 years of market exclusivity after approval
  - Establishment of the Orphan Product Grants Program to fund the development of products for rare diseases or conditions.

What is an Orphan Drug?

  – A drug for a rare disease or condition.

Drugs that are commercially available can be repurposed as orphan drugs and eligible for Office of Orphan Products Development (OOPD) grants. These repurposed drugs are still investigational drugs and are held to the same regulatory standards because they are not FDA-approved for the indication being studied, even if commercially available for other indications.

ORPHAN PRODUCTS CLINICAL TRIAL GRANTS PROGRAM

Applicants awarded orphan grants **are responsible for the proper conduct of clinical investigations**, which includes following…

- Federal laws
- State laws
- All applicable rules and regulations, including adhering to FDA regulations regarding the conduct of clinical investigations
- Institutional rules

PURPOSE OF PRESENTATION

- To provide awareness to sponsors and investigators of important FDA responsibilities to adequately conduct clinical trials
  - Importance of collecting quality data
  - Importance of adhering to U.S. regulatory requirements, including FDA's regulations regarding Good Clinical Practice (GCP)
- This knowledge is important to ensure:
  - Results of an investigation are reliable and valid
  - Rights, safety and welfare of human subjects are protected
  - Investigation is conducted in compliance with regulatory requirements

Please remember that the use of the word **should** in this presentation means that something is suggested or recommended, but not required. When something is **required,** it will be so stated, or the word "must" is used.

QUALITY CLINICAL INVESTIGATIONS

Data Integrity:

Data that are **A**ttributable, **L**egible, **C**ontemporaneous, **O**riginal, **A**ccurate (ALCOA), complete, consistent, and current

Data Quality:

Broadly refers to data that are fit for the intended purpose and are sufficient to conduct the necessary analyses. Quality data must be ALCOA+ (data integrity).

Quality in Clinical Investigations

- Defined as the absence of errors in decision making and results in high quality data
- Conducted in accordance with the IRB approved protocol
- Conducted in accordance with all other applicable regulatory requirements including FDA's regulations on Good Clinical Practice (GCP), timely reporting to ClinicalTrials.gov for applicable clinical trials, and safety reporting.

Quality investigations typically result in high quality data

Good Clinical Practice (GCP)

- Principles/guidelines for conducting a clinical investigation
- Ethical and scientific quality standard for designing, conducting, performing, monitoring, auditing, recording, analyzing and reporting clinical investigations
- FDA's regulations that help ensure clinical trials of drugs are conducted according to GCP standards are located at Parts 11, 50, 56, and 312.
- International Conference on Harmonization (ICH) - E6 Good Clinical Practice Guideline
- OOPD grants require compliance with GCPs

When Clinical Trials are not Conducted as per Applicable Regulatory Requirements

- FDA can impose a clinical hold for ongoing clinical investigations
- FDA can reject data from that clinical site or the entire marketing application
- FDA can terminate funding of the grant
- FDA can issue a Warning Letter (WL) or take a regulatory action against the sponsor or clinical investigator, e.g., disqualify the Clinical Investigator (CI)

Orphan Products Grants Program

- This presentation will focus on Drugs and Biologics

- For Device information, please see CDRH's BIMO training modules under **How to Study and Market Your Device - (Updated module 12/15/22)** 510k, De Novo, IDE, PMA, HUD/HDE, Q-Submissions, Standards, Classification

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TERMS TO KNOW

OOPD (Office of Orphan Products Development)
- Is a funding source for rare disease studies
- Is NOT the Sponsor of the investigation

Grantee
- The recipient or entity that receives the federal award to carry out the activity under a federal program

Principal Investigator
- The individual(s) designated by the applicant organization to have the appropriate level of authority and responsibility to direct the project or program to be supported by the award

Sponsor
- A person who takes responsibility for and initiates a clinical investigation. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator

Sponsor-Investigator
- An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. This individual takes on the dual role of a sponsor and an investigator.

Investigator
- An individual who conducts a clinical investigation (*i.e.*, under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. **"Sub-investigator"** includes any other individual member of that team.

SPONSOR-INVESTIGATOR

Dual Role

An indivi nitiates
and conducts a clinical investigation

Dual Responsibilities

21 CFR § 312.3

SECTION II
THE SPONSOR:
RESPONSIBILITIES IN CLINICAL TRIALS

SPONSOR

- A person who takes responsibility for and initiates a clinical investigation
- May be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization
- The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator

21 CFR § 312.3

KEY SPONSOR RESPONSIBILITIES

- Select qualified clinical investigators
- Obtain the signed Statement of Investigator (Form FDA-1572)
- Obtain the name and address of the IRB responsible for the review and approval of the investigation(s)
- Obtain financial disclosure from all clinical investigators and sub-investigators
- Provide clinical investigators with required information they need to conduct the investigation

21 CFR § § 54, 312.50, and 312.53

KEY SPONSOR RESPONSIBILITIES (CONT.)

- Maintain an effective IND
- Ensure that significant adverse-effects or risks are promptly reported to FDA and participating clinical investigators
- Control of the investigational product (i.e., shipping investigational drug only to investigators participating in the investigation)
- Prepare, maintain and retain investigational records and reports
- Provide each investigator an Investigator Brochure (IB), if there are other investigators participating in the study.

21 CFR § § 54, 312.50, 312.53, 312.55, 312.57

Key Sponsor Responsibilities (cont.)

- Ensure that the clinical investigation is conducted as per investigational plan and protocol
- Ensure proper monitoring of the clinical investigation
- Select qualified monitors to monitor the progress of the clinical investigation
- Ensure that records and reports relating to a clinical investigation are available for FDA inspection
- When electronic systems are used, ensure that the system is 21 CFR Part 11 compliant (or adhere to predicate rules)

21 CFR § § 11, 312.50, 312.53, and 312.58

TRANSFER OF SPONSOR RESPONSIBILITIES

- A sponsor may transfer (in writing) one or more of its responsibilities to a contract research organization (CRO)

- A CRO that assumes a sponsor's responsibilities shall be subject to the same regulatory action as a sponsor

21 CFR § 312.52

MONITORING

- The act of overseeing the progress of a clinical investigation
- Sponsors/CROs retain the responsibility for monitoring investigations
- Sponsors/CROs may delegate monitoring responsibilities to an individual or team
- Monitoring is required for clinical investigations conducted under a United States investigational new drug (IND) application
- It should be an ongoing continuous process until the data are locked and investigation is completed

MONITOR

Sponsor personnel or representatives appointed to evaluate the conduct of clinical investigations, and reporting of data from clinical investigations, including appropriate clinical investigator supervision of study site-staff and third-party contractors.

Monitors must be qualified by training and experience to monitor the investigation.

21 CFR § 312.53(d)

PURPOSE OF MONITORING

- To protect human subjects
- To ensure quality of the data
- To ensure Regulatory Compliance of Personnel
  - Protection of human subjects
  - Investigational plan and Protocol
  - Applicable regulations

Risk-Based Approach to Monitoring 2013 Final

A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Final Guidance published April 2023

SOME DETAILS ABOUT MONITORING

- The exact frequency of monitoring should be tailored to suit the complexity of each clinical investigation
- Monitoring can be accomplished by onsite visits or remotely at a central facility (electronically)
- All monitoring should be documented on a log noting date and time of the monitoring.
- Ideally, it is recommended that monitoring of investigations occur:
  - Prior to initiation of a clinical investigation
  - While the investigation is ongoing
  - Until entire investigation is closed-out

Risk-Based Approach to Monitoring 2013 Final

A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Final Guidance published April 2023

ASPECTS TO MONITOR

- Training of clinical investigator and personnel to conduct investigational procedures
- Adequacy of clinical investigational facilities and equipment to conduct procedures
- Adherence to IRB regulations and consent procedures
- Adherence to Investigational Plan and Protocol
- Adverse Event reporting
- Test product accountability
- Maintenance of adequate and accurate records and reports

Note: FDA doesn't require 100% source data verification. We recommend a risk-based approach and that monitoring be focused on critical to quality factors.

Risk-Based Approach to Monitoring 2013 Final
A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Final Guidance published April 2023

RECOMMENDED SPONSOR'S RECORDS AND REPORTS

Correspondence from:

- Sponsor and CROs (e.g., agreements, reports)
- Monitors (e.g., reports, responses)
- Other investigators/sites (e.g., meetings, discussions)
- Institutional Review Boards (e.g., approvals, reports)
- Data monitoring committees (e.g., minutes, reports)
- FDA (approval letters, etc.)

SPONSOR'S RECORDS AND REPORTS
(CONTINUED)

- Investigational product accountability
- Financial interests
- Records and reports required by 21CFR Part 312 (including electronic records)

IND SAFETY REPORTS

- Sponsors and Sponsor-Investigators are required to submit written IND Safety Reports to FDA and all participating clinical investigators
- IND Safety Reports submitted on FDA Form 3500A, electronic, or narrative format
- Sponsor must report as soon as possible but **no later than 15 calendar days** any potential serious risks from clinical trials, or other sources from the use of the test product including any:
  - Serious and unexpected suspected adverse reaction
  - Findings from other studies that suggest a significant risk in humans exposed to the drug
  - Findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
  - Clinically important increased rate of occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure
- Sponsors are to submit reports of any unexpected fatal or life threatening suspected adverse reaction associated with use of the drug as soon as possible but no later than 7 calendar days after the initial receipt of the information

21 CFR § 312.32

IND ANNUAL REPORTS

IND Annual Reports are due within 60 days of the IND anniversary date and includes…

- Progress of the investigation
- Most frequent and most serious AEs by body system
- Summary of the past year's submitted safety reports
- Additional summary information for clinical and non-clinical investigations

21 CFR § 312.33

OTHER MEANS OF OVERSIGHT FOR AN INVESTIGATION

- IRB's initial review and continuing reviews
- Inspections by US and International Regulatory Agencies or 3rd party audits
- Adjudication Review Committees
- Data and Safety Monitoring Board (DSMB)

STUDY MONITORING VS. DSMB

DSMB = Data and Safety Monitoring Board, which performs clinical monitoring of data and safety profiles

Study Monitoring ≠ DSMB Monitoring

DATA AND SAFETY MONITORING BOARD

- A group that periodically reviews and evaluates accumulated data from a clinical investigation for:
  - Subject safety
  - Study conduct and progress, and
  - As necessary, efficacy
- They make recommendations to the sponsor regarding the continuation, modification, or termination of the trial

Establishment and Operation of Clinical Trial Data Monitoring Committees – March 2006

REPORTING NON-COMPLIANCE

- Sponsors should promptly secure compliance of investigators or discontinue investigational product shipment to investigators the sponsor discovers are non-compliant

- If compliance cannot be secured, end the non-compliant clinical investigator's participation

- Ensure the disposal or return investigational products

- Notify IRB and FDA

21 CFR § 312.56(b)

SECTION III
THE INVESTIGATOR:
RESPONSIBILITIES IN CLINICAL TRIALS

KEY INVESTIGATOR RESPONSIBILITIES

- Protect the rights, safety and welfare of subjects in the clinical investigation

- Conduct clinical investigation according to signed statement of investigator (Form 1572), investigational plan and applicable regulations

21 CFR § 312.60

STATEMENT OF INVESTIGATOR (FORM FDA-1572)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014
Expiration Date: March 31, 2025
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

Name of Clinical Investigator			
Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED *(Select one of the following.)*

☐ Curriculum Vitae ☐ Other Statement of Qualifications

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED

CONTINUATION PAGE for Item 3

Name of Medical School, Hospital, or Other Research Facility

STATEMENT OF INVESTIGATOR

Form FDA-1572 includes:

- Name and address of the clinical investigator
- Name and code number of any protocol(s)
- Name and address of research facility(ies) and any clinical labs
- Name and address of the responsible IRB
- Names of sub-investigators
- **Signed commitment by the investigator**

21 CFR § 312.53

STATEMENT OF INVESTIGATOR

A Signed Commitment by the Investigator to:

- Conduct the investigation according to the protocol, and make changes only after notifying sponsor, except to protect the safety, welfare and rights of subjects
- Personally conduct or supervise the investigation
- Inform subjects that the test product is being used for investigational purposes and ensure requirements for informed consent and IRB review and approval are met
- Report to the sponsor adverse experiences that occur during the investigation
- Read and understand the Investigator's Brochure, including potential risks and side effects of the drug

21 CFR § 312.53

STATEMENT OF INVESTIGATOR

A Signed Commitment by the Investigator to:

- Assure that those assisting in the trial are informed of their obligations in meeting these commitments
- Comply with all other regulatory requirements regarding obligations of a clinical investigator
  - Maintain adequate and accurate records
  - Obtain initial and continuing review and approval from an IRB that is in compliance with the regulatory requirements listed under 21 CFR Part 56
  - Promptly report to the IRB all changes in the research and all unanticipated problems involving risk to subjects or others
  - Not make changes in the research without IRB approval except to eliminate immediate hazards to human subjects

INVESTIGATOR RESPONSIBILITIES (CONT.)

- Obtain IRB approval prior to enrolling any subjects

- Obtain and document informed consent signed and dated by subject or legally authorized representative (LAR)

- Ensure that changes to the protocol are reported to the sponsor and approved by the IRB prior to initiating the change

21 CFR § § 50, 56, 312.60, 312.66

INVESTIGATOR RESPONSIBILITIES (CONT.)

- Ensure the investigation is conducted according to the investigational plan
- Control the investigational products, and use test products only in/on subjects enrolled in the clinical investigation
- Ensure adverse effects/events (AEs) are appropriately documented and reported. Must report any SAE to the sponsor and must report SUSARs reported to FDA as unanticipated problem to IRB.
- Maintain adequate clinical investigational records and reports
- Ensure that all investigational records and reports are available for FDA inspection

21 CFR § § 312.61, 312.62, 312.64 & 312.68

INVESTIGATOR'S RECORDS AND REPORTS

- All clinical investigational correspondence should be accurate, complete and current
- These records and reports may include:
  - IRB correspondence and approvals
  - Monitoring reports
  - Any correspondence with FDA
  - Correspondence with other investigators, sponsors, monitors, etc.

REQUIRED INVESTIGATOR'S RECORDS AND REPORTS

Case Histories (either on paper or electronic format):

- Case Report Forms (CRFs)
- Informed Consent Forms
- Drug disposition records
- Source Documents

21 CFR § 312.62(b)

REQUIRED INVESTIGATOR'S RECORDS AND REPORTS

- **Case Report Forms (CRFs)** are documents designed to record pertinent protocol required information to be reported to the sponsor for each trial subject
  - Data on CRFs is generally organized by subject number, initials, visit number, and sequential/chronological order of data capture
  - CRFs provide data elements for analyses and reporting
  - CRFs may be in paper or electronic (eCRF) format

Electronic Records in Clinical Trials

- All 21 CFR Part 312 regulations apply equally to both paper records and electronic records

- 21 CFR Part 11

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ADDITIONAL INVESTIGATOR'S RECORDS AND REPORTS INCLUDE:

Investigators Maintain:

- Protocols
  - All Sponsor and IRB approved amendments
  - Documentation of approvals
  - Documentation of protocol deviations
  - Dates and reasons for any deviations

- Approvals from the sponsor, and IRB for changes or deviations from the investigational plan
- IRB-approved informed consent document
- Other pertinent clinical investigational records and reports
  - including electronic records

21 CFR § § 312.62, & 312.64

SECTION IV
Certificates of Confidentiality (CoCs)

42 CFR PART 11

Certificates of Confidentiality (CoCs)

The 21st Century Cures Act (Public Law 114-255) amended the Public Health Service Act (PHS Act), section 301(d) (42 U.S.C. 241(d)) relating to the issuance of Certificates of Confidentiality (CoCs) and broadened the protections by affirmatively prohibiting holders of CoCs from disclosing identifiable and sensitive information, unless specific exceptions apply.

- Obtaining COCs is a responsibility of sponsors, sponsor-investigators, or their representatives. However,
  - Grantees do not have to obtain COCs, because COCs automatically apply to federally funded research.
  - CoCs are mandatory and automatically provided **(mandatory CoCs)** for all federally-funded human research subject research that collects or uses identifiable, sensitive information.
  - CoCs are not required but issued at FDA's discretion **(discretionary CoCs)** for non-federally-funded research
  - Protections afforded by mandatory and discretionary CoCs are identical and the statutory responsibilities are the same

Certificates of Confidentiality (CoCs)

CoCs are intended to protect the privacy of individuals participating in research. Researchers obtaining CoCs shall not disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.

The disclosure prohibition shall not apply to disclosure or use that is-

(i) required by Federal, State, or local laws, excluding instances described in subparagraph (D);

(ii) necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;

(iii) made with the consent of the individual to whom the information, document, or biospecimen pertains; or

(iv) made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

Certificates of Confidentiality (CoCs)

- Any person to whom a certificate is issued shall not, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, disclose or provide the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research.

- Identifiable, sensitive information, and all copies thereof, shall be immune from the legal process, and shall not, without the consent of the individual to whom the information pertains, be admissible as evidence or used for any purpose in any action, suit, or other judicial, legislative, or administrative proceeding.

- Identifiable, sensitive information collected, and all copies thereof, shall be subject to the protections afforded by this section for perpetuity.

- Additional details are available in the Certificates of Confidentiality Guidance for Sponsor, Sponsor-Investigators, Researchers, Industry, and Food and Drug Administration Staff.

SECTION V
ClinicalTrials.gov
REQUIREMENTS FOR REGISTRATION AND RESULTS INFORMATION SUBMISSION

42 CFR PART 11

WHAT IS ClinicalTrials.gov?

- ClinicalTrials.gov is a registry and results information database of publicly and privately supported clinical studies of human participants conducted around the world.
- Timeline:
  - 1997: ClinicalTrials.gov data bank established under the Food and Drug Administration Modernization Act (FDAMA)
  - 2000: ClinicalTrials.gov website launched
  - 2007: Title VIII of the Food and Drug Administration Amendments Act (FDAAA) expands ClinicalTrials.gov to require registration of more trials and submission of results information for certain trials, and adds penalties for noncompliance
  - 2016: Final rule implementing the ClinicalTrials.gov requirements issued (effective January 18, 2017)
- The ClinicalTrials.gov requirements are codified in 42 CFR part 11

AGENCY ROLES AND RESPONSIBILITIES

- The National Institutes of Health (NIH) has the following responsibility:
  - Developing and maintaining the ClinicalTrials.gov data bank

- HHS Funding Agency (FDA, NIH, AHRQ) has the following responsibility:
  - Verifying compliance with the clinical trial information submission requirements for applicable clinical trials (ACTs) for which the grantee is the responsible party before releasing remaining funding or funding future grants

- FDA is responsible for enforcing the following requirements:
  - Informed consent statement regarding ClinicalTrials.gov (21 CFR 50.25(c))
  - Certification of Compliance (Form FDA 3674)
  - Registration and submission of results information

KEY DEFINITIONS

- Applicable Clinical Trial (ACT) [42 U.S.C. 282(j)(1)(A)(i); 42 CFR 11.10(a)]
  - Defined as an applicable drug clinical trial or an applicable device clinical trial
  - Not all trials are ACTs
- Applicable Drug Clinical Trial [42 U.S.C. 282(j)(1)(A)(iii); 42 CFR 11.10(a)]
  - Controlled clinical investigation, other than a phase 1 clinical investigation, of a drug product subject to section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) or a biological product subject to section 351 of the Public Health Service Act (PHS Act)
    - "Clinical investigation" has the meaning given in 21 CFR 312.3
    - "Phase 1" has the meaning given in 21 CFR 312.21
  - Clinical trial of combination product with drug primary mode of action (PMOA) meeting all the above requirements

KEY DEFINITIONS

- Primary Completion Date: (42 CFR 11.10(a))
  - For a clinical trial, including applicable clinical trial, defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
  - In the case of clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcomes.
  - For purposes of this part, completion date is referred to as “primary completion date.”

FINAL RULE - KEY DEFINITIONS (Cont.)

Responsible Party [42 CFR 11.10(a)]

- Sponsor of the clinical trial (as defined at 21 CFR 50.3); or

- Principal investigator (PI) of the clinical trial, if so designated by a sponsor, grantee, contractor, or awardee, so long as the PI:
  1. Is responsible for conducting the trial
  2. Has access to and control over the data from the trial,
  3. Has the right to publish the results of the trial, and
  4. Has the ability to meet all the requirements for the submission of clinical trial information.

Note: There can be only one Responsible Party. Default is sponsor.

KEY ClinicalTrials.gov REQUIREMENTS

- **Registration**: Certain ACTs must be registered on ClinicalTrials.gov
- **Results Information**: Summary results information for certain ACTs must be submitted to ClinicalTrials.gov
- **Updating**: The ClinicalTrials.gov records for ACTs must be periodically updated
- **Informed consent statement**: The informed consent document for an ACT must contain a specific statement about ClinicalTrials.gov
- **Certification of Compliance**: A certification of compliance with section 402(j) of the PHS Act must accompany certain human drug, biological product, and device applications and submissions to FDA

ClinicalTrials.gov - Registration Requirements

Clinical Trial Registration

- Registration is required for ACTs that were either initiated after September 27, 2007, or initiated on or before that date and were still ongoing as of December 26, 2007
- Responsible parties must submit registration information within 21 calendar days of first human subject enrolled [42 CFR 11.24]
- Registration information submissions are subject to quality control [42 CFR 11.64(b)(1)]
  - Responsible party must correct or address issues within 15 calendar days of electronic notification

ClinicalTrials.gov Requirement - Informed Consent

- For ACTs initiated on or after March 7, 2012, informed consent documents must include a specific statement that refers to the trial's description on www.ClinicalTrials.gov (21 CFR 50.25(c)). The statement is:

"A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

- This statement must be reproduced **word-for-word** in the informed consent document

- The statement is not required to appear in a particular section of the informed consent document

ClinicalTrials.gov - Certification of Compliance (Form FDA 3674)

- Mandated by section 402(j)(5)(B) of the PHS Act
  - A certification of compliance with section 402(j) of the PHS Act must accompany certain human drug, biological product, and device applications and submissions to FDA
  - The certification must include NCT Numbers, if available
- Submission of Form FDA 3674 may be used to meet the certification requirement
  - List the NCT Number(s) for which the sponsor/applicant/submitter is the Responsible Party
  - Certifies compliance with section 402(j) of the PHS Act as of the date form is submitted
- Willfully and knowingly submitting a false certification is a criminal offense
- Refer to FDA Final Guidance on Form FDA 3674
  - Describes the types of applications and submissions that should be accompanied by a certification of compliance
  - Outlines four categories of applications and submissions where FDA intends to exercise enforcement discretion with regard to the submission of certifications of compliance

ClinicalTrials.gov – When Must Study Results be Reported?

- Responsible parties for ACTs subject to the final rule requirements are required to submit results information
- Results information *generally* due no later than 12 months after the ACT's primary completion date
- ACTs with a primary completion date after Jan. 18, 2017, are required to post results in all cases, regardless if the product studied in the trial was approved, licensed or cleared for any use as of the primary completion date
- Submission of data in tabular format:
  - Participant flow, demographics and baseline characteristics, primary and secondary outcomes
- Must submit copy of protocol and statistical analysis plan as part of results information for ACTs with a primary completion date on or after Jan. 18, 2017
- The Results information submission is subject to NIH quality control review process. Any corrections or issues identified must be addressed within 25 calendar days of electronic notification.

DELAYED SUBMISSION OF RESULTS INFORMATION

Certifications of Delay

- A responsible party may submit a certification to delay the submission of results information for an ACT by no more than 2 years in the following situations:
  - Seeking approval, licensure, or clearance of a new use for the product studied in the ACT [42 CFR 11.44(b)]
  - Seeking initial approval, licensure, or clearance of an FDA-regulated drug, biological, or device product [42 CFR 11.44(c)]
- A certification of delay must be submitted prior to the standard submission deadline (i.e., 12 months after the primary completion date) for results information

Extension Requests

- A responsible party may request an extension of the deadline for submitting results information for good cause [42 CFR 11.44(e)]
- Decisions to grant or deny extension requests made by NIH

When Must ClinicalTrials.gov Record be Updated?

ClinicalTrials.gov record must be updated (See 42 CFR 11.64(a))

- At least every 12 months
- Certain data elements, within 30 days
  - Expanded Access Information
  - Overall Recruitment Status
  - Study Start Date
  - Individual Site Status
  - Intervention Name(s)
  - Human Subjects Protection Review Board Status
  - Primary Completion Date
  - Study Completion Date
  - Responsible Party
- Certain data elements, within 15 days
  - Device Product Not Approved or Cleared by U.S. FDA

OTHER REGISTRATION AND REPORTING POLICIES

NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

- All NIH-funded clinical trials must be registered and submit results to ClinicalTrials.gov
- Clinical Trial means "a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes"
- Includes phase 1 drug trials, device feasibility studies and any intervention not regulated by FDA

International Committee of Medical Journal Editors (ICMJE)

- Recommends that all medical journal editors require registration of clinical trials in a public trial registry at or before the time of first patient enrollment as a condition of consideration for publication

ClinicalTrials.gov – Grantee's Research Performance Progress Report (RPPR)

Grantee's Federal Grant Obligations:

- Grantees are required to self certify in the Research Performance Progress Report (RPPR) (http://grants.nih.gov/grants/rppr/index.htm), that the ClinicalTrials.gov entry is complete, valid and updated at each annual program progress report required for ACT

- By submitting the required annual RPPR, the Signing Official certifies that the grantee organization is in compliance with the terms and conditions specified in the Notice of Award and Grants Policy Statement including if the research is an ACT under section 402(j)(1)(i)-(iii) of the PHS Act (42 U.S.C. 282(j))

- That the applicant organization will be in compliance with the registration and results information submission requirements of section 402(j) of the PHS Act and its implementing regulations in 42 CFR Part 11.

ClinicalTrials.gov Record

For Orphan Clinical Trial Grants:

- FDA OOPD should be listed as a funding source for the trial by inserting the following text in the “Brief Summary” field found under the “Tabular View.”

  “Funding Source – FDA OOPD”

- FDA OOPD should not be listed as either the “collaborator” or the “sponsor” of the clinical trial.

ClinicalTrials.gov Compliance & Enforcement Activities

- Are addressed in the following BIMO compliance programs (CPs):
  - CP 7348.809 - Institutional Review Boards
  - CP 7348.810 - Sponsors and Contract Research Organizations
  - CP 7348.811 - Clinical Investigators and Sponsor-Investigators

- The CPs provide FDA Field Investigators standard instructions for BIMO inspections if conducted

- Non-compliance to ClinicalTrials.gov requirements are identified through:
  - Inspections
  - Evaluation of complaint
  - Surveillance efforts

ClinicalTrials.gov - Possible Legal Consequence of Non-Compliance

Possible Legal Consequences of Non-Compliance:

- Notice of Noncompliance Letter (generally preceded by a Pre-Notice of Noncompliance Letter)
- Civil monetary penalties (amounts adjusted annually to reflect inflation; see 45 CFR part 102)
  - Up to $10,000 for all violations adjudicated in a single proceeding
  - Up to $10,000/day for each day if not corrected within 30 days after notice of noncompliance
- Grant Funding Implications
  - HHS Grant progress report - Certification that all required clinical trial information has been submitted
  - If not verified that required clinical trial information for ACTs has been submitted, remaining grant funding or funding for future grant may not be released to grantee
- Injunction and/or criminal prosecution

42 CFR 11.66

ClinicalTrials.gov PROHIBITED ACTS

Prohibited acts under the FD&C Act:

1. Failure to submit a certification required by 402(j)(5)(B) of the PHS Act or knowingly submitting a false certification

2. Failure to submit required clinical trial information

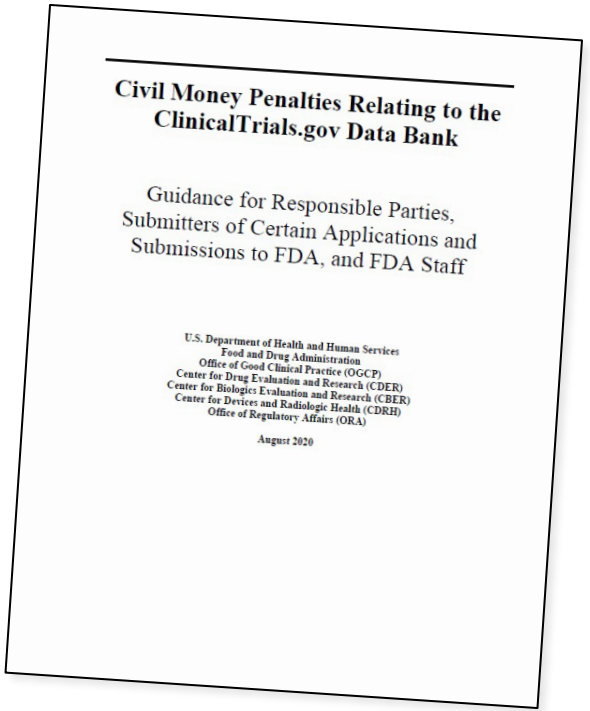
3. Submission of clinical trial information which is false or misleading in any particular manner

CIVIL MONEY PENALTY GUIDANCE

The Civil Money Penalty (CMP) final guidance addresses how FDA intends to identify :

- Whether responsible parties have failed to submit required clinical trial registration and/or results information to ClinicalTrials.gov or submitted false or misleading information

- Whether applicants or submitters have failed to submit a certification of compliance or knowingly submitted a false certification



Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank

Guidance for Responsible Parties, Submitters of Certain Applications and Submissions to FDA, and FDA Staff

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

August 2020

CIVIL MONEY PENALTY GUIDANCE (cont'd)

The CMP final guidance also outlines:

- When FDA intends to issue a Preliminary Notice of Noncompliance Letter or Notice of Noncompliance Letter
- The circumstances under which FDA may seek civil money penalties against a responsible party or applicant/submitter
- What procedures apply when FDA seeks civil money penalties
- What civil money penalty amounts may be assessed

RISK-BASED COMPLIANCE APPROACH

FDA uses a risk-based approach to evaluate potential non-compliance. The Agency intends to focus its attention in the following areas:

- Responsible parties who have failed to submit required clinical trial information for ACTs of products that potentially may pose a higher risk to human subjects or that are intended to address a significant public health need

- Responsible parties/submitters with a pattern of previous noncompliance with the ClinicalTrials.gov requirements

- ACTs for which noncompliance exists in conjunction with noncompliance with other statutory and/or regulatory requirements pertaining to the conduct of the trial

Resources

- NIH Information on 42 CFR Part 11
- NIH Clinical Research Policy Page
- ClinicialTrials.gov Website
- NIH ClinicalTrials.gov Training Materials
- NIH Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial
- FDA's Role: ClinicalTrials.gov Information

Resources

- ClinicalTrials.gov Final Rule (42 CFR part 11)
- Statutory language of Title VIII of FDAAA
- Form FDA 3674
- FDA Guidance on Form FDA 3674
- FDA Guidance on Informed Consent Element at 21 CFR 50.25(c)
- FDA Guidance on Civil Money Penalties Related to the ClinicalTrials.gov Data Bank
- FDA.gov Webpage for ClinicalTrials.gov Notices of Noncompliance and Civil Money Penalty Actions

SECTION VI
FDA'S OVERSIGHT OF A CLINICAL INVESTIGATION

APPROACHES FOR EVALUATING CLINICAL INVESTIGATIONS

- FDA Product Review Divisions
  - Review and analyze efficacy and safety data submitted to the agency

- FDA BIMO Inspections
  - Evaluate data integrity and validity of data
  - Protect the rights, safety, and welfare of human subjects and animals involved in FDA regulated research

- OOPD Grant Evaluations (Teleconference or On-site)
  - Assess the progress and status of OOPD funded studies

APPROACHES FOR EVALUATING CLINICAL INVESTIGATIONS (CONT.)

OOPD Grant Evaluations are . . .

- To discuss progress and current status of each OOPD funded study, compliance with the regulatory requirements, and discuss plans for continued product development
- An important part of OOPD's grant oversight responsibilities
- Not an FDA Regulatory Inspection
- To ensure that communication between OOPD and the grantee is optimized on any issue relevant to the grant

OOPD GRANT EVALUATIONS

Items Covered:

- General overview and progress of the clinical study
- Study protocol Information and procedures
- Study Site/Investigator Information
- Institutional Review Board Information
- Informed Consent Form and procedures
- Record Keeping
- Correspondence with sponsor and FDA

OOPD GRANT EVALUATIONS (CONTINUED)

Items Covered:

- Study Procedures and Study records information
- Progress of Study
- Interim Analyses and DSMB activities
- Adverse Events and Reporting Process
- Study Monitoring
- ClinicalTrials.gov Information
- Test Product Accountability, Manufacturing, Preparation and Storage
- Budget Information and Use of Funds
- Discuss Questions/Concerns; Product Development
- **For On-site Grant Evaluations**: If time permits, a tour of pertinent areas of the research facility

OOPD GRANT EVALUATIONS (CONTINUED)

Post Grant Evaluation Actions:

- Observations, findings or concerns are discussed with sponsor or investigator
- Corrective actions/follow-up to prevent repeat of findings may be requested for review
- Applicable Study Procedures related to findings and corrective actions are reviewed to address the findings
- Serious findings may be referred for appropriate regulatory action and follow-up

OTHER MEANS OF OVERSIGHT

- Investigator's study oversight and supervision
- IRB's initial and continuing reviews
- Sponsor/CRO monitoring and audits
- Audits by US and International Regulatory Agencies
  - On-site Inspections
  - Conducting Remote Regulatory Assessments (RRAs) Questions and Answers
  - Adjudication Review Committees
- Data and Safety Monitoring Board (DSMB)

FDA BIORESEARCH MONITORING INSPECTION

Also called **BIMO Inspections**

Objectives:

- To protect human research subjects/participants from undue hazard or risk
- To ensure the quality and integrity of data submitted in support of product marketing applications
- To assess compliance with FDA regulations governing the conduct of clinical trials, including those for informed consent and ethical review

WHOM DOES FDA INSPECT?

FDA BIMO COMPLIANCE PROGRAMS:

- In Vivo Bioavailability-Bioequivalence Studies – Clinical (CP 7348.003) and Analytical (CP 7348.004)
- Inspection of Nonclinical Laboratories conducting Animal Rule-Specific Studies (CP 7348.007) or Good Laboratory Practices (Nonclinical Laboratories) (CP 7348.808)
- Institutional Review Boards (CP 7348.809) and Radioactive Drug Research Committees (CP 7348.809A)
- Sponsors and Contract Research Organizations (CP 7348.810)
- Clinical Investigator and Sponsor-Investigators (CP 7348.811)
- Post marketing Adverse Drug Experience (PADE) Reporting Inspections (CP 7353.001)
- Risk Evaluation and Mitigation Strategies (REMS) Reporting Inspections (CP 7353.001C)

Bioresearch Monitoring Compliance Programs

Why Does FDA Inspect Clinical Sites?

- Routine
  - Usually, inspection of data submitted in support of a marketing application
  - Usually, pre-announced
  - CDER utilizes a risk-based model for clinical site selection

- For Cause
  - Usually initiated as a follow-up of a complaint or data integrity concern
  - Inspection is focused
  - May be unannounced

- CBER Quality Systems or Surveillance Inspection
  - Generally done for all applicable BIMO programs in CBER
  - Inspect ongoing clinical investigations conducted under an IND or IDE
  - “Real-time” surveillance of clinical investigations in Phases 1, 2, or 3

What Does FDA Inspect?

In general FDA compares data on:

Case Report Forms (paper CRFs and e-Records from investigational site)

vs

Case Histories (source records – paper and e-Records)

vs

Data Listings (submitted to FDA by sponsor)

What Does FDA Inspect?

- Source data is compared to data submitted to FDA
- Available Standard Operating Procedures (SOPs)
- Protocol (original & revisions)
- IRB submissions and approvals
- Signed Investigator Agreements (Form FDA 1572)
- Financial Disclosure Statements
- Correspondence between Sponsor, IRB, FDA, and clinical investigator
- Documentation on test article storage, distribution, accountability
- Available monitoring plans, visit logs, and monitoring reports
- Training records
- Case Histories (e.g., CRFs, Source Documents, Informed Consent Forms)
- Adverse event records and reports
- Compliance with ClinicalTrials.gov registration and reporting requirements

CPGM 7348.810 Part III, and/or CPGM 7248.811

INSPECTION CONCLUSION AND FORM FDA 483

- A Form FDA 483, Inspectional Observations, is issued to the most responsible individual at the site, at the time of inspectional close out, if significant objectionable conditions (potential regulatory violations) are observed by an FDA investigator.

- The individual receiving the Form FDA 483 may agree-with or refute the inspectional observations either orally or in writing - include supporting documentation.

- A well thought out written response (within 15 days) is strongly recommended.

RESPONDING TO A FORM FDA 483

When writing a response to Form FDA 483 observations, consider the following:

- Include a commitment from senior leadership.
- Address each observation separately.
- Note whether you agree or disagree with each 483 observation, and provide documentation to support your disagreements, if any.
- Provide both corrective and preventive actions.
- Provide both completed and planned actions.
- Provide timelines for completion.
- Provide a method of verification or monitoring the effectiveness of the actions.
- Submit documentation (training, SOPs, corrective and preventive actions (CAPAs), records and reports).
- **Submit the response within 15 working days from close of inspection (for FDA to consider the response prior to issuing a Regulatory Letter**)

INSPECTION CLASSIFICATIONS

After FDA evaluation of inspection report, outcomes will be classified as:

- NAI – No Action Indicated, no objectionable conditions or practices were found during an inspection (or the objectionable conditions found do not justify further regulatory action).

- VAI – Voluntary Action Indicated, objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action.

- OAI – Official Action Indicated, regulatory and/or administrative actions will be recommended, which can result in issuance of a Warning Letter (WL) or Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE).

SECTION VII
HELPFUL HINTS FOR CONDUCTING A QUALITY CLINICAL INVESTIGATION

EXAMPLES OF SPONSOR DEFICIENCIES

- Lack of FDA authorization of an IND
- Inadequate monitoring
- Failure to submit Progress Report
- Failure to secure investigator compliance
- Inadequate reporting of adverse events
- Failure to inform investigators of pertinent changes in the protocol and provide information they need to conduct the investigation properly
- Failure to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug
- Failure to obtain signed Investigator agreement
- Unqualified monitors

EXAMPLES OF CLINICAL INVESTIGATOR DEFICIENCIES

- Failure to follow investigational plan, investigator agreement, or protocol
- Inadequate case histories
- Inadequate subject protection or informed consent
- Inadequate test article accountability
- Lack of IRB approval
- Failure to submit required reports to the sponsor

PREPARING FOR FDA INSPECTION

- Conduct a mock inspection using the pertinent compliance programs (sponsor and clinical-investigator)
- Routine FDA inspections are announced at least a few days before the start of the inspection
- Have all clinical investigational records and reports, including available standard operating procedures, organized at all times
- FDA Inspections typically last 2-5 days (but may be longer if necessary)
- Have available:
  - A person knowledgeable about the clinical investigation
  - A place to review records with access to a photocopier

RECOMMENDATIONS FOR PERSONNEL INVOLVED IN A CLINICAL INVESTIGATION

- Keep ALL files always organized
- Keep all source documents and materials
- Keep ALL correspondence:
  - Sponsor, IRB, monitors, study subject letters, faxes, e-mails, memos and phone contacts
- Know your IRB's requirements
- Know the sponsor's/IRB's adverse event reporting requirements
- Know the protocol:
  - Inclusion/exclusion criteria, study windows, study procedures
- Know each study staff member's roles and responsibilities:
  - The clinical investigator is ultimately responsible

RECOMMENDATIONS FOR PERSONNEL INVOLVED IN A CLINICAL INVESTIGATION (CONTINUED)

- Remember that sponsor responsibilities may be transferred to a CRO
- CRO assumes the regulatory responsibility and obligations for transferred tasks that are specified in writing
- Responsibilities that are not contracted in writing will remain the obligation of the sponsor
- Keep all test article accountability records current, complete and accurate:
  - Shipping receipts, enrollment logs, dispensing logs
- Written procedures are recommended:
  - SOPs, Quality Policy, Training procedures, Job descriptions, etc.
- Have a Preventive and Corrective Action Plan if problems arise

CONCLUSION

It is important to
capture the highest quality data
To best determine whether the investigational product
is safe and effective

SECTION VIII
PERTINENT REFERENCES

REGULATIONS
(All Products)

- 21 CFR 50: Protection of Human Subjects
- 21 CFR 54: Financial Disclosure
- 21 CFR 56: Institutional Review Boards
- 21 CFR 58: Good Laboratory Practice for Non-Clinical laboratory Studies

REGULATIONS
(Drugs and Biologics)

- 21 CFR 312: Investigational New Drug Application (IND)
- 21 CFR 314: New Drug Application (NDA)
- 21 CFR 316: Orphan Drugs
- 21 CFR 320: Bioavailability and Bioequivalence Requirements
- 21 CFR 601: Biological Licensing (BLA)

FOR MORE INFORMATION

- FDA Home Page
- Office of Orphan Products Development (OOPD)
- FDA Good Clinical Practice
- Code of Federal Regulations (CFR)
- Center for Drug Evaluation and Research (CDER) Office of Scientific Investigations (OSI)
- Center for Biologics Evaluation and Research (CBER) Division of Inspections and Surveillance
- Center for Devices and Radiological Health (CDRH) Bioresearch Monitoring (BIMO)

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