CHAPTER 48 – Bioresearch Monitoring

SUBJECT: SPONSORS AND CONTRACT RESEARCH ORGANIZATIONS	IMPLEMENTATION DATE September 15, 2021
DATA REPORTING	
PRODUCT CODES: Bioresearch Monitoring inspections do not require product codes	
PROGRAM ASSIGNMENT CODES	
09810 Foods, Food Additives and Color Additives	
41810 Biologics (Human Cellular, Tissue and Gene Therapies)	
42810 Biologics (Blood and Blood Products)	
45810 Biologics (Vaccines and Allergenic Products)	
48810 Human Drugs and Therapeutic Biologics	
68810 Animal Products (Animal Drugs and Food Additives)	
83810 Medical Devices	
98810 Tobacco Products	

Note: For purposes of this compliance program, the term “sponsor” is intended to refer to the entity that initiates and takes responsibility for clinical and nonclinical investigations and/or has been so identified by FDA through receipt of an investigational exemption or application for research or marketing permit. Therefore, the term may be inclusive of applicants, petitioners, and notifiers. Unless otherwise specified, hereinafter, the term “sponsor” also refers to any entity to whom one or more of the obligations of the sponsor has been transferred in writing (i.e., contract research organization). Refer Part II Section B (Program Management Instructions) of this CP for further information about program coverage.

FIELD REPORTING REQUIREMENTS:

For both domestic and foreign inspections, a preliminary summary of inspectional findings, as well as any Form FDA 483 Inspectional Observations (FDA 483) that was issued, should be emailed to the center's Bioresearch Monitoring (BIMO) program Point of Contact (center POC) as identified in the inspection assignment, as soon as possible, but generally no later than 3 business days after the inspection has completed.

For domestic inspections, all establishment inspection reports (EIRs), complete with attachments and exhibits, are to be submitted promptly via eNSpect to the center POC. If there are hard copy originals of the attachments and exhibits, those documents, along with the printed eNSpect cover sheet, should be routed to the file room of the home district where the firm is geographically located.

For foreign inspections, all EIRs, complete with attachments and exhibits, are to be submitted via eNSpect to the center POC.

All EIRs should be completed in accordance with Field Management Directive (FMD) 86: Establishment Inspection Report (EIR) Conclusions and Decisions.

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PART I - BACKGROUND

In 1977, the Food and Drug Administration (FDA or Agency) established the Bioresearch Monitoring (BIMO) program to ensure the protection of the rights, safety, and welfare of human research subjects involved in FDA-regulated clinical studies; to verify the accuracy and reliability of study data submitted to FDA in support of research or marketing applications; and to assess compliance with statutory requirements and FDA's regulations.[1]

The BIMO program is implemented through multi-center compliance programs (CPs) to ensure regulated entities are operating in accordance with applicable laws, regulations, and standards. These CPs were developed to provide uniform guidance and specific instructions for inspections.

FDA's Office of Regulatory Affairs (ORA) Office of Bioresearch Monitoring Operations (OBIMO) conducts inspections of clinical investigators, sponsors, sponsor-investigators, contract research organizations (CROs), institutional review boards (IRBs),[2] radioactive drug research committees (RDRCs), nonclinical (animal) studies, and bioavailability and bioequivalence (BA/BE) studies in support of preapproval, licensing, premarket and marketing applications submitted to FDA, and of post-marketing adverse drug experience reporting (PADE), and risk evaluation and mitigation strategies (REMS) reporting to ensure compliance with certain postmarketing requirements, as part of the BIMO program, among other activities.

This CP applies to all FDA centers[3] and ORA, and addresses inspections of sponsors and CROs who take responsibility for and initiate clinical and nonclinical investigations. ORA investigators conduct inspections to evaluate compliance with applicable statutory and regulatory requirements and to assure the reliability of the study data and assess whether studies were performed under ethical and scientific quality standards. These inspections are conducted to assure the quality and reliability of data submitted to FDA in support of research or marketing applications, as well as protect the public health by ensuring safety and efficacy of human and animal drugs, biological products, foods, and medical devices, and minimize the public health risk of tobacco products; and by ensuring the protection of subjects' safety, rights, and welfare.

Title 21 of the Code of Federal Regulations (21 CFR) includes most of the regulations pertaining to drugs, biological products, medical devices, most foods, food additives, color additives, and tobacco

[1] FDA External Fact Sheet about Office of Bioresearch Monitoring Operations, and Laws FDA Enforces

[2] Institutional Review Boards and Independent Ethics Committees are hereinafter referred to inclusively as institutional review boards (IRBs)

[3] Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), Center for Food Safety and Applied Nutrition (CFSAN), Center for Tobacco Products (CTP), and Center for Veterinary Medicine (CVM)

products.

The following is a non-exhaustive list of the regulations and requirements that govern sponsor's activities and oversight of clinical and nonclinical investigations:

- Sponsor's requirements for initiating and taking responsibility for clinical studies of human drugs or biological products are provided in 21 CFR 312 (Investigational New Drug Application (IND)). Additional requirements pertaining to the conduct of drug and biologic studies are contained in 21 CFR 314 (Applications for FDA Approval to Market a New Drug). Additional requirements pertaining to the applicability of IND regulations to the conduct of bioequivalence studies are contained in 21 CFR 320.

- Sponsor's requirements for initiating and taking responsibility for clinical studies of human medical devices are provided in 21 CFR 812 (Investigational Device Exemptions). Additional requirements pertaining to the conduct of studies of human medical devices are contained in 21 CFR 814 (Premarket Approval of Medical Devices). Premarket approval is not required for devices intended for animal use (animal medical devices).

- Sponsor's requirements for the conduct of nonclinical laboratory studies are provided in 21 CFR 58 (Good Laboratory Practice for Nonclinical Laboratory Studies).

- Requirements pertaining to the conduct of human studies are provided in 21 CFR 50 (Protection of Human Subjects, including pediatric studies in 21 CFR 50, subpart D), 21 CFR 54 (Financial Disclosure by Clinical Investigators), and 21 CFR 56 (Institutional Review Boards).

- Requirements pertaining to the use of new animal drugs for clinical investigations in animals are provided under 21 CFR 511 (New Animal Drugs for Investigational Use) and 21 CFR 514 (New Animal Drug Applications). Premarket requirements pertaining to abbreviated new animal drug applications are found in Section 512 of the Federal Food, Drug, and Cosmetic Act.

- Requirements pertaining to the investigational use of foods, food additives, and color additives are provided under 21 CFR 25, 70, 71, 74, 80, 82, 101, 107, 170, 171, 180, 190, 570, and 571.

- Regulations pertaining to electronic records and electronic signatures are provided in 21 CFR 11.

- Regulations pertaining to clinical trials registration and submission of results information, specifically to the National Institutes of Health (NIH) via https://ClinicalTrials.gov, are provided in Title 42 CFR 11.

See Part VI (References and Program Contracts) of this CP for a list of applicable regulations and guidance documents for industry.

PART II - IMPLEMENTATION

A. OBJECTIVES

The objectives of the BIMO Program with respect to FDA-regulated research are:

1. To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials;
2. To verify the accuracy and reliability of study data submitted to FDA in support of research or marketing applications; and
3. To assess compliance with FDA's regulations governing the conduct of clinical and nonclinical studies.

The purpose of this CP is to provide uniform guidance and specific instructions to ORA and center personnel for conducting inspections of sponsors and for gathering and preparing the evidence to support recommendations as part of the regulatory decision-making process.

B. PROGRAM MANAGEMENT INSTRUCTIONS

1. Coverage

   This program covers domestic and foreign inspections of:

   a. Sponsors

      Such entities that take responsibility for and initiate clinical investigations[4] and/or have been so identified by FDA through receipt of an investigational exemption, or application for research or marketing permit. A sponsor is defined in the regulations at 21 CFR 58.3(f), 312.3(b), 510.3(k), 511.3, and 812.3(n).

   b. Contract Research Organizations (CROs)

      Such entities to whom one or more of the obligations of a sponsor have been transferred in writing[5] (e.g., design of protocol, selection of investigators and study monitors, monitoring, evaluation of reports, preparation of materials to be submitted

[4] 21 CFR 312.3, 511.3, and 812.3(i)

[5] Transfer of responsibility is permitted by written agreement. Responsibilities that are not specified in a written agreement are not considered to be transferred. When operating under written agreements, the CROs are subject to the same regulatory actions as sponsors for any failure to perform any of the obligations assumed.

to FDA). A CRO is defined in the regulations at 21 CFR 312.3(b), 511.1(f), and 511.3.

The medical device regulations (21 CFR 812) do not define or delineate responsibilities for CROs. Device sponsors are, therefore, held responsible for any regulatory noncompliance by a CRO.

c. Sponsor-Investigators

A sponsor-investigator[6] is an individual who initiates and also conducts the clinical investigation. A sponsor-investigator must comply with regulatory requirements applicable to both sponsors and clinical investigators.

While inspections of sponsor-investigators are assigned under Compliance Program 7348.811: Clinical Investigators and Sponsor-Investigators, this CP should be referred to for areas applicable to the sponsor responsibilities of the sponsor-investigator.

d. Monitors

Monitors[7] are employed or designated by a sponsor or CRO to oversee the progress of an investigation. The monitor may be an employee or a consultant to the sponsor or CRO and are commonly referred to as clinical research associates (CRAs).

2. Inspection Assignments

a. Centers issue sponsor inspection assignments with background materials (e.g., study protocol, case report forms (CRFs), data line listings, complaint summary, or any additional information).

i. Domestic inspection assignments are assigned through ORA OBIMO headquarters to the appropriate ORA OBIMO division.

ii. Foreign inspection assignments are issued to ORA OBIMO headquarters.

b. If the inspection involves a U.S. Department of Veterans Affairs (VA) facility, refer to Part II Section B.6. (Inspections of Facilities under the Jurisdiction of the Department of Veterans Affairs) of this CP for additional instructions.

[6] 21 CFR 312.3, 511.3, 812.3(o)
[7] 21 CFR 812.3(j)

3. Communication between the Centers and ORA

   a. Prior to an Inspection

      i. The center generates an inspection assignment, including contact information for the center POC, and issues the inspection assignment in eNSpect.

      ii. The ORA investigator contacts the center POC:

         a. At least two weeks prior to scheduling the inspection, to establish initial contact and to discuss the focus and intent of the inspection and any special instructions or additional information; and

         b. To coordinate inspection arrangements if center personnel plan to participate in the inspection. Refer to Part II Section B.4.c. (Center Participants) of this CP for additional information about center participation in inspections.

      iii. A pre-inspection meeting may be arranged by the center or ORA to discuss complex products or studies, data concerns, unique or urgent circumstances, compliance history, etc.

         These pre-inspection meetings may include the following participants:

         a. Center POC and other center personnel as appropriate;

         b. Center review division primary clinical reviewer and team leader, as appropriate, and other application reviewers, as needed;

         c. ORA investigator(s) assigned to the inspection and the ORA investigator's supervisor;

         d. Other ORA OBIMO division management or OBIMO headquarters staff such as a national expert or program expert, as appropriate; and

         e. Foreign regulatory counterparts, as applicable.

   b. During an Inspection

      The center POC and ORA investigator should strive to be accessible to one another as much as possible during the inspection.

i. The center POC contacts the ORA investigator if new significant information becomes available or if there is a change in the scope of the inspection.

ii. The ORA investigator contacts the center POC if advice or clarification of the inspection assignment is needed or if evidence of concern is uncovered that warrants discussion with the ORA investigator's supervisor and center personnel.

c. After an Inspection

i. As soon as possible, but no later than 3 business days after the conclusion of the inspection, the ORA investigator emails a preliminary summary of inspectional findings and a copy of any FDA 483 issued to the center POC.

ii. The ORA OBIMO division forwards a copy of any firm's response to the FDA 483 to the center POC. The center POC forwards to the appropriate ORA OBIMO division correspondence email address a copy of any response to the FDA 483 that does not appear to have been shared with the ORA OBIMO division.

iii. The ORA investigator completes the EIR within the timeframes outlined in FMD-86 (Establishment Inspection Report Conclusions and Decisions) or by the inspection assignment due date, whichever is sooner.

iv. The center POC/reviewer consults with the ORA investigator as needed when reviewing the EIR.

v. The center consults with the appropriate ORA personnel (e.g., ORA investigator, supervisory investigator, investigations branch director (DIB)) prior to determining center final classification if the center final classification differs from the ORA OBIMO division's recommended classification.

If the center's final classification is different from the ORA OBIMO division's recommended classification, the center should ensure that ORA personnel are aware of the change and the reasons for the change.

vi. The center enters the final classification into eNSpect and sends a copy of the post-inspectional correspondence to the appropriate ORA OBIMO division email address.

4. Responsibilities of ORA Investigators, Inspection Team Leaders, and Center Participants

   a. ORA Investigators

      The ORA investigator's responsibilities include, but are not limited to, the following:

      i. Reviewing inspection assignment and background materials and attending pre-inspection meetings (as needed) prior to the start of the inspection;

      ii. Discussing with ORA management the need to adjust the workload in order to meet specific inspection due dates;

      iii. Scheduling domestic inspections and communicating with ORA OBIMO international work planner to confirm scheduling of foreign inspections;

      iv. Conducting the assigned inspection;

      v. Communicating inspectional issues and inspectional observations with the sponsor during the inspection, as appropriate;

      vi. Communicating inspectional observations and issues to the ORA investigator’s supervisor and the center POC;

      vii. Preparing and issuing any FDA 483; discussing any inspectional observations listed on the FDA 483 and/or any discussion items at the close of the inspection; informing the sponsor they may submit a written response to the FDA 483 for consideration within 15 business days of the close of the inspection;

      viii. Preparing and submitting an EIR within established timeframes; and

      ix. When appropriate, participating in post-inspectional discussions with the center and inspected entity.

   b. Inspection Team Leader

      When inspections are conducted by a team, an ORA investigator serves as the inspection team leader and is responsible for the cooperative conduct of the inspection. In addition to the responsibilities listed above in 4.a., the team leader's responsibilities include, but are not limited to, those listed in Investigations Operations Manual (IOM) Chapter 5, Establishment Inspections, subchapter 5.1.2.5, Team Inspections.

c. Center Participants

The center participant's responsibilities include, but are not limited to, the following:

i. Identifying specific objectives to be covered by the inspection;

ii. Providing information pertinent to the inspection;

iii. Contacting ORA BIMO Inspection POC regarding seeking approval to participate in inspections;

iv. Obtaining inspection credentials and a regulatory notebook to be used during the inspection;

v. Preparing for the inspection including review of the IOM, CP, inspection assignment and background materials;

vi. Attending pre-inspection meetings as needed;

vii. Providing guidance and expertise during the inspection as a subject matter expert; and

viii. Completing inspection tasks (e.g., reviewing documents, preparing inspection notes, and writing specific sections of the EIR within guidelines and timeframes).

5. Resolution of Disagreements

If there is disagreement among members of the inspection team, the issue should be discussed privately and resolved cooperatively. Any difficulties in conducting team inspections should be discussed with appropriate ORA OBIMO division management and the center management, and, if not resolved, referred to ORA OBIMO headquarters management.

6. Inspections of Facilities under the jurisdiction of the Department of Veteran Affairs

a. Pre-Inspection

The center will provide the Veterans Affairs Office of Research Oversight (VA-ORO) with written notification of FDA's intention to inspect a VA facility at the time an inspection assignment is being issued to ORA (MOU 225-82-8400).

This notification can be emailed to the current VA-ORO executive director or sent to the

address below:

Executive Director
Office of Research Oversight (10R)
Veterans Health Administration
Department of Veterans Affairs
810 Vermont Avenue, N.W.
Washington, D.C. 20420

The ORA investigator should contact the VA Medical Center Director before conducting the inspection.

b. Post-Inspection

The center will provide the VA-ORO a redacted copy of post-inspectional correspondence following an inspection at a VA facility. If, following receipt of FDA correspondence, the VA-ORO requests a copy of the EIR, the center should request a redacted copy of the report from the appropriate ORA OBIMO division, and the center will provide it to the VA-ORO.

The centers are authorized to provide the VA's ORO Executive Director redacted copies of post-inspectional correspondence issued to VA facilities or employees following any BIMO inspection (including any FDA 483). Such materials should be sent to the VA-ORO.

Centers should contact ORA's Office of Strategic Planning and Operational Policy for detailed instructions for such disclosures and key contact information. This activity is subject to 21 CFR 20.85 (Disclosure to other Federal government departments and agencies) and supported by FDA's continuing Memorandum of Understanding (MOU) with the VA, which provides for the exchange of information between the two agencies.

PART III - INSPECTIONAL

The primary focus of sponsor inspections is to evaluate the sponsor's practices and procedures to determine compliance with applicable regulations and adherence to good clinical practice standards to ensure subject protection and data quality and integrity. These inspections may include, but are not limited to, a review of the sponsor's practices and procedures related to clinical trial oversight, including activities such as site monitoring, vendor audits, training, and data collection, handling, and management. The inspectional focus is not to scientifically evaluate the results of the study or the quality of the protocol.

A. GENERAL

The following instructions apply to all sponsor inspections:

1. Sponsor inspections are product-type specific (i.e., human drugs, biological products, and devices; animal drugs; animal feed; foods, food additives, and color additives; and tobacco products). Apply the applicable regulations accordingly to each sponsor inspection.

2. Inspections under this program may be pre-announced unless otherwise instructed in the inspection assignment and at the discretion of the ORA OBIMO division. Pre-announcement should generally be no less than 5 calendar days in advance of the inspection. Inspections may be conducted sooner than 5 calendar days if requested by or acceptable to the establishment and if this date is acceptable to the ORA investigator. The ORA investigator should immediately report to their supervisor, DIB, and the center POC, any attempt by the sponsor to delay an inspection without sufficient justification. Refer to IOM Chapter 5, Establishment Inspections for further instruction.

   For inspections conducted at military installations, the ORA investigator should contact the Chief of Professional Services at the facility to be inspected. If the inspection involves a U.S. Department of Veterans Affairs (VA) facility, refer to Part II Section B.6. (Inspections of Facilities under the Jurisdiction of the Department of Veterans Affairs) of this CP for additional instructions.

3. If the ORA investigator encounters a refusal to permit entry or inspection, or a refusal of information, including a refusal to permit access or copying of requested records, consult IOM Chapter 5, Establishment Inspections, and applicable statutory and regulatory requirements[8] and follow current policy/procedures.

4. If any observations or suspected observations of regulatory or statutory deviations affect data

[8] Sections 301(f) and 704 of the Federal Food, Drug and Cosmetic Act (FD&C Act), Sections 351(c), 360A(a), (b) & (f); 360B(a); and 361(a) of the Public Health Service (PHS) Act, and 21 CFR 312.68 and 812.145

reliability or endanger subject rights, safety, or welfare, immediately discuss with your supervisor, DIB, and the center POC and continue the inspection. The assigning center will promptly determine if the inspection should be expanded or modified and provide direction on how to proceed in order to obtain appropriate documentation for the noted observations.

5. When deviations from FDA regulations are observed, issue an FDA 483 at the conclusion of the inspection. Any observations that may constitute significant deviations from the regulations should be listed on the FDA 483. Those inspectional observations that represent less significant deviations from regulations should be discussed during the close out discussion with management and reported in the EIR. Refer to IOM Chapter 5, Establishment Inspections, subchapter 5.2.3, Reports of Observations. Contact your supervisor and the center POC if there are questions regarding whether observations should be listed on the FDA 483.

6. Inform the sponsor that they may submit a written response to the FDA 483 to the appropriate ORA OBIMO division correspondence email box regarding any inspection observations listed on the FDA 483. Advise the sponsor that if FDA receives an adequate response to the FDA 483, or other objectionable conditions and discussion items, within 15 business days of the close of the inspection, the response may impact FDA's determination of the need for subsequent action.

7. ORA personnel who become aware of complaints or problems during an inspection related to a clinical investigator, sponsor-investigator, nonclinical laboratory, IRB, RDRC, other sponsor, or CRO are encouraged to refer the information to the appropriate center for the center to evaluate and handle in accordance with its own procedures. The ORA investigator's supervisor should include this information and the following details, if available, in the endorsement of the EIR:

    a. The name, address, and phone number (and email address, if available) of the clinical investigator, sponsor-investigator, IRB, RDRC, nonclinical laboratory, other sponsor, or CRO;

    b. If available, the name(s) of the investigational product(s) being investigated, the protocol number(s) and title(s), and the application or file number(s) (e.g., IND, IDE, or INAD); and

    c. The details of the complaint or problem and any relevant documentation.

B. INSPECTION PROCEDURES

The center POC may provide background information and special instructions with the inspection assignment. Contact the center POC prior to initiating the inspection to verify the focus and intent

of the inspection.

This CP provides only the minimum scope of the inspection. Inspections should be sufficient in scope to cover special instructions in the inspection assignment, to determine if the sponsor's practices and procedures comply with applicable regulations, and to assess data integrity and reliability.

If significant deviations are found during the inspection that may have an impact on the safety of study subjects or accuracy and reliability of the data, contact your supervisor and the center POC immediately to discuss expanding the scope of the inspection.

Full narrative reporting of any deviations from applicable regulations, or other significant concerns related to data reliability, should be thoroughly documented. Collect copies of records or other documentation that support inspectional observations, including discussion items. For example, if the sponsor failed to perform proper monitoring, such that the sponsor failed to identify and correct a clinical investigator's failure to report serious adverse events (SAEs) within protocol-specified timeframes, the ORA investigator should collect copies of study-specific site monitoring plan(s) and relevant standard operating procedures (SOPs), monitoring visit reports, monitoring logs, SAE reports sent to the sponsor by clinical investigators, other documentation to support and describe the SAEs, and any other supporting evidence, and document the observation in the EIR.

If there are any potential violations involving fraud subject to Title 18 of the United States Code (18 U.S.C.), the ORA investigator should discuss with their supervisor, DIB, and the center POC for potential referral.

C. ORGANIZATION AND PERSONNEL

Determine the overall organization of research activities and monitoring of the selected studies by performing the following actions:

1. Obtain relevant organizational charts that document the structure and responsibilities for all activities involving investigational products.

    a. Identify all departments, functions, and key individuals responsible for areas of sponsor activities, such as development of study protocol, selection of investigators, data management, statistical analysis, clinical supplies, monitoring, and quality assurance.

    b. Determine who has the authority to review and approve study reports, data listings, and datasets submitted in support of study reports.

    c. Determine who is responsible for final evaluations and decisions in the review of adverse events and safety information.

d. Confirm that there are no staff with responsibilities for which they are not qualified (such as medical decision-making) and/or should not be performing (such as blinded staff performing unblinded duties).

2. Obtain a list of individuals and entities contracted by the sponsor to provide services (e.g., contractors, sub-contractors, and vendors to whom services are outsourced). Document the services they provide and who at the sponsor site is responsible for their selection and oversight. Also document the physical location, point of contact, and contact information (address, phone number, and email address) of these contracted parties.

   When a sponsor transfers responsibility for their obligations to a CRO:

   a. Obtain and review copies of any written agreements or contracts transferring responsibilities, with appendices. If there is a separate transfer of regulatory obligations (TORO) document, obtain a copy.

   b. Determine if the sponsor submitted a statement to the FDA identifying the transfer of any and/or all regulatory obligations, as required by 21 CFR 312.23(a)(1)(viii), 21 CFR 314.50(d)(5)(x), 21 CFR 511.1(b)(4)(vi), and 21 CFR 514.1(a)(8)(viii).

      (Note: Device regulations (21 CFR 812) do not provide for the transfer of regulatory obligations to CROs; therefore, device sponsors are held responsible for regulatory noncompliance by a CRO.)

   c. Document any instance where transfer of responsibilities was not reported to the FDA.

   d. If the sponsor has contracted out all or part of their responsibilities, the ORA investigator should notify the center POC and continue the inspection. The center will decide whether to follow-up with an inspection at the CRO and issue any additional inspection assignments.

D. CLINICALTRIALS.GOV REQUIREMENTS

Sponsors, sponsor-investigators, or designated clinical investigators (i.e., responsible parties[9]) of human drugs, biological products, and devices are required to register and submit results

[9] 42 CFR 11.10(a) defines responsible party, with respect to a clinical trial, as the sponsor of the clinical trial, as defined in 21 CFR 50.3; or the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results information about the trial, and has the ability to meet requirements under 42 CFR 11 for the submission of clinical trial information. For a pediatric postmarket surveillance of a device product that is not a clinical trial, the responsible party is the entity who FDA orders to conduct the pediatric postmarket surveillance of the device product.

information to https://ClinicalTrials.gov (also referred to as the ClinicalTrials.gov database or ClinicalTrials.gov databank; hereinafter, ClinicalTrials.gov) for applicable clinical trials.[10]

An applicable clinical trial (ACT) is defined in 42 CFR 11 as:[11]

a. For studies involving human drugs and biological products:

   Controlled clinical investigations, other than phase 1 clinical investigations, of a drug product subject to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or a biological product subject to section 351 of the Public Health Service Act (42 U.S.C. 262), where "clinical investigation" has the meaning given in 21 CFR 312.3 and "phase 1" has the meaning given in 21 CFR 312.21.

   A clinical trial of a combination product with a drug primary mode of action under 21 CFR 3 is also an ACT, provided that it meets all other criteria of the definition of an "applicable drug clinical trial" under 42 CFR 11.

b. For studies involving human medical devices:

   A prospective clinical study of health outcomes comparing an intervention with a device product subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(k), 21 U.S.C. 360e, 21 U.S.C. 360j(m)) against a control in human subjects (other than a small clinical trial to determine the feasibility of a device product, or a clinical trial to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes);

   A pediatric postmarket surveillance of a device product as required under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360l); or

   A clinical trial of a combination product with a device primary mode of action under 21 CFR 3, provided that it meets all other criteria of the definition of an applicable device clinical trial under 42 CFR 11.

Contact the center POC with any questions related to ClinicalTrials.gov, including registration or submission of results information, or submission of certifications of compliance (Form FDA 3674)

[10] Detailed information about FDA's compliance/enforcement role and responsibilities related to ClinicalTrials.gov, including a link to the relevant statutes (e.g., the Food and Drug Administration Amendments Act of 2007 (FDAAA)), implementing regulations in 42 CFR 11, Federal Register preambles, and historical background information is available at FDA's Role: ClinicalTrials.gov Information.

[11] For assistance in evaluating whether a trial is an ACT, refer to Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT) Under 42 CFR 11.22(b) for Clinical Trials Initiated on or After January 18, 2017.

to the FDA.

Collect copies of correspondence or other documentation that support inspectional observations. Inspectional observations associated with applicable requirements for ClinicalTrials.gov registration and clinical trial results information submission should be discussed with the sponsor and documented in the narrative of the EIR.

For each study involving human drugs, biological products, and/or devices that is being inspected:

1. Determine whether the study is an ACT.
2. Determine the responsible party (RP) for the ACT. Obtain their contact information (address and email address).

If the study is an ACT:

3. Determine whether the ACT is registered on ClinicalTrials.gov.
4. Confirm the National Clinical Trial (NCT) number for the study listed on ClinicalTrials.gov.[12, 13]
5. Determine the date that the study was registered on ClinicalTrials.gov.
6. Determine the date of the first subject's enrollment[14] in the study.
7. Determine the primary completion date[15] for the study.
8. Determine the study completion date[16]. Determine whether the study concluded according to

[12] NCT number is a unique identification code given to each clinical trial registered on ClinicalTrials.gov. The format is "NCT" followed by an 8-digit number (for example, NCT00000001).
[13] For ACTs studying a device product not previously approved or cleared by FDA for any use and that are required to be registered, full posting of the clinical trial information on ClinicalTrials.gov ordinarily is delayed until after the device product has been approved or cleared. See 42 CFR 11.35(b)(2).
[14] 42 CFR 11.10(a) defines enroll or enrolled means a human subject's, or their legally authorized representative's, agreement to participate in a clinical trial following completion of the informed consent process, as required in 21 CFR 50 and/or 45 CFR 46, as applicable. For purposes of 42 CFR 11, potential subjects who are screened for the purpose of determining eligibility for a trial, but do not participate in the trial, are not considered enrolled, unless otherwise specified by the protocol.
[15] 42 CFR 11.10(a) defines primary completion date 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. For pediatric postmarket surveillance of a device product that is not a clinical trial, the completion date is the date on which the final report of the pediatric postmarket surveillance of the device product is submitted to FDA. For a pediatric postmarket surveillance of a device product that is not a clinical trial, the responsible party must submit clinical trial results information not later than 30 calendar days after the date on which the final report was submitted to FDA.
[16] 42 CFR 11.10(a) defines study completion date as the date the final subject was examined or received an intervention for

the pre-specified protocol or was terminated.

9. Determine if required results information for the study has been submitted to ClinicalTrials.gov.

10. Determine if a certification to delay results information submission (certification of delay), or a request to extend the deadline for submitting results information (extension request), or a request for a waiver of the requirements for submission of results information, for the study has been submitted to ClinicalTrials.gov.

11. When examining informed consent documents related to an ACT registered on ClinicalTrials.gov, determine whether the appropriate required statement referencing ClinicalTrials.gov is included as required by 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.''

E. SELECTION AND MONITORING OF CLINICAL INVESTIGATORS

1. Obtain a list of clinical investigators, including site number and site location, and identify which of these clinical investigators completed a Form FDA 1572 Statement of Investigator (FDA 1572) for human drug and biologic studies conducted under an IND or a signed Investigator Agreement (for medical device and animal drug studies and non-IND sites), or a waiver from the FDA 1572 signature requirement was received from FDA.[17] This list should also include:

    a. For foreign sites, identification of any foreign clinical investigators who did not conduct the study or studies under an IND – Refer to Part III Section V (International Data) of this CP.

    b. Identification of all clinical investigators whose participation has been terminated from the study and the reason for termination.

    c. Identification of all clinical investigators who have been placed on enrollment hold and the reason for enrollment hold.

purposes of final collection of data for the primary and secondary outcome measures and adverse events (e.g., last subject's last visit).

[17] Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions Statement of Investigator (Form FDA 1572)

d. Identification of any healthcare providers or facilities contracted to provide data relating to patient health status and/or the delivery of health care collected to support a marketing application. Collect any related contractual agreements with these healthcare providers or facilities.

2. Review the sponsor's criteria for selecting clinical investigators (e.g., requirements for site selection, sponsor's previous experience with the clinical investigator or site, workload of the clinical investigator and study staff, and resource availability).[18]

3. Verify whether the clinical investigators are qualified by training and experience to conduct the study. If protocol-specific requirements are applicable, for example evaluation by a particular medical specialist, verify if the criteria are met. Conduct a more detailed review as necessary to determine the sponsor's overall practices and/or to determine the extent of any observations (21 CFR 312.53(a), 511.1(b)(7)(i), and 812.43(a)).

4. Determine whether the sponsor has procedures for checking the FDA Debarment List (Drug Product Applications) and previous administrative and regulatory actions against a clinical investigator.

5. Determine if the sponsor provided the clinical investigators with information necessary to conduct the investigation properly prior to initiation of and during the clinical trial. This may include clinical protocols or investigational plans, labeling, investigator brochures, site user manuals for electronic systems (e.g., Interactive Web Response System (IWRS), electronic data capture (EDC) system, or other web-based portal for exchanging information) or digital health technologies (e.g., electronic patient-reported outcome (ePRO), wearables) used in the trial, and contingency plans as appropriate for how the site is to conduct study processes and procedures in the event of their inability to access electronic systems or when there is a malfunction or failure of the electronic systems. Collect and review a list of the documents (e.g., investigator manual, electronic system guide, newsletters) provided to the clinical investigators. Determine what training was supplied to the sites.

6. Determine how the sponsor handles a clinical investigator's deviations from the protocol and investigational plan or applicable regulations (i.e., determine how deviations are communicated, to whom, and in what timeframe; determine if the sponsor has an escalation plan and how escalation is documented).

7. Determine if the sponsor identified any clinical investigators who did not comply with the protocol, investigational plan or applicable regulations. Determine who (i.e., what company, what department, which individual) has the responsibility to follow-up on noncompliance and

[18] Id.

secure clinical investigator compliance. If clinical investigator noncompliance occurred, evaluate if prompt compliance was secured; evaluate whether a corrective action plan was put into effect; determine whether instances of continued clinical investigator noncompliance were identified; review monitoring reports for those clinical investigators and the circumstances involved; and obtain evidence of prompt correction or termination of the clinical investigator's participation in the study.

8. If a clinical investigator site was terminated, determine what happened to the active subjects (e.g., determine whether the subjects' participation ended; determine whether the subjects were transferred to another site). Determine if the sponsor has a written plan on site termination and subject transfer and, if so, determine if the sponsor followed their plan.

    a. For human drug and biologic studies:

        i. Determine if the sponsor notified FDA of termination of an investigator's participation in the investigation and the clinical investigator sites where studies were terminated, per 21 CFR 312.56(b). If possible, determine whether the IRB was notified of the investigator's termination.

        ii. If the sponsor determines the investigational product presented an unreasonable and significant risk to subjects and discontinues investigations that present the risk, determine if the sponsor notified FDA, all reviewing IRBs and clinical investigators who have at any time participated in the investigation, per 21 CFR 312.56(d).

    b. For human device studies, determine if the sponsor notified FDA and all reviewing IRBs of any request that a clinical investigator return, repair, or otherwise dispose of any units of a device, per 21 CFR 812.150(b)(6).

    c. For investigational new animal drug studies, determine if the sponsor recalled or destroyed the unused supplies of the new animal drug, per 21 CFR 511.1(d)(2).

9. Identify any non-compliant clinical investigators who were neither brought into compliance nor removed from the study (participation in the study terminated) by the sponsor as required by 21 CFR 312.56(b), 511.1(b)(8)(ii), 812.46(a). Determine the reason their participation in the study was not terminated.

10. If there are changes to the clinical investigators responsible for conducting the study, determine the reason(s) for the changes, and names of the clinical investigators assuming responsibility for the study.

F. OUTSOURCED SERVICES

Oversight of outsourced services may include a broad range of activities to ensure all outsourced services and activities associated with the clinical investigation are performed according to the protocol and investigational plan, Good Clinical Practice (GCP), and applicable FDA regulations.

For additional information regarding oversight of outsourced services for nonclinical laboratory studies, refer to Part III Section W (Nonclinical Laboratory Studies) of this CP.

Review and evaluate the sponsor's oversight of outsourced services, as appropriate (as defined in contracts, written processes and procedures, and SOPs), with a focus on outsourced services that played a significant role in the clinical trial (e.g., management of primary efficacy endpoint or safety data) and/or were involved in any significant deviations from FDA regulations. Contact your supervisor and the center POC for further guidance and instruction, as needed.

1. Determine if the sponsor has processes and procedures (e.g., SOPs, plans, or other work instructions) for selection of outsourced services and activities, and determine what criteria were used to select the CRO (and as applicable, other individuals or organizations providing outsourced services) and whether they meet those criteria.

    a. Determine if the sponsor evaluated and selected the CRO (and as applicable, other individuals or organizations providing outsourced services) based on their ability to comply with FDA regulations and follow GCP standards.

    b. Determine if there is a preferred vendor list or prequalified vendor list. Determine the criteria for selection and inclusion on this list, if any.

2. Obtain copies of all versions of written agreements (e.g., master service agreements, statements of work and/or scope of work, quality agreements and/or service level agreements) for any critical services or activities that the sponsor outsourced. Examples of critical services or activities may include, but are not limited to: site monitoring, drug management, data handling (e.g., EDC systems, Interactive Response Technology (IRT) systems), ePRO, registries used to capture clinical trial data, and other clinical outcome assessments (COAs), electronic system vendors, data management, statistical analysis, central laboratories, and safety management.

    a. Determine if the written agreements define roles, tasks, and responsibilities of the sponsor and CRO (and as applicable, other individuals or organizations providing outsourced services), including responsibilities for compliance with FDA regulations.

b. Determine who has the ultimate responsibility for approving final decisions related to each of the individual trial-related activities outlined in these written agreements.

3. Determine if the employees of the CRO (and as applicable, other individuals or organizations providing outsourced services) providing the outsourced services and activities have the appropriate qualifications for providing such services.

4. Review SOPs for audits, communication plans, escalation plans, and contingency plans. Obtain copies of the written SOPs, including attachments, and other pertinent records (e.g., forms, templates) that support any inspectional observations.

   a. Determine whose SOPs were followed; for example, determine whether the sponsor followed the CRO's or vice versa, or a combination of both.

   b. Identify whether deviations from the SOPs occurred and if so, what processes did the sponsor and the CRO (and as applicable, other individuals or organizations providing outsourced services) follow for detecting, documenting, reporting, and fixing the issue (e.g., was an impact assessment performed and were any corrective/preventative actions implemented).

5. Review the sponsor's communications (e.g., teleconference meeting minutes, emails) with the CRO (and as applicable, other individuals or organizations providing outsourced services):

   a. Determine if meetings were held between the sponsor and the CRO.

   b. Determine how often meetings were held between the sponsor and the CRO.

   c. Determine the type, purpose, frequency, and documentation for the meetings.

   d. Obtain copies of meeting minutes and correspondence relevant to any deviations or issues identified, previously by the sponsor and/or during the inspection, with services or activities performed by the CRO.

6. Determine if and what protocol-specific training was provided to the CRO (and as applicable, other individuals or organizations providing outsourced services).

7. Determine whether the sponsor provided oversight of the CRO (and as applicable, other individuals or organizations providing outsourced services). Obtain a copy of any oversight plans that were developed for outsourced services or activities that support any inspectional observations.

   a. Determine any audit arrangements, and if (and when) they were conducted.

b. Determine the scope of audits. For critical data integrity issues or significant deviations from FDA regulations, contact the center POC and your supervisor for instructions on whether to obtain a copy of the audit report. In general, during routine inspections and investigations, the ORA investigator should review and confirm audit certificates but not request for review or copy reports and records that result from audits, unless directed by the assigning center.

G. SELECTION OF MONITORS

1. Obtain a list of individuals performing monitoring activities for the studies being inspected.

2. Review the sponsor's criteria for selecting monitors and determine if monitors meet those criteria, particularly when insufficient monitoring has been observed at certain clinical investigator sites (e.g., late monitoring visits and/or reports, unreported protocol deviations).

3. Determine the responsibilities of the monitors and how the sponsor assigns responsibilities, particularly when various monitoring functions are assigned to different monitors (e.g., remote monitors; onsite monitors; unblinded versus blinded).

H. MONITORING PROCEDURES AND ACTIVITIES

Regulations state that sponsors are required to ensure proper monitoring of the study (21 CFR 312.50 and 812.40) and to select monitors qualified by training and experience to monitor the study (21 CFR 312.50, 312.53(d), 511.1(b)(8)(ii), 514.117, and 812.43(d)). However, regulations are not specific about how sponsors are to conduct such monitoring (e.g., it may be onsite, remote, and/or involve centralized monitoring practices).

Sponsors may utilize a systematic, prioritized, risk-based approach in monitoring practices appropriate to a given study.[19] No single approach to monitoring is appropriate or necessary for every clinical study. As such, the extent and nature of monitoring may vary.

Each sponsor should design a monitoring plan that is tailored to the specific risks of the trial. In general, monitoring activities should focus on preventing or mitigating important and likely sources of error in the conduct, collection, and reporting of critical data (e.g., efficacy endpoint data, safety data) and processes necessary for subject protection and trial integrity.

Review the sponsor's procedures (e.g., written SOPs or stated practices), and study-specific plans for studies under review, for the following:

[19] Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring

1. Monitoring Procedures

   a. Review written monitoring plans/guidelines/procedures[20] for monitoring the conduct and progress of the study to ensure that the clinical investigator complied with the protocol, applicable regulations, and any requirements and conditions of an IRB.

   b. Determine if the monitoring plans/guidelines/procedures were followed for the selected study (e.g., monitoring visits performed by required timeline, monitoring reports completed by the required timeline, monitoring letters/communications given to the sites by the required timeline).

   c. Determine if the sponsor, or the entity conducting the monitoring needed to modify the monitoring plan once the study was initiated. If the plan was changed, obtain a copy of the most recent monitoring plan and determine why the changes were made.

   d. In the absence of a monitoring plan/written monitoring procedures, conduct interviews to determine how monitoring was conducted, and document in the EIR.

   e. Determine whether the sponsor implemented on-site co-monitoring visits (i.e., a function whereby a monitor's supervisor or another evaluator designated by the sponsor or CRO oversees monitoring activities).

2. Monitoring Activities

   a. Describe monitoring activities (e.g., site initiation visit, routine monitoring visits, closeout monitoring visits), including timing, frequency, extent, and nature of monitoring (e.g., risk-based monitoring).

   b. Determine how the sponsor assures that IRB or Institutional Animal Care and Use Committee (IACUC) approval is obtained prior to the enrollment of subjects in the study, if applicable. Determine how the sponsor assures that informed consent is obtained, if applicable.

   c. Review the sponsor's monitoring reports and other records related to monitoring that may be located in the, trial master file (TMF), and/or clinical trial management system (CTMS) to evaluate monitoring activities.

   d. Determine whether monitoring included a comparison of source documents (e.g., source document verification, source document review) with CRFs submitted to the sponsor. Determine if CRFs were verified according to the pre-specified monitoring plan (i.e., were

[20] 21 CFR 812.25(e)

all CRFs, or if a representative sample of CRFs verified or reviewed).

i. Determine if a form is used for source data verification and/or review and obtain a copy.

ii. Determine how data clarification requests or queries are communicated.

iii. Determine whether monitoring included verification of corrections made in response to data clarification requests or queries.

e. If remote monitoring was conducted, determine how monitors accessed clinical site records and ensured the security and confidentiality of the records was maintained (e.g., was the monitor given direct access to the site records via an online portal, were access controls used, were copies sent via a secured email).

I. QUALITY ASSURANCE ACTIVITIES

Although not required by regulations, many sponsors establish quality assurance departments, quality assurance units (QAUs) or similar entity to perform independent audits or data verifications and to critically review processes, procedures, and reports to determine their compliance with protocols and procedures. These quality assurance (QA) activities (e.g., independent audits, data verifications) may be conducted with or without the establishment of a QAU. All QAUs and/or auditing personnel should be independent of, and separate from, routine monitoring or quality control functions. The sponsor is ultimately responsible for the integrity of the study submitted to FDA.

In general, during routine inspections and investigations, the ORA investigator should review and confirm audit certificates but not request for review or copy reports and records that result from audits, unless directed by the assigning center. For additional guidance on this matter, refer to Compliance Policy Guide (CPG) 130.300: FDA Access to Results of Quality Assurance Program Audits and Inspections. Contact the center POC for further clarification or instruction.

J. SAFETY AND ADVERSE EVENT REPORTING

The inspection assignment may include specific instructions regarding the review of safety and adverse event reporting and documentation. The inspection should be sufficient in scope to assess general compliance with safety reporting requirements. Expand as necessary to evaluate any systemic issues with safety reporting.

1. Determine procedures for sponsor review of investigator reports of SAEs. Confirm that the sponsor has a process in place to determine if the SAE meets safety reporting criteria per applicable FDA regulations (e.g., 21 CFR 312.32). Confirm that the sponsor followed

procedures for each report received from investigators.

2. Review safety tracking sheets and/or lists of SAEs and adverse events of special interest, and determine whether safety information/unanticipated adverse drug and device effects were reported to FDA and participating clinical investigators (and to reviewing IRBs for device studies), as required by regulations and within the required regulatory timeframe:

   a. Drugs/biological products (21 CFR 312.32(c)) – IND safety reports of potential serious risks no later than 15 calendar days after the sponsor determines that the information qualifies for reporting; if unexpected fatal or life-threatening suspected adverse reaction, communication to the FDA no later than 7 calendar days after the sponsor's initial receipt of the information; (21 CFR 312.32(d)) – follow-up reports as soon as the information is available; (21 CFR 312.32(c)(3) and 21 CFR 312.10) – alternative reporting requirements.[21]

   b. Drugs in bioavailability and bioequivalence studies that are exempt from the IND requirements (21 CFR 320.31(d)(3)) – Reports of any serious adverse event within 15 calendar days after becoming aware of its occurrence; if fatal or life-threatening adverse event, within 7 calendar days after becoming aware of its occurrence; follow-up reports as soon as information is available.

   c. Animal drugs (21 CFR 511.1(b)(8)(ii)) – Promptly investigate and report any findings associated with the use of the new animal drug that may suggest significant hazards.

   d. Devices for human studies (21 CFR 812.150(b)(1)) – Report within 10 working days after the sponsor first receives notice of the unanticipated adverse device effect.

   e. Food Additive Petitions (21 CFR 571.1(c)(E)) – Provide full reports of investigations and tests to address the safety of the food additive for the intended use.

3. Review the procedures (e.g., frequency, scope) the sponsor/CRO uses for the receipt, evaluation, and monitoring of safety information/unanticipated adverse device effects, as well as the process for updating the investigator's brochure.

4. Determine the process for notifying investigators of any safety reports.

K. DATA AND SAFETY MONITORING BOARD/DATA MONITORING COMMITTEE

Some studies require monitoring by a formal committee that may be external to the trial

[21] Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies

organizers, sponsors, and investigators.[22] Even where such monitoring is not required, sponsors may establish such committees for certain trials.

Determine whether the sponsor established an independent data and safety monitoring board (DSMB), data monitoring committee (DMC), or similar entity to assess the progress of the clinical study, including evaluation of safety data and the critical efficacy endpoints. If so, determine if the DSMB/DMC has oversight of one or several clinical trials.

1. Determine if the DSMB/DMC has written operating procedures (e.g., charter) and if those procedures were followed.

2. Determine how members were selected and how conflicts of interest are determined and managed.

3. Confirm that all members received required training.

4. Determine who compiled the data for the meeting reports, including any reports with unblinded data, and how these reports were transmitted to the board/committee members.

5. Determine if there were any meetings where unblinded data was reviewed. If so, review the meeting minutes and attendance. Describe how meeting minutes were archived and how access was controlled.

6. Determine how DSMB/DMC decisions were communicated to the sponsor.

L. SAFETY OVERSIGHT

1. Determine if the sponsor has a risk management plan or other written procedures and if they were followed. Determine if the sponsor has a safety monitoring plan or safety management plan. If not, determine if the sponsor has safety SOPs.

2. Determine if the sponsor has a designated safety team or safety department. If so, review the composition and function of the safety team (for drugs and biological products).

    a. Determine if the safety team is tasked with monitoring aggregate safety data across the drug development program. If this task has been delegated to a DMC, confirm that the DMC reflects this role in its charter.

    b. Determine the safety team processes and procedures for safety surveillance and decision making on risk management and risk minimization activities.

    c. Determine whether the sponsor designated a medical monitor or team of medical

[22] Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees

monitors. If not, determine who the sponsor designated as the appropriately qualified medical personnel to advise on trial related medical questions or problems.

d. Review the sponsor's criteria for selecting medical monitors and determine if all medical monitors meet those criteria.

e. Determine the responsibilities of the medical monitor on the study and how the sponsor assigns responsibilities, particularly those pertaining to medical and safety-related aspects of the studies.

3. Review all processes and procedures for collection, assessment, and communication of accumulating safety data. Confirm that the sponsor followed all SOPs/written procedures.

   a. Determine if there is a separate safety database. If so, determine who is responsible for the database, who has access to the database, and if and how information from the safety database is transferred to the study's electronic data capture system, including reconciliation of all data.

   b. Review the handling of SAE reports (how they are received from the sites, who receives and tracks them, who initially evaluates them, who codes them, how the evaluations are documented, how accumulating SAEs are assessed).

   c. Review the process for unblinding following an SAE(s). Determine if there was any accidental unblinding and, if so, how was it handled?

   d. If an international trial, determine how translation of documents occurred, and how different units of measurement for safety laboratory results were handled.

   e. Determine criteria and methods for conducting safety analyses to detect events meeting the criteria for safety reporting. Determine whether the sponsor uses methods to detect signals hidden in the volume of safety data accumulated (e.g., statistical methods or aggregate data analyses).

   f. Determine who makes the decision that a safety report is needed.

   g. Review the process for safety reporting (who writes the narrative, who reviews and has final sign-off, how are they tracked, who is responsible for communications and submission of the reports).

   h. Determine what entity or entities are tasked with conducting aggregate analyses of the accumulated safety data.

i. Determine what procedures are in place for conducting aggregate data analyses. Confirm that procedures were followed.

j. Determine the procedures in place for the entity tasked with conducting aggregate data analyses to be appropriately firewalled from those conducting the trial in the event of trial unblinding. Confirm that procedures were followed.

k. Review the process for periodic updates of the investigator's brochure (IB) based on accumulating safety information. Determine how frequently the IB is reviewed and whether the sponsor followed written procedures for updating the IB.

l. Review the process for including aggregate safety information across the entire development program of the investigational product in annual IND reports, development safety update reports (DSURs), and IND safety reports. Refer to Part III Section M (Progress Reporting) of this CP.

4. Determine if any SAEs were determined to be an endpoint (e.g., pre-identified events) or safety event of special interest per the protocol and confirm that the sponsor's processes and procedures were followed.

   a. Determine if a clinical endpoint committee (CEC)/endpoint adjudication committee (EAC) was established to adjudicate events (e.g., endpoints, safety events of special interest). If so, review the written procedures (e.g., charter) for its establishment and determine that all procedures were followed, including selection of members and training. Determine whether members of the committee are independent of the sponsor.

   b. Determine who had oversight of the CEC/EAC.

   c. Determine if a separate database was used for handling adjudicated events. If so, determine who is responsible for the database, who has access to the database, and if and how information from the adjudication database is transferred to the study's electronic data capture system.

   d. Review the handling of events (how they are received from the sites, who receives and processes them including making needed redactions, who tracks them, how are the cases transmitted to the CEC/EAC members, how are the evaluations documented, how SAEs determined not to be an endpoint or safety event of special interest are assessed and handled).

   e. Determine if meeting minutes were generated for CEC/EAC meetings. If so, review the meeting minutes and determine whether sponsor/CRO staff were involved. Determine

where meeting minutes were stored, who had access, and how access was controlled.

5. Determine whether there were any sponsor-investigator-initiated studies that used the investigational product. If so, determine how safety data from those studies were communicated to the sponsor.

6. Determine if the sponsor has processes or procedures for evaluating safety findings from other sources, including nonclinical studies and scientific literature, studies that suggest a significant risk in humans exposed to the investigational product. Confirm that the sponsor followed these processes and procedures and whether the sponsor evaluated all such safety findings to determine if they met requirements for safety reporting.

M. PROGRESS REPORTING

For human devices:

1. Determine if the sponsor submitted progress reports at least yearly to all reviewing IRBs, and to FDA in the case of a significant risk device, in accordance with 21 CFR 812.150.

2. For sponsors of treatment IDEs, determine if the sponsor submitted semi-annual progress reports to all reviewing IRBs and to FDA in accordance with 21 CFR 812.36(f) and annual reports in accordance with 21 CFR 812.150.

N. DATA COLLECTION AND HANDLING

Data collection and handling procedures generally address the aggregating, cleaning, transforming, integrating, analyzing, reporting, and archiving of data, which may be maintained in paper and/or electronic systems. Regulatory requirements for records and data do not change regardless of the media (i.e., paper, electronic, or combination) or trial design (e.g., traditional, decentralized, or hybrid clinical trials).

In some cases, data relating to patient health status and/or the delivery of health care may be collected[23, 24] and submitted to support a marketing application. The original source of information for such data may include electronic health records (EHRs), registries, and information gathered

[23] Framework for FDA's Real-World Evidence Program (December 2018): FDA defines real-world data (RWD) as data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, and real-world evidence (RWE) as the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

[24] Section 505F(b) of the FD&C Act defines RWE as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials." The definition of RWE provided by section 3022 of the 21st Century Cures Act was subsequently revised by a technical amendment in Section 901 of the FDA Reauthorization Act of 2017 (Public law 115-52).

from other sources outside the inspected study or studies that inform on the patient's health status. If such data are to be reviewed during the inspection, it will be indicated in the inspection assignment.

As described in Part III Section B (Inspection Procedures), consult with the center POC if questions arise related to significant discrepancies in data collection and handling processes and procedures that may have impact on the safety of study subjects or the accuracy or reliability of the data.

Conduct a review of data collection, handling, and management procedures to ensure compliance with FDA regulations and to ensure study data is collected, recorded, handled, managed, and stored in a way that allows its accurate reporting, interpretation, and verification.[25] When significant issues and deviations from the protocol and investigational plan are observed during the routine review of the data collection, handling, and management procedures (e.g., protocol deviations or dosing errors that occurred due to electronic system programming errors, accidental unblinding, unlocking of final databases without sponsor approval, and instances of breach of subjects' confidentiality), a more comprehensive review should be conducted of the sponsor's processes and procedures for the operational use of electronic systems (as outlined below).

Consult with the center POC for instructions as to the extent of the review of data collection, handling, and management processes and procedures and data integrity controls of these electronic systems that should be covered during an inspection.

Collect copies of correspondence or other documentation that support inspectional observations and discussion items, and document in the EIR.

1. Determine the data flow from initial source generation to reporting in clinical study reports, as applicable.

    a. Describe the data collection methods (electronic-based, paper-based, and hybrid approaches) used to capture and analyze data in the conduct of the clinical study.

    b. Determine whether the sponsor has:

        i. Identified what constitutes source records and source data in the protocol and investigational plan(s);

        ii. Authorized direct capture of source data into electronic systems (e.g., electronic source in electronic case report forms (eCRFs), Interactive Response Technology (IRT));

        iii. Authorized other alternative data capture methods in case of electronic system

[25] Guidance for Industry: E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)

unavailability; and

iv. Validated processes and procedures for data transfer (e.g., data transfer specifications).

c. Describe the flow of data and collect a copy of the data flow diagram (if available), including location of servers maintaining study data.

d. Determine who or what entities were responsible for activities related to data collection and handling, and data management for the study.

2. Review any study specific data management plan(s) and associated SOPs that describe data collection, handling, and management procedures to be followed for the study under review and whether the study-related activities were performed in accordance with the protocol and investigational plan. The inspection should focus on critical data (e.g., primary efficacy endpoint and safety data) and critical study procedures (e.g., randomization, blinding, emergency unblinding).

3. Review any contracts, agreements, and vendor management plans, as applicable, between the sponsor and data collection, handling, and management service providers, as needed, to assist in evaluation of the study conduct and the sponsor's oversight of these vendors.

4. Determine who or what entities were responsible for activities related to maintaining electronic system data integrity and security controls (e.g., access controls, audit trails, electronic system validation, training of users, SOPs for the use of the electronic system).

5. Review software problem reports that describe anomalies discovered and/or reports that describe technical issues experienced by users of electronic systems (e.g., sample of helpdesk tickets, log of helpdesk staff communications with clients). Determine whether root-cause analysis was performed, and whether specific corrective and preventative actions were taken to fix each anomaly and to avoid recurrence. ***If there are no issues or concerns, proceed to #6. If significant issues or potential concerns with data reliability are observed or noted in software problem reports/reports that describe issues with electronic systems, review the following related to validation of the electronic system and transfer of data. Also note that these reports may identify issues related to the use of the other electronic system controls (e.g., access controls, external security safeguards, audit trails). In such cases, refer to the specific subsection below that discusses specific electronic system control for further instruction.***

a. Determine if the sponsor has procedures and documentation regarding validation of

electronic systems[26] (e.g., validation documentation, documentation of user acceptance testing (UAT)) used to perform the following clinical trial activities:

i. Clinical trial data collection and handling (e.g., electronic data capture (EDC) systems, IRTs)

ii. Adverse event and safety data management

iii. Outcomes and endpoint data generation and management (e.g., systems in which endpoint adjudications are processed, electronic patient-reported outcomes (ePROs) and other electronic clinical outcome assessment (eCOA) systems, wearables, and other digital health technologies)

iv. Drug dispensing, administration, and accountability (e.g., IRTs)

v. Statistical analyses

vi. Data integration

b. Review whether the sponsor followed processes and procedures for transferring or transmitting data, including but not limited to:

i. Data transmission methods or file transfer protocols.

ii. Frequency of transfer and which transfers are retained.

iii. If there is an automated system-to-system electronic exchange of data, was validation testing of the integration/ interoperability performed.

iv. Data format and whether transferred files were locked or editable.

c. Review SOPs and study-specific plans for system development, setup/installation, risk-based approach to validation testing, including SOPs for validating the study specific eCRFs, IRT functionalities (e.g., screening, randomization, dosing, drug supply, and emergency unblinding modules), and other electronic systems that were in effect for the study.

d. Review documentation (including approval documentation) related to initial validation testing and any revalidation testing that occurred for changes made to the electronic system post implementation to ensure that the system was validated in accordance with the SOPs and study-specific plans and that the sponsor ensured system accuracy,

[26] Guidance for Industry: Part 11, Electronic Records; Electronic Signatures — Scope and Application

reliability, and consistent intended performance of critical functionality of the systems (e.g., IRT dosing titrations and reductions; drug supply chain management; unblinding; the capture and management of endpoint data). Such validation documents might include, but are not limited to, the following:

- User Requirements Document
- Traceability Matrix Document
- Functional Specifications Documents
- Validation reports/test scripts and user acceptance testing (UAT) reports

e. For systems supplied by vendors, determine whether the sponsor performed independent UAT prior to system implementation. Review sponsor UAT procedures, processes, and reports to evaluate extent of sponsor testing, including for sponsor's customized systems built in-house. Review electronic system sign-off and Go-Live documentation including, but not limited to:

i. eCRF/EDC and IRT sign-off/approval forms
ii. All deployment and Go-Live approval forms for electronic systems used for data capture

f. Review SOPs, including change control SOPs, for the management of clinical trial databases post-implementation.

g. Obtain a list of all system and/or software changes made to the databases post-implementation. Determine if a risk-based assessment[27] was used to re-validate the system change in accordance with the SOPs. Determine if all approved documents (e.g., specifications, user manuals) that have been affected were updated, as needed.

h. Determine if there were any software upgrades or security or performance patches for electronic systems used during the clinical trial to collect and manage the study data.

6. Determine whether those who use the electronic systems are provided training to perform the specific operations before use, and whether the training was conducted by qualified individuals on a continuous basis. Determine whether the training for post-implementation changes and updates occurred, as applicable.

7. Determine if the sponsor provided technical support for users to answer questions and resolve issues that occurred before and during the conduct of the trial.

[27] Id.

8. Determine whether the electronic systems are equipped with external security controls (e.g., back-up, firewalls, encryption, antivirus, and anti-spy software). Review and collect relevant documents, if needed, to understand any potential data integrity issues. Document any instances of attempted or confirmed unauthorized access to electronic systems or electronic records (e.g., unauthorized login), and determine whether the security breach was communicated to, or identified by, the sponsor.

9. Review the protocol, associated study plans, and SOPs to determine blinding procedures and to determine which entities were to be blinded to the investigational product. This may include data verification of a sampling of electronic source data entered directly into electronic systems against the sponsor data line listings submitted in the application.

    a. Determine if the inspected entity has procedures in place for identifying unauthorized or accidental unblinding. Confirm whether or not procedures were followed.

    b. Determine whether there are reasons why the clinical investigator or clinical sites should not have access to certain electronic data (e.g., potential for unblinding).

    c. Review access controls for electronic systems to ensure unauthorized unblinding did not occur and to determine whether clinical investigators/study personnel had authorized access to unblinding information. Ask the inspected entity if there was any accidental unblinding. Identify and document any instances reported in which the clinical investigator or study staff had unauthorized access to this restricted information.

    d. Identify:

        i. Who authorizes and provides access to authorized users and if all users at the sites, the sponsor, CRO, and data processing center have appropriate user IDs, passwords, and access privileges;

        ii. How the sponsor/CRO ensures that only authorized personnel have access to study data (e.g., if there is a log of authorized users for each clinical site);

        iii. How authorized users access the systems (e.g., use of username and password combinations, multifactor authentication, biometrics); and

        iv. Whether these security credentials are deactivated when the user is no longer involved with the study.

10. Determine if the sponsor had processes and procedures for data modifications/corrections. If so, review a sampling of data modifications/corrections, and determine if these processes and procedures were followed including, but not limited to:

a. Evaluate data modification processes with respect to the following:

   i. Who requested the data change(s) and when it was requested;
   ii. Who authorized the change(s) and when it was authorized;
   iii. Was the change(s) implemented;
   iv. If so, who implemented the change(s) and when was it implemented; and
   v. Reason(s) for the change(s).

b. Determine if original data entries and changes could be made by anyone other than the clinical investigators and delegated site personnel.

   i. Document what data could be changed without clinical investigator authorization (e.g., unauthorized entries, unauthorized changes made to original data).

   ii. Determine if all unauthorized entries were communicated to the clinical investigator.

c. Determine if electronic systems contain audit trails and whether audit trails fully capture the creation, modification, or deletion of all system data, including the ability to capture metadata (e.g., date and time stamps, data originator, reason for the change, and other audit trail information associated with the data).

   i. Review a sample of the audit trails for electronic systems to determine whether electronic source data (eSource) was entered contemporaneously at the time of collection.

   ii. Determine the process or methods of electronically signing documents and whether each electronic signature is unique to one individual.

d. Determine if the audit trail could be turned on and off, and when such functionality is available, if it was ever turned off during data capture and handling during the trial and the reason why.

11. Determine if the sponsor had processes and procedures for data locking and unlocking and whether these processes and procedures were followed. Review records for database locking and unlocking to determine the date of the database lock(s), who approved, and reasons for any unlock or relock events. If there was any unlocking of the locked database, document any changes that were made to the study data after final database lock. Consult the center POC if there are questions related to any changes made.

12. Review the data reconciliation plan and statistical analysis plan. ***If there are no issues or concerns, proceed to #13. If significant issues or potential concerns are observed, review the following related to data reconciliation, integration, and transformation:***

a. Review processes and procedures for performing data reconciliation, integration, and transformation and determine whether they were performed in accordance with the protocol, SOPs, and study specific investigational plans, including but not limited to:

   i. Reconciliation of raw data extracts or transfers from electronic systems for study data with particular attention to efficacy and safety data;

   ii. Integration of data from different systems;

   iii. Conformance of study data to data standards (e.g., Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) standards);

   iv. Creation of analysis datasets (e.g., ADaM datasets) from original data (e.g., raw data, SDTM domains);

   v. Use of only fully masked or mock datasets to perform dry runs of data for creation of summarized study results in tables, listings, and graphs or figures (commonly referred to as TLGs or TLFs) prior to database lock;

   vi. Maintenance of appropriate access controls for server folders containing original data and analysis datasets (e.g., raw, SDTM, and ADaM datasets), particularly for folders containing unmasked data prior to database lock.

13. Determine if the sponsor had processes and procedures for retention and access to all records and data, including metadata associated with those records and data. Refer to Part III Section P (Records Custody and Retention) of this CP.

14. Review disaster recovery/contingency plans against data loss. Document any instances in which the electronic system(s) did not function as was intended for the specific study protocol (e.g., disaster recovery, blinding the study, recording data in metric units), or in which it did not prevent errors in data creation, modification, maintenance, archiving, retrieval, or transmission.

O. ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES

Electronic systems, electronic records, electronic signatures, and handwritten signatures executed to electronic records used in studies may be subject to regulations found in 21 CFR 11 (Electronic Records and Electronic Signatures) (Part 11). In general, Part 11 requirements apply to electronic records and electronic signatures and to the electronic systems used in clinical investigations and nonclinical laboratory studies to create, modify, maintain, archive, retrieve, or transmit them.

Electronic systems and records include: electronic data capture (EDC) systems, electronic case

report forms (eCRFs), electronic patient-reported outcomes (ePRO), interactive response technology (IRT), electronic clinical outcome assessments (eCOA), electronic informed consent (eIC) systems, and other digital health technologies, such as mobile apps, wearables, and remote and ingestible sensors. Refer to FDA's Guidance for Industry: Part 11, Electronic Records; Electronic Signatures– Scope and Application.

If significant deviations or discrepancies related to electronic records or electronic signatures are found during the inspection that may have impact on the safety of study subjects or the accuracy or reliability of the data (e.g., falsification, fabrication, or alteration of study-related information or signatures on electronic systems or electronic records), prior to noting an observation on an FDA 483 regarding noncompliance with Part 11, contact your supervisor and the center POC immediately for further guidance.

In general, FDA intends to exercise enforcement discretion regarding certain Part 11 provisions for validation, record copying, record retention, and audit trails (21 CFR 11.10(a), (b), (c), and (e), respectively). Compliance with regulatory requirements on recordkeeping, record copying, and record retention will be evaluated in accordance with appropriate predicate rules.

Refer to Part III Section N (Data Collection and Handling) of this CP for instructions pertaining to review of data collection, handling, and management procedures, including evaluation of electronic systems and data with respect to validation, access controls, and authorization of user's actions, audit trail review, data transfer, data cleaning, integration and transformation, and data retention.

Refer to IOM Chapter 5, Establishment Inspections for instruction and guidance on read-only access to electronic records. If issues such as errors with programming, unblinding, record retention, and/or breach of subject's confidentiality are identified, and prior to noting an observation on an FDA 483 regarding non-compliance with Part 11, discuss the issue with your supervisor and the center POC.

1. Describe the electronic systems used to manage critical data and study procedures to create, modify, maintain, archive, retrieve, transmit, or analyze data and records. Include how the data were collected or entered into the system.

   For example, specify whether (a) the electronic system was owned and controlled by the sponsor or a third party; (b) data were entered by clinical sites into an electronic database at the clinical site or into a third-party database or EDC system located on a secure central server (e.g., eCRFs, IRT, eCOAs); (c) data were entered by the study subject in an electronic diary or captured by other digital health technology directly from the subject; (d) data were integrated via an automated system-to-system electronic exchange of study data (e.g., IRT data that were

electronically transferred to the eCRFs); (e) data were electronically transferred from an EHR to the eCRFs.

2. Determine the processes or methods for electronically signing documents (e.g., computer readable ID cards, biometrics, digital signatures, username and password combinations), and whether conditions are controlled (e.g., measures for automatic log off if the user is inactive; fixed, short time frame login). Determine whether each electronic signature is unique to one individual, and if possible, verify whether the signature was used only by that unique individual. Electronic signatures shall contain the following information associated with the signature:

   a. Printed name of the signer;
   b. Date and time when the signature was executed; and
   c. The meaning (e.g., review, approval, responsibility, authorship) associated with the signature.

Document any instances in which the electronic system does not function as it was intended for the specific study protocol. Describe the corrective actions, if any, that were taken.

P. RECORDS CUSTODY AND RETENTION

Verify that the sponsor maintained required records (e.g., study conduct related records, investigational product disposition records, financial disclosure information from investigators) for the prescribed period of time, as required by 21 CFR 312.57, 511.1(b)(8)(i), and 812.140.

Q. INTERVIEWS OF PERSONNEL

For guidance on obtaining affidavits (Form FDA 463a), refer to IOM Chapter 5, Establishment Inspections, subchapter 5.2.9, Interviewing Confidential Informants. Contact your supervisor and the center POC for additional guidance.

R. FINANCIAL DISCLOSURE

1. Determine if the sponsor obtained financial disclosure information from each investigator before their participation in the clinical trial, as required by 21 CFR 54, 312.53(c)(4), 812.110(d), and 812.43(c)(5).

2. Determine if and how the sponsor received prompt updates regarding relevant changes in financial disclosure information from investigators during the study and for one year after study completion.

3. Determine if the sponsor reported to FDA all pertinent certifications and investigator

disclosures of financial information as required by 21 CFR 54.4.

4. Determine if the sponsor retained the documentation to support the certifications and disclosures of investigators' financial information that was reported to FDA as required by 21 CFR 54.6.

S. INVESTIGATIONAL PRODUCT

1. Integrity

   Review the sponsor's processes and procedures regarding maintaining the integrity of the investigational product:

   a. Determine how the sponsor maintained integrity of the investigational product during shipment (e.g., temperature and humidity controls). If the investigational product was shipped directly to a subject, confirm that the investigator approved the shipment and the sponsor's processes and procedures were followed.

   b. If the investigational product is not in its final form and requires preparation or processing at the clinical site, determine if the sponsor ensured that this was done in accordance with the protocol, investigational plan, and/or study specific-pharmacy manual (or equivalent).

   c. Determine whether the investigational product was stored in accordance with the protocol and investigational plan prior to shipment.

   d. Determine if the investigational product was properly labeled, including whether the product was labeled in accordance with applicable regulations, the protocol, and the investigational plan.

   e. Determine if the investigational product was withdrawn, removed from distribution, or recalled, and if so, collect relevant documentation.

   f. For drugs and biological products, and medical devices with a drug or biologic component, confirm whether Certificates of Analysis are available.

   g. For device studies, determine how the sponsor controls and monitors the use of investigational device products between uses for products that are not single use, such as lithotripters or excimer lasers.

2. Accountability

   Review the sponsor's processes and procedures for investigational product accountability and

evaluate investigational product accountability to determine compliance with applicable regulations.

a. Determine the process flow of shipment, receipt, and other disposition of investigational product (e.g., allocation, destruction).

b. Determine how the sponsor tracks accountability of the investigational product (e.g., IRT).

c. Determine whether shipment, receipt, or other disposition of the investigational product is documented, including:

   i. Names and addresses of clinical investigators receiving investigational product. For DCTs, names and addresses of clinical investigators responsible for controlling the release of investigational product from central distribution facilities to study participants.

   ii. Shipment date(s)

   iii. Quantity

   iv. Batch or code mark or other identification number of investigational product(s) shipped

   v. Final disposition of the investigational product

d. Determine whether the sponsor's records demonstrate reconciliation of the shipment, receipt, and disposition of investigational product (i.e., by comparing the amount of investigational product shipped with the amount used and returned or disposed).

e. Determine whether the sponsor charged for the investigational product[28, 29]. If so, determine if the sponsor was authorized by FDA to charge for the investigational product and document the fees charged.

f. In addition, for animal drugs, determine final disposition of food-producing animals treated with the investigational product, and the name and location of the packing plant where the animals will be processed.

T. HUMAN DEVICES

1. Significant and Non-Significant Risk Devices

[28] Information Sheet: Charging for Investigational Products
[29] Guidance for Industry: Charging for Investigational Drugs Under an IND – Questions and Answers

The regulations for investigational devices are found in 21 CFR 812. Investigational devices are classified as posing a significant risk (requiring an Investigational Device Exemption (IDE)), non-significant risk, or are IDE exempt as determined by the center and verified by the IRB. The 21 CFR 812 regulations contain abbreviated requirements for non-significant risk devices (21 CFR 812.2(b)) and requirements for exempted investigations (21 CFR 812.2(c)).

Note, in general, clinical investigations covered under the IDE regulation (21 CFR 812) are subject to differing levels of regulatory control depending upon the level of risk. Sponsors are responsible for making the initial risk determination with justification and providing it to the IRB.

Refer to the inspection assignment for specific instructions and the extent to which the inspection should be expanded beyond the identified study.

a. Determine if FDA has already made a risk determination for the study.[30]

b. If the FDA has not already made a risk determination for the study, determine whether the IRB reviewed the sponsor's risk determination for the device study reviewed and modified the determination if the IRB disagrees with the sponsor.

c. Evaluate compliance with the applicable regulations and requirements governing device studies based on the risk determination for the study.

   i. **Significant Risk Devices**

      For significant risk (SR) device studies, determine whether the sponsor is in full compliance with the IDE regulations at 21 CFR 812, and 21 CFR 50, 54, and 56.

   ii. **Non-Significant Risk Devices**

      For non-significant risk (NSR) device studies, determine whether the sponsor was in compliance with the abbreviated IDE requirements (21 CFR 812.2(b)(1)), addressing labeling (21 CFR 812.5), IRB approval (21 CFR 812.62), monitoring (21 CFR 812.46), records (21 CFR 812.140), reports (21 CFR 812.150), prohibition against promotion (21 CFR 812.7), and 21 CFR 50, 54, and 56.

   iii. **Exempt Devices**

      For studies exempt from 21 CFR 812 requirements, determine whether the sponsor is in compliance with 21 CFR 50 and 56.

[30] Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies

2. Humanitarian Use Devices and Humanitarian Device Exemptions

A Humanitarian Use Device (HUD)[31] is a device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 8,000 individuals in the United States per year. Refer to 21 CFR 814.3(n).

a. Determine if the sponsor is conducting studies of HUDs. If so, verify that the study, if it is considered a significant risk device study, is conducted under an IDE (i.e., has IDE approval from FDA as well as IRB approval), or IRB approval with concurrence that it is a non-significant risk device study, or is exempt from IDE requirements under 21 CFR 812.2(c).

b. Determine if IRB approval was obtained for a HUD with an approved Humanitarian Device Exemption (HDE) before use in a facility, with the exception of emergency use (21 CFR 814.124).

c. Determine if the HDE holder maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with the reviewing IRBs, and any other information required by the reviewing IRB or FDA (21 CFR 814.126(b)(2)).

d. Determine if the HDE holder adhered to reporting requirements (21 CFR 814.126(b)(1)), including monitoring how many devices are distributed each year and periodically providing FDA with updated information, including information to demonstrate that the HUD designation is still valid.

e. Determine if the sponsor is conducting a clinical investigation to collect safety and effectiveness data for an HDE-approved indication(s) without an IDE. If so, verify that the study is being conducted in compliance with 21 CFR 50 and 56.

f. Determine if the sponsor is conducting a study of a HUD for a different indication than the HDE-approved indication. If so, verify that the study is being conducted in compliance with 21 CFR 812, 50, and 56.

U. EMERGENCY RESEARCH

For “emergency research” studies (i.e., clinical studies conducted to determine the safety and effectiveness of FDA-regulated products, including drugs, biological products, and devices, in emergency settings when an exception from the informed consent requirements is requested),[32,]

[31] Guidance for Industry and Food and Drug Administration Staff: Humanitarian Device Exemption (HDE) Program
[32] Guidance for IRBs, Clinical Investigators and Sponsor: Exception from Informed Consent Requirements for Emergency Research

[33] assess the sponsor's compliance with 21 CFR 50.24.

Consult your supervisor and/or the center POC if there are any questions related to emergency research studies.

1. Determine if the sponsor obtained written authorization from FDA before proceeding with the study.

2. Determine if the sponsor has evidence of IRB approval (i.e., the IRB must find and document that specific conditions have been met).

3. Determine if the sponsor received any determination from an IRB that the IRB could not approve an emergency research study under 21 CFR 50.24. If so, determine if the sponsor promptly provided this information in writing to FDA, provided this information to clinical investigators who are participating or asked to participate in the same or a substantially equivalent clinical investigation of the sponsor, and provided this information to other IRBs that have been or are asked to review this or a substantially equivalent investigation by that sponsor as required by 21 CFR 50.24(e). Refer to 21 CFR 312.54(b) and 812.47(b).

4. Review the sponsor's compliance with other aspects of the emergency research regulations, particularly in the areas of planning and conducting community consultation and public disclosure activities, and establishing informed consent procedures to be used when feasible. For example:

    a. Determine if consultation with representatives of the community occurred (21 CFR 50.24(a)(7)(i)).

    b. Determine if public disclosure was provided to the communities in which the investigation is conducted and from which the subjects will be drawn prior to initiation of the investigation (21 CFR 50.24(a)(7)(ii)).

    c. Determine if public disclosure was provided to the communities in which the investigation is conducted and from which the subjects will be drawn following completion of the investigation (if applicable), including demographic characteristics of the research population and its results (21 CFR 50.24(a)(7)(iii)).

    d. Determine if information the sponsor received from the IRB concerning the required public disclosures was submitted to the Division of Dockets Management and, if possible, to the IND or IDE file (as applicable) (21 CFR 312.54(a) and 812.47(a)).

[33] 21 CFR 50.24

e. Determine if an independent DMC was established to exercise oversight of the clinical investigation (21 CFR 50.24(a)(7)(iv)).

V. INTERNATIONAL DATA

1. Inspections by Foreign Regulatory Authorities

Regulatory authorities from countries in the European Union (EU) or other countries (e.g., United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA), Japan's Pharmaceutical and Medical Devices Agency (PMDA), Canada's Health Canada) may also conduct inspections of sponsors, CROs, clinical investigator sites, and contractors providing clinical trial services.

If the ORA investigator becomes aware that the sponsor has been inspected by a non-U.S. inspectorate, this should be noted in the EIR under the Administrative Data section (which inspectorate and the dates of the inspection).

2. Studies with Foreign Data

a. Human Drugs and Biological products

When inspecting a clinical study with foreign data, ask the sponsor whether the foreign sites conducted the study under US IND. Confirm that the sponsor provided to the center a list of clinical sites specifying which clinical sites were or were not conducting the study under a US IND.

Determine how the sponsor collected the FDA 1572 information from the non-IND sites or those sites that did not sign an FDA 1572. For example, some sponsors have created an alternate form based on the FDA 1572 without the FDA references or IND commitments (See ii(b) below).

Determine whether the sponsor has requested FDA to waive any applicable requirements under 21 CFR 312.120(a)(1) and (b), or whether FDA has granted a waiver of the requirements under an IND (e.g., FDA 1572 signature waiver, IEC waiver). ORA investigators should verify any applicable documentation during the inspection. Refer to the inspection assignment about the need to collect copies of such documentation and contact the center POC with any questions.

Except to the extent such waivers apply, conduct the inspection as usual following the instructions in Part III (Inspectional) of this CP.

i. Foreign clinical studies not conducted under an IND

When a clinical trial conducted at a foreign clinical site is not conducted under an IND, the sponsor must ensure that the study complies with the requirements in 21 CFR 312.120 to use the study data as support for an IND or application for marketing approval. Under 21 CFR 312.120, FDA will accept a well-designed, well-conducted, non-IND foreign study as support for an IND or application for marketing approval if the study was conducted in accordance with GCP and if FDA is able to validate the data from the study through an onsite inspection, if necessary.[34] The GCP requirements under 21 CFR 312.120 help ensure that studies conducted at foreign sites not under IND are conducted in a manner comparable to that required for IND studies.

Review the sponsor's processes for handling clinical studies conducted at foreign clinical sites that are not under an IND, including processes for obtaining and submitting documentation describing the actions taken by the sponsor to ensure that the study was conducted in accordance with GCP, as required under 21 CFR 312.120(b). Verify the supporting information required under 21 CFR 312.120(b), particularly with respect to the following items, for the foreign clinical sites identified in the inspection assignment and additional foreign clinical sites as necessary to determine the sponsor's overall practices and/or to determine the extent of any observations.

a. Clinical investigator's qualifications;
b. Description of the research facilities;
c. Independent ethics committee (IEC) that reviewed the study (all central IECs and those with oversight of the chosen clinical sites) and a statement that the IEC meets the definition in 21 CFR 312.3;
d. Summary of the IEC's decision to approve or modify and approve the study or to provide a favorable opinion;
e. Description of how informed consent was obtained;
f. Description of what incentives, if any, were provided to subjects to participate;
g. Description of how the sponsor monitored the study and ensured that the study was consistent with the protocol; and
h. Description of how investigators were trained to comply with GCP and to conduct the study in accordance with the study protocol, and a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained (any signed commitments must be maintained and available for agency review).

[34] Guidance for Industry and FDA Staff: FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions

As specified in 21 CFR 312.120(c), a sponsor or applicant may ask FDA to waive any applicable requirements under 21 CFR 312.120(a)(1) and (b).

ii. Foreign clinical studies conducted with a waiver under an IND

As specified in 21 CFR 312.10, a sponsor or applicant may ask FDA to waive any applicable requirements under 21 CFR 312. For example:

a. A sponsor wishing to conduct a foreign study under IND may seek a waiver of the IRB requirements so that it may conduct the study using an IEC operating in accordance with GCP.[35]

b. A sponsor may also seek a waiver from the FDA 1572 signature requirement for clinical investigators at foreign sites conducting studies under IND.[36] Sponsors of studies that are conducted under IND with an FDA 1572 signature waiver are asked to provide documentation of the waiver to the clinical site(s) to which the waiver applies. Documentation maintained by the sponsor related to the waiver may include: a completed but unsigned FDA 1572 (or alternative form) for the clinical investigator, a signed commitment from the clinical investigator and sponsor to follow ICH GCP, and a letter indicating approval of the FDA 1572 signature waiver from the FDA review division for each protocol. ORA investigators should request a copy of any applicable documentation during the inspection, if available.

b. Human Devices

Effective February 21, 2019, 21 CFR 812.28 imposed new regulatory requirements for FDA acceptance of clinical data from foreign sites outside of the United States (OUS) being submitted to support an IDE or marketing application or submission (PMA, 510(k), HDE, PDP, or De Novo). All clinical data being submitted to support an IDE or marketing application or submission from a clinical investigation having OUS sites that began after this effective date (as indicated by the first subject signing informed consent documents) would be subject to the requirements under 21 CFR 812.28.[37]

Clinical investigations that began before the effective date of February 21, 2019, would be

[35] Information Sheet Guidance for Sponsors, Clinical Investigators and IRBs: Waiver of IRB Requirements for Drug and Biological Product Studies

[36] Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions – Statement of Investigator (Form FDA 1572)

[37] 83 FR 7366 at 7368, February 21, 2018

subject to the prior version of 21 CFR 814.15[38]:

> For clinical investigations conducted wholly or in part OUS and began before February 21, 2019, FDA will accept data in support of a Premarket Approval (PMA), provided that the data are valid and the studies are conducted in conformance with the "Declaration of Helsinki," or the laws and regulations of the country in which the research is conducted, whichever accords greater protection to the human subjects.

Clinical investigations that began on or after February 21, 2019 are subject to 21 CFR 812.28:

> When data from an OUS site of a device clinical investigation will be used to support an IDE or marketing application or submission, the sponsor must ensure that the investigation complies with the requirements in 21 CFR 812.28. FDA will accept data from a clinical investigation that began on or after February 21, 2019, that was conducted wholly or in part OUS, and submitted to support an IDE or a device marketing application or submission, if the investigation is well-designed and well-conducted and the conditions of 21 CFR 812.28 are met, including: providing a statement that the investigation(s) was conducted in accordance with GCP, as described in 21 CFR 812.28(a)(1); supporting information is provided as applicable and described in 21 CFR 812.28(a)(2) and (b); and FDA is able to validate the data from the investigation through an onsite inspection, if necessary, as described in 21 CFR 812.28(a)(3). If the sponsor intends to submit data from a device clinical study conducted at an OUS site to support an IDE or marketing authorization, the sponsor is required to submit documentation to FDA as specified in 21 CFR 812.28(b). Refer to the inspection assignment about the need to verify such documentation and contact the center POC with any questions.
>
> As specified in 21 CFR 812.28(c), a sponsor or applicant may ask FDA to waive any applicable requirements under 21 CFR 812.28(a)(1) and (b). FDA may receive this request for waiver as part of an IDE or a device marketing application or submission or as a standalone request. Refer to the inspection assignment to determine whether FDA has granted a waiver of the above requirements.
>
> Inspections of device studies at OUS sites should be conducted as usual following the instructions in Part III (Inspectional) of this CP.

c. Animal Drugs

[38] Id.

The data generated from studies conducted in foreign countries, meaning countries other than the United States, undergo the same assessment process as data generated in the United States. We would consider foreign data to be data generated OUS both by entities based within or OUS.

The sponsor is expected to show that the conditions of use are representative of those in the U.S. if part or all of the foreign data is to be considered towards product approval. The sponsor should have documentation to address the similarities and differences in the following areas between the U.S. and each foreign site: [39]

i. Conditions of use of the investigational drug product;
ii. The standard of practice of veterinary medicine with respect to any differences that may impact the study;
iii. Management and husbandry practices;
iv. Species, breeds, or classes used in the study;
v. Bacterial strains, including target pathogen virulence, and target pathogen susceptibility to the investigational antimicrobial;
vi. Parasitic strains, including source, age, and susceptibility (if applicable); and
vii. Any other practices or conditions (if applicable) that could impact the study conduct or results.

If the study was conducted under an alternate regulatory standard (e.g., Organisation for Economic Cooperation and Development (OECD) principles, US Environmental Protection Agency (EPA) regulations), ask the sponsor to briefly explain the differences between the alternate regulatory standard and 21 CFR 58, and its potential impact on the quality or integrity of study data.

Inspections of animal drug studies at OUS sites should be conducted as usual following the instructions in Part III (Inspectional) of this CP.

d. Animal Food Additives

The data generated from studies conducted in foreign countries undergo the same assessment process as data generated in the United States.[40]

[39] CVM Program Policy and Procedural Manual 1243.4068: See section pertaining to "Specific Considerations Regarding Foreign Effectiveness Field Studies"
[40] CVM GFI #262 Pre-Submission Consultation Process for Animal Food Additive Petitions or Generally Recognized as Safe (GRAS) Notices

The sponsor should have documentation to address the similarities and differences in the following areas between the U.S. and each foreign site:

i. Scientific methods and principles of experimentation;
ii. Animal feeding and husbandry practices; and
iii. Nutritional requirements and maximum tolerable levels of ingredients used in experimental diets.

If any of the foreign data originated wholly or in part from a nonclinical laboratory study that was conducted under an alternate regulatory standard (e.g., OECD principles, US EPA, or a standard of the host country), ask the sponsor to briefly explain the differences between the alternate regulatory standard and 21 CFR 58, and its potential impact on the quality or integrity of study data.

3. Translation to English Language

Translation services will be arranged prior to the inspection by the ORA Division of Travel Operations (DTO) trip coordinator. Refer to IOM Chapter 5, Establishment Inspections, for specific information regarding translations during inspections.

W. NONCLINICAL LABORATORY STUDIES

Refer to the inspection assignment for specific instructions and the extent to which the following information should be verified. Contact the center POC with any questions related to coverage of nonclinical laboratory studies.

Determine whether the sponsor utilized the services of a contractor, consulting laboratory, or grantee to perform an analysis or other services for the conduct of nonclinical studies subject to the regulations at 21 CFR 58, Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies.[41] If so, collect copies of information documenting how the notification was, and where and when the nonclinical studies were, conducted. For contracted studies, collect copies of the agreement with the contractor. For additional information regarding oversight of outsourced services, refer to Part III Section F (Outsourced Services) of this CP.

1. Determine if the sponsor documented in a statement that the studies were conducted in compliance with 21 CFR 58. If the study was not conducted in compliance with these regulations, determine if the sponsor or contractor documented in a statement, the reason why the studies were not conducted in compliance with the regulations.[42] Review and obtain

[41] 21 CFR 58.10 Applicability to studies performed under grants and contracts
[42] A statement regarding compliance with 21 CFR 58 or the reason for not conducting the studies in compliance with 21 CFR

copies of these statements and other documentation to support inspectional observations. If the sponsor's statement indicates that the study was conducted in accordance with 21 CFR 58, describe the methods or processes used by the sponsor to assure that the nonclinical laboratory had adequate personnel, facilities, equipment, controls, and SOPs to perform the study. If there is no compliance statement or the study does not appear to have been conducted in accordance with 21 CFR 58, describe the methods or processes used by the sponsor to ensure validity of the study results, including audit(s) of the final report and supporting documentation.

2. Determine the sponsor's methods and processes related to:

   a. Monitoring of the laboratory prior to the initiation of and during the study.

   b. Examination by the sponsor of the procedures used by the nonclinical laboratory's quality assurance unit (QAU) and testing facility management (TFM) to determine that such procedures were adequate to obtain compliance.

   c. Review of the final study report by the sponsor.

   d. Use of a fully functional, entirely separate QAU to fulfill the quality assurance requirements in the conduct of the study at the nonclinical laboratory.

   e. Any TFM responsibilities performed by the sponsor to assure that the nonclinical laboratory had adequate personnel, facilities, equipment, and SOPs to perform the study properly.

3. If the study was conducted under an alternate regulatory standard (e.g., OECD principles, EPA regulations), ask the sponsor to briefly explain the differences between the alternate regulatory standard and 21 CFR 58, and its potential impact on the quality or integrity of study data.

4. Determine whether the study director approved the protocol, by dated signature, including any amendments. Determine if the nonclinical study protocols contain the sponsor name, sponsor approval date, and amendments.

5. Determine whether the sponsor performed characterization and stability testing of test, control, and reference (as applicable) articles and documented methods of synthesis, per 21

58 must appear in the Food Additives, Food Additive Petitions, Notice of Claimed Investigational Exemption for New Animal Drug studies, IND and IDE applications, marketing applications, and premarket approval applications (21 CFR 170, 171, 312.23(a)(8)(iii), 314.50(d)(2)(v), 314.125(b)(15), 511.1(b)(4)(ii), 514.1(b)(12)(iii), 570, 571, 601.2(a), 812.27(b)(3), 814.20(b)(6)(i)).

CFR 58.105, including but not limited to:

a. Stability testing;

b. Documentation for each batch of the identity, strength, purity, and composition or other characterization that defines the test and control articles; and

c. Documentation of methods of synthesis, fabrication, or derivation.

6. Review documentation regarding where and when the test and control article characterization and stability testing was conducted and sent to the testing facility as well as copies of any resulting reports.

7. Determine the location and contact information of archives of the sponsor or designated storage location (name, address, email and phone, where appropriate), including archives of data, documentation, specimens, and reserve samples. In your determination, include location and security of the data center where the EDC data are retained or archived.

8. If a facility conducting nonclinical testing goes out of business, determine if all data, documentation, specimens, and reserve samples required to be retained were transferred to the sponsor's designated archives and determine if FDA was informed of this transfer (21 CFR 58.195(h)).

X. SAMPLE COLLECTION

Collect samples of the investigational product during sponsor inspections only upon specific instructions by the center with ORA concurrence. Contact your supervisor and the center POC prior to collecting an investigational sample.

Y. ESTABLISHMENT INSPECTION REPORTS

The Establishment Inspection Report (EIR), complete with attachments, exhibits, and any related correspondence, is a crucial document used in the decision-making process for marketing applications/submissions, general surveillance, and for evaluation of referrals (e.g., complaints, reports of noncompliance). The EIR must clearly and completely document all inspectional observations that may have impact on the decision-making process. The endorsement to the EIR provides a summary of the major observations noted during the inspection.

The EIR consists of the following: eNSpect EIR Coversheet with endorsement, the ORA investigator's narrative report, attachments, and exhibits.

The ORA investigator should refer to the Investigations Operations Manual (IOM), Chapter 5,

Establishment Inspections, subchapter 5.10 Bioresearch Monitoring, as well as subchapter 5.11 Reporting for guidance on reporting inspectional findings.

The sponsor EIR requires detailed narratives for the following sections and subsections covered during the inspection.

Required elements:

- Summary
- Administrative Data
- History
- Interstate Commerce
- Jurisdiction
- Individual Responsibility and Persons Interviewed
- Firm's Training Program (including site training)
- ClinicalTrials.gov Requirements (as applicable)
- Selection and Monitoring of Clinical Investigators
- Oversight of Outsourced Services
- Monitoring Procedures and Activities (including selection of monitors)
- Quality Assurance
- Data and Safety Monitoring Board/Data Monitoring Committee
- Safety Oversight
- Safety and Adverse Event Reporting
- Progress Reporting
- Data Collection and Handling
- Electronic Records and Electronic Signatures
- Records Custody and Retention
- Financial Disclosure
- Investigational Product
- Objectionable Conditions and Management's Response
    - Supporting Evidence and Relevance
    - Discussion with Management
- Refusals
- General Discussion with Management
- Samples Collected
- Voluntary Corrections
- Exhibits Collected
- Attachments

Refer to IOM Chapter 5, Establishment Inspections, subchapter 5.2.9, Interviewing Confidential Informants, for information on how to document information obtained from a confidential source.

The BIMO EIR will utilize the Standard Narrative Report format but must also include content required by compliance programs and specific inspection assignment instructions. ORA investigators are encouraged to add additional report headings as needed to communicate important information about the inspection, relevance of inspectional observations that may impact public health and/or to address specific requests from directed assignments.

PART IV - ANALYTICAL

Centers will provide specific instructions if sample collection of investigational product for analysis is needed. Contact your supervisor and the center POC for additional guidance. Refer to Part III Section X (Sample Collection) of this CP.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

The following information is to be used in conjunction with the instructions in FMD-86 (Establishment Inspection Report Conclusions and Decisions) for initial ORA OBIMO division and final center classification of inspections under this CP:

No Action Indicated (NAI) – No objectionable conditions or practices were found during an inspection or the significance of any objectionable conditions found does not justify further regulatory action.

Voluntary Action Indicated (VAI) – Objectionable conditions or practices were found, but FDA is not prepared to take or recommend any regulatory action since the objectionable conditions or practices do not meet the threshold for regulatory action.

Official Action Indicated (OAI) – Objectionable conditions and/or practices were found, and regulatory action should be recommended. The scope, severity, or pattern of the violation(s) support findings that:

1. Subjects under the care of the sponsor would be or have been exposed to an unreasonable and significant risk of illness or injury; or
2. Subjects' rights, welfare, or safety would be or have been seriously compromised; or
3. Data integrity or reliability is or has been compromised.

The ORA OBIMO division should consult with the center POC when an OAI classification is recommended to allow for discussion of the recommendation.

The center is responsible for the final classification of inspections. The center is responsible for drafting, developing, and issuing all regulatory and enforcement letters. Post-inspectional correspondence for VAI inspections may identify significant issues and, when needed, state that FDA expects prompt, voluntary corrective action by the sponsor. Post-inspectional correspondence for NAI inspections issued by the center may indicate that no objectionable conditions or practices were identified that would justify enforcement action.

Advisory, administrative, and judicial actions may be pursued based on the inspectional observations and will be in accordance with federal laws and regulations. FDA can invoke legal sanctions under the Federal Food Drug and Cosmetic Act (FD&C Act) and/or Title 18, U.S.C. where appropriate. FDA may pursue the following based on inspectional observations:

1. An Untitled Letter (UL) cites violations that do not meet the threshold of regulatory significance for a Warning Letter.

2. A Warning Letter may be considered when the violations can be corrected through specific

action(s) by the sponsor (e.g., preparation of, and compliance with, a detailed corrective action plan that is acceptable to FDA) and adherence to the corrective action plan has a high probability of preventing similar or other violations from occurring in the future.

3. Rejection of data
4. Seizure of investigational product
5. Injunction
6. Civil Money Penalties
7. Prosecution under the FD&C Act or other Federal statutes (e.g., 18 U.S.C. 2, 371, 1001, and 1341).

The Agency may also pursue other necessary actions (e.g., consent agreements, follow-up inspections, clinical hold for studies subject to 21 CFR 312, terminate the investigational new animal drug (INAD) exemption subject to 21 CFR 511.1(d), refuse to approve or withdraw the approval of new animal drug application (NADA) subject to 21 CFR 514, terminate the exemption or withdrawal of approval of IDE application for studies subject to 21 CFR 812, regulatory meetings, or device detention based on the inspectional observations). See FMD-86 and Regulatory Procedures Manual (RPM).

Referral of pertinent matters may be made, with center concurrence, to other federal, state, or local agencies for such action as that agency deems appropriate.

For sponsor-investigators, additional administrative/enforcement actions that may be applicable are described in the Clinical Investigators and Sponsor-Investigators Compliance Program (CP 7348.811).

Follow-up Inspections:

1. ORA OBIMO division follow-up actions, including re-inspection, will be made at the request of the center. Centers should evaluate whether the violations found indicate systemic problems with the conduct of the study or the reliability of the data and whether additional inspection assignments should be issued.
2. Following issuance of a Warning Letter, centers should periodically review their databases for entries, including whether a Warning Letter recipient is actively conducting other clinical investigations. If such information becomes available, the center should issue a follow-up inspection assignment to verify if the sponsor is fulfilling the terms of any corrective action plans and in compliance with applicable regulations.

PART VI – REFERENCES AND PROGRAM CONTACTS

A. REFERENCES

1. FDA laws

   Federal Food, Drug, and Cosmetic Act (FD&C Act)

2. Most Relevant 21 CFR Regulations

Part 50	Protection of Human Subjects
Part 54	Financial Disclosure by Clinical Investigators
Part 56	Institutional Review Boards
Part 58	Good Laboratory Practice for Nonclinical Studies
Part 312	Investigational New Drug Application
Part 511	New Animal Drugs for Investigational Use
Part 812	Investigational Device Exemptions

3. Other 21 CFR Regulations

Part 11	Electronic Records; Electronic Signatures
Part 25	Environmental Impact Considerations
Part 54	Financial Disclosure by Clinical Investigators
Part 70	Color Additives
Part 71	Color Additive Petitions
Part 74	Listing of Color Additives Subject to Certification
Part 80	Color Additive Certification
Part 82	Listing of Certified Provisionally Listed Colors and Specifications
Part 101	Food Labeling (Petitions for Nutrient Content Claims and Health Claims)
Part 107	Infant Formula
Part 170	Food Additives (Food Contact Substance and Generally Recognized as Safe)
Part 171	Food Additive Petitions
Part 180	Food Additives Permitted in Food or in Contact with Food on an Interim Basis Pending Additional Study
Part 190	Dietary Supplements (New Dietary Ingredient Notification)
Part 314	Applications for FDA Approval to Market a New Drug
Part 361.1	Radioactive Drugs for Certain Research Uses (Radioactive Drug Research Committee)
Part 320	Bioavailability and Bioequivalence Requirements
Part 510	New Animal Drugs (Subpart A)

Part 514	New Animal Drug Applications
Part 570	Investigational Use of Food Additives
Part 571	Food Additive Petitions
Part 601	Licensing (Applications for FDA Approval of a Biologic License)
Part 807	Premarket Notification Procedures (Subpart E)
Part 814	Premarket Approval of Medical Devices (includes HDE requirements in 814.100)
Part 1100	Tobacco Products Subject to FDA Authority

4. 42 CFR Regulations

Part 11	Clinical Trials Registration and Results Information Submission

5. FDA Guidelines, Guidance Documents, and Inspection Guides

General

Inspection Processes: Investigations Operations Manual (IOM), Chapter 5 – Establishment Inspections. Updated annually.

Field Management Directive (FMD)-86 Establishment Inspection Report Conclusions and Decisions

Guidance documents, including information sheets and ICH/VICH guidance documents, and notices pertaining to the conduct of clinical and nonclinical studies are accessible on FDA's website at this link: Guidance Documents (Including Information Sheets) and Notices. (Guidance documents and information sheets can also be found here.)

Compliance Policy Guides (CPG)

Compliance Policy Guide (CPG) Section 120.100. Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities

Compliance Policy Guide (CPG) Section 130.300. FDA Access to Results of Quality Assurance Program Audits and Inspections

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

Guidance for Industry and FDA Staff: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Framework for FDA's Real-World Evidence Program

B. PROGRAM CONTACTS

1. When medical, technical, or scientific questions or issues arise about a specific inspection assignment or if additional information is required about a specific inspection assignment, consult your supervisor and center POC identified in the inspection assignment.

2. For questions about GCP, specific to a center product area, contact:

   Center for Drug Evaluation and Research (CDER) Office of Compliance (OC)
   Office of Scientific Investigations (OSI)
   (301) 796-3150, FAX (301) 847-8748
   CDER-OSI-GCPReferrals@fda.hhs.gov

   Center for Biologics Evaluation and Research (CBER)
   Office of Compliance and Biologics Quality (OCBQ)
   FAX (301) 595-1304
   CBERBIMONotification@fda.hhs.gov

   Center for Veterinary Medicine (CVM)
   Office of Surveillance and Compliance
   (240) 402-7001, FAX (240) 276-9241
   CVMBIMORequests@fda.hhs.gov

   Center for Devices and Radiological Health (CDRH)
   Office of Clinical Evidence and Analysis
   Division of Clinical Science and Quality
   (301) 796-5490
   BIMO-CDRH@fda.hhs.gov

   Center for Food Safety and Applied Nutrition (CFSAN) BIMO Program Staff
   (240) 402-1757, FAX (301) 436-2668
   CFSANBIMO@fda.hhs.gov

   Center for Tobacco Products (CTP)
   Office of Compliance and Enforcement (OCE)
   (240) 402-7970
   CTP-BIMO@fda.hhs.gov

3. For crosscutting questions about GCP policy and program issues impacting FDA's BIMO Programs for GCP, or suggestions to improve this Compliance Program, contact:

   Office of Good Clinical Practice (OGCP)
   Office of Clinical Policy and Programs (OCPP)
   (301) 796-3707, FAX (301) 847-8640
   gcp.questions@fda.hhs.gov (Please use this mailbox for all non-urgent questions and requests)

4. For information about administrative warrants, contact:

   Division of Enforcement (DE)
   Office of Strategic Planning and Operational Policy (OSPOP)
   Office of Regulatory Affairs
   (240) 632-6862, FAX (240) 632-6859

PART VII – HEADQUARTERS RESPONSIBILITIES

A. CENTERS

1. Identifies the sponsors to be inspected, issues inspection assignments, and provides background materials (e.g., protocols, correspondence, data line listings) to ORA BIMO Inspection POC.

2. Communicates specific concerns, if any, to the ORA investigator prior to inspection.

3. Addresses inquiries regarding sponsor inspection assignments and compliance issues.

4. Attends inspections as a subject matter expert (SME), if needed. Refer to Part II (Implementation) of this CP for additional information regarding Responsibilities of Center Participants when participating on an inspection.

5. Provides guidance and support to the ORA investigator during all phases of inspections and investigations.

6. Reviews and evaluates EIRs, attachments/exhibits, and regulatory recommendations from ORA OBIMO divisions.

7. Submits regulatory (administrative/advisory) actions to the Office of Chief Counsel (OCC), if required.

8. Determines final classifications of inspections and enters the classification into the appropriate information technology system.

9. Initiates and develops follow-up regulatory (administrative/advisory) actions, as appropriate.

10. Issues post-inspectional correspondence regarding inspection classification and release of foreign inspection reports to the inspected firm.

11. Promptly Provides copies of all relevant correspondence between the sponsor and FDA to the ORA OBIMO division.

12. Notifies center review divisions, as appropriate, of significant violations.

B. OFFICE OF REGULATORY AFFAIRS

1. OFFICE OF BIORESEARCH MONITORING OPERATIONS (OBIMO)

    a. Provides inspection quality assurance, training of ORA personnel, and operational

guidance.

b. Liaises with centers, ORA OBIMO divisions, and OGCP, and resolves operational questions.

c. Receives and reviews all sponsor inspection assignments from the centers and forwards to the appropriate division.

d. Tracks inspection assignments and accomplishments.

e. Coordinates foreign inspections and joint inspections with foreign regulatory authorities.

f. Reviews and approves center requests to participate in BIMO inspections or investigations, and coordinates credentialing for center participants.

g. Releases redacted domestic EIRs to the inspected entities, per FMD-145.

2. DIVISION OF ENFORCEMENT

a. Serves as the ORA clearance point and coordinator for all administrative warrants and actions; liaises with ORA and centers to ensure coordination of cases.

b. Reviews and issues Notice of Noncompliance Letters related to ClinicalTrials.gov with the signature of the Associate Commissioner for Regulatory Affairs (ACRA), and coordinates actions.

3. OFFICE OF REGULATORY SCIENCE

a. Assigns laboratories for sample analysis and responds to inquiries about analytical methods.

C. OFFICE OF GOOD CLINICAL PRACTICE (OGCP)

1. Coordinates crosscutting clinical BIMO policy program activities.

2. Provides expert technical guidance, advice, information, interpretation, and analysis relevant to FDA's GCP and human subject protection (HSP) policies and clinical BIMO Program implementation to internal and external program constituents to assure program consistency.

3. Serves as agency liaison to other federal agencies (e.g., Office Human Research Protections, VA) for coordination of clinical BIMO and HSP subject protection issues.