CHAPTER 48- BIORESEARCH MONITORING

SUBJECT: CLINICAL INVESTIGATORS AND SPONSOR-INVESTIGATORS	IMPLEMENTATION DATE 07/22/2020
DATA REPORTING	
PRODUCT CODES: Bioresearch Monitoring inspections do not require product codes	
PROGRAM ASSIGNMENT CODES:	
Clinical Investigators	**Sponsor-Investigators**
09811 Foods, Food Additives and Color Additives	No PAC for Foods, Food Additives and Color Additives
41811 Biologics (Cell and Gene Therapy Products)	41812 Biologics (Cell and Gene Therapy Products)
42811 Biologics (Blood)	42812 Biologics (Blood)
45811 Biologics (Vaccines and Allergenic Products)	45812 Biologics (Vaccines and Allergenic Products)
48811 Human Drugs and Therapeutic Biologics	48812 Human Drugs and Therapeutic Biologics
48811F Human Drugs and Therapeutic Biologics (For-Cause)	No PAC for Human Drugs and Therapeutic Biologics (For-Cause)
48811S Biosimilars	No PAC for Biosimilars
68811 Animal Products	68812 Animal Products
83811 Medical Devices	83812 Medical Devices
98811 Tobacco Products	No PAC for Tobacco Products

Note: Clinical investigator and sponsor-investigator are hereafter collectively and individually referred to as “clinical investigator(s).”

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 three 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. The hard copy originals of the attachments and exhibits, 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 promptly via eNSpect to the center POC. The hard copy originals of the attachments and exhibits, along with the printed eNSpect cover sheet, should then be routed directly to the center POC.

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

TABLE OF CONTENTS

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 clinical study data submitted to FDA in support of research or marketing applications; and to assess compliance with statutory requirements and FDA's regulations governing the conduct of clinical studies, including those for informed consent and ethical review.[1]

FDA's Office of Regulatory Affairs (ORA) conducts inspections of clinical investigators, sponsors, sponsor-investigators, monitors, contract research organizations (CROs), institutional review boards (IRBs),[2] nonclinical (animal) laboratories, bioavailability and bioequivalence studies, post-marketing adverse drug experience reporting, and risk evaluation and mitigation strategies reporting, in support of preapproval, licensing, premarket and marketing applications submitted to the Agency for products regulated by all FDA product centers as part of the BIMO program, among other activities.

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.

The Clinical Investigator and Sponsor-Investigator CP applies to all six of FDA's centers[3] and addresses inspections of clinical investigators and sponsor-investigators who conduct FDA-regulated clinical studies. FDA's ORA investigators conduct clinical investigator inspections to determine if clinical studies are conducted in compliance with applicable statutory and regulatory requirements, and 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

[1] History of FDA's Centers and Offices, FDA External Fact Sheet about Office of Bioresearch Monitoring Operations, and Laws FDA Enforces

[2] Institutional Review Boards and Independent Ethics Committees (IEC) are hereafter 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)

efficacy of human and animal drugs, biologics, foods, and medical devices, and minimize the public health risk of tobacco products; and 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, biologics, medical devices, most foods, food additives, color additives and tobacco products.

The regulations listed below govern the activities and oversight of clinical studies, including, but not limited to the responsibilities and conduct of clinical investigators.

- Clinical investigator's responsibilities in conducting clinical studies of human drugs or biologics are provided in 21 CFR 312 (Investigational New Drug Application). 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 clinical investigators conducting bioequivalence studies under an Investigational New Drug (IND) application are contained in 21 CFR 320.
- Clinical investigator's responsibilities in conducting clinical studies of medical devices are provided in 21 CFR 812 (Investigational Device Exemptions). Additional requirements pertaining to the conduct of device studies are contained in 21 CFR 814 (Premarket Approval of Medical Devices).
- Additional requirements pertaining to the conduct of human studies are contained 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 conduct of clinical studies of animal drugs are provided under 21 CFR 511 (New Animal Drugs for Investigational Use) and 21 CFR 514 (New Animal Drug Applications); however, these regulations do not provide specific clinical investigator requirements.
- Regulations pertaining to electronic records and electronic signatures are provided in 21 CFR 11.
- Regulations pertaining to clinical trials registration and submission of results, specifically to the National Institutes of Health (NIH) via https://ClinicalTrials.gov, are provided in Title 42 CFR 11.

Refer to Part VI (References and Program Contacts) of this CP for a list of applicable regulations and guidance for industry.

PART II - IMPLEMENTATION

A. OBJECTIVES

The objectives of the BIMO program with respect to clinical studies are:

1. To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical studies;
2. To verify the accuracy and reliability of clinical 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 studies.

The purpose of this CP is to provide uniform guidance and specific instructions to ORA and center personnel for conducting inspections of clinical investigators and sponsor-investigators 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. Clinical Investigators

      A clinical investigator is the individual who conducts the clinical investigation.[4] The clinical investigator is responsible for overall conduct of the study at the clinical site, including directing the administration or dispensing of the investigational product to the subject and ensuring that data are collected and maintained in accordance with the protocol and applicable regulatory requirements. When the investigation is conducted by a team of individuals, the clinical investigator is the responsible leader of the team.

[4] 21 CFR 312.3; 21 CFR 511.3; 21 CFR 812.3(i)

b. Sponsor-Investigators

A sponsor-investigator 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.[5] While inspections of sponsor-investigators are assigned under this CP, Compliance Program 7348.810: Sponsors, Contract Research Organizations and Monitors should be referred to for areas applicable to the sponsor responsibilities of the sponsor-investigator.

2. Inspection Assignments

a. Centers issue clinical investigator inspection assignments with background materials (e.g., study protocol, case report forms (CRFs), data line listings, or any additional specific data, if appropriate), using the approved work instructions and template.

i. Domestic inspection assignments are issued to ORA BIMO headquarters and assigned to the appropriate ORA BIMO division.

ii. Foreign inspection assignments are issued to ORA BIMO 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 Veterans Affairs) of this CP for additional instructions.

c. Inspection assignments should be issued with due dates according to pre-defined timeframes. When requesting expedited inspections, centers should provide justification for the requested expedited timeframe. Refer to the approved job aid.

d. Once an inspection assignment has been issued, any change in the due date by the center will be routed through the appropriate ORA BIMO division investigations branch director(s) and any request to extend the due date by ORA OBIMO should be routed, with division investigations branch director concurrence, through ORA's management to the center POC.

3. Communication between the Centers and ORA

a. Prior to an Inspection

[5] 21 CFR 312.3; 21 CFR 511.3; 21 CFR 812.3(o)

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, and 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 BIMO 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 three business days after the conclusion of the inspection, the ORA investigator sends a preliminary summary of inspectional findings and a copy of any FDA 483 issued to the center POC.

ii. The ORA BIMO division forwards a copy of any response to the FDA 483 to the center POC. The center POC forwards to the appropriate ORA BIMO division correspondence email address a copy of any response to the FDA 483 that does not appear to have been shared with the ORA BIMO 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) prior to determining center final classification, if the center final classification differs from the ORA BIMO division recommended classification.

vi. If the center's final classification is different from the ORA BIMO division's recommended classification, the center should ensure that ORA BIMO personnel are aware of the change and the reasons for the change. Refer to the approved work instruction.

vii. The center enters the final classification into eNSpect and sends a copy of the post-inspectional correspondence to the appropriate ORA BIMO 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 BIMO international work planner to confirm scheduling of foreign inspections;

iv. Conducting the assigned inspection;

v. Communicating inspectional issues and inspectional observations with the clinical investigator and the study personnel 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 clinical investigator they may submit a written response to the FDA 483;

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

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

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 participation in inspections as per the approved work instruction;

iv. Obtaining inspection credentials through ORA OBIMO headquarters as per the approved work instruction;

v. Attending pre-inspection meetings as needed;

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

vii. Completing inspection tasks (e.g., auditing documents, preparing inspection notes and 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 BIMO division management and the center, and, if not resolved, immediately referred to ORA OBIMO headquarters management.

6. Inspections of Facilities under the Jurisdiction of the Veterans 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 clinical investigator at 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 inspecting a clinical investigator at a VA facility, in addition to the clinical investigator.

b. Post-Inspection

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 BIMO division, and then provide it to 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 MOU with the VA, which provides for the exchange of information between the two agencies.

PART III - INSPECTIONAL

Inspections involve evaluation of the clinical investigator's practices and procedures to determine compliance with applicable regulations. When the inspection occurs as a result of FDA's receipt of a marketing application or submission, it will include a comparison of the data submitted to FDA with source documents, or for animal drug studies, copies of source documents, and case report forms (CRFs). For surveillance inspections or for-cause inspections of ongoing studies, data comparison may only involve source documents and CRFs because data for ongoing studies may not be available.

A. GENERAL

The following instructions apply to all inspections of clinical investigators:

1. Clinical investigator inspections are product-type specific (i.e., human drugs, biologics, and devices; animal drugs; foods, food additives, and color additives; and tobacco products). ORA investigators must apply the applicable regulations to each clinical investigator inspection.

2. Inspections under this program will be preannounced unless otherwise instructed in the inspection assignment or a determination is made not to preannounce by ORA. The ORA investigator should keep the time span between initial contact and start of the inspection as short as possible. For inspections conducted at military installations, the ORA investigator should contact the Chief of Professional Services at the facility to be inspected in addition to the clinical investigator. The ORA investigator should immediately report to the ORA investigator's supervisor, ORA director of investigations, and center POC, any attempt by the clinical investigator to delay an inspection by more than ten business days without sufficient justification.

3. Prior to the inspection, the ORA investigator will review the inspection assignment, the study protocol, and background materials.

4. If the ORA investigator encounters a refusal to permit entry or inspection, or a refusal of information, including a refusal to permit access to or copying of requested records, the

appropriate section of IOM Chapter 5 (Establishment Inspections) and applicable regulatory requirements[6] should be consulted and current policy/procedures followed.

5. If the ORA investigator observes or suspects regulatory or statutory deviations that may affect data reliability or endanger subject rights, safety, or welfare, they will immediately contact their supervisor, ORA director of investigations, and center POC, and then continue the inspection.

   Prior to contacting subjects to be interviewed, the ORA investigator should review IOM Chapter 5 (Establishment Inspections) and refer to Part III Section J (Interviews of Subjects/Personnel) of this CP, as well as consult with their supervisor and center POC.

6. The ORA investigator issues an FDA 483 at the conclusion of the inspection when deviations from applicable regulations are observed. Any inspectional observation that does not constitute a deviation from the regulations will not be listed on the FDA 483. Those inspectional observations that do not constitute deviations from regulations will be discussed during the closeout discussion with management and reported in the EIR.

   For animal studies, regulations pertaining to animal drug studies do not provide specific clinical investigator requirements, and therefore, it is unlikely that an FDA 483 will be issued as a result of a CVM clinical investigator inspection. Therefore, inspectional observations will be discussed during the close out discussion with management and reported in the EIR.

7. The ORA investigator informs the clinical investigator that they may submit a written response to the FDA 483, within 15 business days of the end of the inspection, to the appropriate ORA BIMO division correspondence email address. Refer to IOM Chapter 5 (Establishment Inspections).

8. If, during a clinical investigator inspection, the ORA investigator identifies an IRB that has never been inspected or has not been inspected within the past five years, the ORA investigator's supervisor should include this recommendation in the endorsement of the EIR.

9. ORA BIMO personnel who become aware of complaints or problems related to a clinical investigator, IRB, sponsor or CRO are encouraged to refer the information to the

[6] Section 301(f) of the FFDCA, applicable sections of the PHS Act, and applicable regulations (21 CFR 312.68, 812.145.)

appropriate center to evaluate. The ORA investigator's supervisor should include this information and the following details, if available, in the endorsement of the EIR:

a. Name, address, phone number, and e-mail address of the clinical investigator, IRB, sponsor or CRO;

b. Name(s) of the investigational product(s), protocol number(s) and title(s), and application or file number(s) (e.g., IND, IDE, or INAD); and

c. Details of the complaint or problem and any relevant information.

B. INSPECTION PROCEDURES

The ORA investigator will review the inspection assignment and background materials and contact the center POC prior to the start of the inspection to verify the focus and intent of the inspection.

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

This CP provides only the minimum scope of the inspection, and the ORA investigator should expand the inspection as the circumstances warrant after consulting with their supervisor and center POC. Inspections should be sufficient in scope to cover special instructions in the inspection assignment and to determine if the clinical investigator's practices and procedures comply with applicable regulations. The ORA investigator should not attempt to scientifically evaluate the study data or protocol(s).

When the inspection occurs as a result of FDA's receipt of a marketing application, data line listings, (i.e., tabulations) may be provided by the center POC for purposes of data verification, which is a process by which data line listings are compared to the original source of information (e.g., source documents) for completeness and accuracy. Review of records includes assessing the quality of source documents and reviewing protocol compliance.

Full narrative reporting of any deviations from applicable regulations should be thoroughly documented. Collect copies of correspondence or other documentation that support inspectional observations. For example, copies of records demonstrating discrepancies

between source data, case report forms, and/or data submitted to FDA should be collected, and the observation described in the EIR.

The ORA investigator should discuss any potential violations involving fraud subject to Title 18 of the United States Code (18 U.S.C.) with their supervisor, ORA director of investigations, and center POC, for appropriate referral to the Office of Criminal Investigations (OCI).

C. AUTHORITY and ADMINISTRATION

1. If available at the clinical site, compare the Form FDA 1572 Statement of Investigator (FDA 1572) for human drug and biologic studies conducted under an IND, or the Investigator Agreement for medical device and animal drug studies, with the background materials provided with the inspection assignment. If different, or if not provided with the assignment, obtain a copy.

   In addition, review the records and determine when the clinical investigator assumed responsibility of the study and if there were any changes to the clinical investigator responsible for the study. If there are any changes to the designated clinical investigator throughout the study, determine the reason(s) for change in the clinical investigator. Determine the name of the clinical investigator who assumed responsibility for the study and collect relevant documentation. Consult with your supervisor and the center POC to confirm the focus and scope of the inspection and to discuss any further instruction on how to proceed.

   For inspections of clinical studies conducted at foreign clinical sites, refer to Part III Section S (International Inspections) of this CP for additional information related to FDA 1572 requirements.

2. Obtain a list of all studies conducted by the clinical investigator during the timeframe indicated in the inspection assignment. If no timeframe is specified, obtain a list of studies conducted by the clinical investigator in the past five years or since the previous inspection. This list should include available information for each study, such as:

   a. Protocol number or other identifier;
   b. Protocol title, including the investigational product name, and application or file number, if available;

c. Name of sponsor (including government agencies and commercial sponsors);
d. Status of study (e.g., completed, recruiting);
e. Study dates; and
f. Number of subjects enrolled at the clinical site.

3. For each of the inspected studies, document in the EIR:

   a. The names and addresses of all locations where study visits were conducted;

   b. How the sponsor provided information and training to the clinical investigator about the investigational product, protocol, electronic systems, and the obligations of a clinical investigator (e.g., telephone, written correspondence, investigator meetings, sponsor presentations on the protocol);

   c. Whether the authority for the conduct of the various aspects of the study was contracted and/or delegated properly so that the clinical investigator retained control and knowledge of the study. If there are concerns about appropriate delegation, obtain information (e.g., curriculum vitae, medical or other license, delegation of authority log) about the qualifications and training of the person performing the delegated task and the clinical investigator's oversight of the study.

   d. The following dates:

      i. IRB approvals including initial and continuing review of the protocol, any changes to the protocol (e.g., amendments), the original informed consent document and all revised informed consent documents;

      ii. When the FDA 1572 or Investigator Agreement was signed by the clinical investigator (or the date that the sponsor obtained a waiver from this requirement), including when revisions and updates were made, if applicable;

      iii. When the first subject signed the informed consent document;

      iv. When the first subject was screened;

      v. When the first and last subjects were randomized;

      vi. When the first and last administration of the investigational product occurred;

      vii. When the last subject visit or follow-up occurred; and

      viii. When the study closed.

e. If the clinical investigator discontinued participation in the study, obtain the date and describe the reason(s) for discontinuation. Include the date(s) that the clinical investigator notified the sponsor and IRB (if applicable) of the discontinuation.

4. List the name and address of the facility or facilities performing laboratory or diagnostic tests required by the protocol. For human drugs and biologics studies conducted under an IND, verify that this information is included on the FDA 1572. Describe the clinical investigator's documentation of the laboratory or diagnostic testing facility's qualifications (e.g., certification under Clinical Laboratory Improvements Act (CLIA)). If any laboratory testing was performed at the clinical site, determine whether the clinical site is equipped to perform each test specified. Consult with your supervisor and the center POC if there are questions related to a clinical site's qualifications or necessary documentation.

5. Determine the process used to recruit subjects. If any recruitment protocols, promotional materials (e.g., advertising, social media), or phone scripts were employed, document their review and approval by the IRB, or note the absence of such approval. Refer to Part III Section F (Institutional Review Board/Institutional Animal Care and Use Committee) of this CP.

   Document any instances in which the clinical investigator utilized methods or distributed information that appeared to be coercive in nature,[7] distributed any promotional material (e.g., brochure, website, social media) or otherwise represented the investigational product as safe and effective for the purpose for which it is under investigation, or implied in any manner a favorable outcome or other benefits beyond what was outlined in the consent document and protocol.

6. Obtain a copy of the clinical site logs used to record screening, enrollment, study visits and/or sign-in sheets with subject identification and confirm that the number of subjects listed on the logs reflects accurately the number of subjects screened and enrolled by treatment arm. If the clinical site did not use such logs for any inspected

[7] FDA's Guidance for Institutional Review Boards and Clinical Investigators, "Payment and Reimbursement to Research Subjects," states, "While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document."

studies, document in the EIR.

D. CLINICALTRIALS.GOV REQUIREMENTS

Sponsors, sponsor-investigators, or designated clinical investigators (i.e., "responsible parties") of drugs, biologics, and medical devices are required to register and submit results information to https://ClinicalTrials.gov (also referred to as the ClinicalTrials.gov database or ClinicalTrials.gov databank; hereafter, ClinicalTrials.gov) for applicable clinical studies.[8]

For sponsor-investigator inspections, or if the clinical investigator is designated as the responsible party by the sponsor, refer to CP 7348.810 Sponsors, Contract Research Organizations and Monitors for further instruction. Contact the center POC with any questions related to registration or submission of results information to ClinicalTrials.gov, or submission of certifications to the FDA.

Inspectional observations associated with applicable requirements for ClinicalTrials.gov registration and results information submission should be discussed with the clinical investigator and documented in the EIR.

E. PROTOCOL

1. Compare the protocol and/or amendments provided as background material with the inspection assignment to those maintained at the clinical site. If different, or if a protocol amendment was not provided with the inspection assignment, obtain a copy.

2. Determine whether the protocol was approved by the IRB, and by FDA for significant risk device studies, prior to initiation of any study-related procedures and prior to implementing any changes to the protocol (e.g., amendments) at the clinical site. For animal drug studies, protocols are not required to be approved by an institutional animal care and use committee.

[8] Detailed information about FDA's compliance/enforcement role and responsibilities, including a link to the relevant statutes, implementing regulations, Federal Register preambles, and historical background information is available at FDA's Role: ClinicalTrials.gov Information

Section 801 of the Food and Drug Administration Amendments Act (FDAAA) amended the Public Health Service Act by adding this certification requirement under section 402(j)(5)(B) (codified at 42 U.S.C. 282(j)(5)(B)), including its implementing regulations at 42 CFR 11.

a. Protocol amendments: During the course of a study, the sponsor may change the protocol through a protocol amendment. A protocol amendment is prospectively planned and implemented. Determine whether all protocol amendments and/or changes were reviewed and approved by the IRB prior to implementation by the clinical investigator, and for medical devices, submitted to the FDA, as applicable.

b. Protocol deviations: A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the approved protocol.

   Protocol deviations may include unplanned instances of protocol noncompliance. For example, situations in which the clinical investigator failed to perform tests or examinations as required by the protocol or failures on the part of subjects to complete scheduled visits as required by the protocol, would be considered protocol deviations.

   In the case of deviations which are planned exceptions to the protocol such deviations should be reviewed and approved by the IRB, the sponsor, and by the FDA for medical devices, prior to implementation, unless the change is necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 312.66), or to protect the life or physical well-being of the subject (21 CFR 812.150(a)(4)).

3. Verify whether the clinical investigator followed the protocol with respect to the following study-related procedures:

   a. Subject selection (i.e., inclusion and exclusion criteria);

   b. Number of subjects enrolled (e.g., total number of subjects enrolled by treatment arm);

   c. Randomization scheme (if applicable);

   d. Blinding and emergency unblinding procedures employed;

   e. Required study procedures and evaluations (e.g., efficacy and safety assessments, concomitant therapies and conditions, monitoring and reporting of adverse events and serious adverse events);

   f. Storage and maintenance of investigational product;

   g. Administration of the investigational product:

i. For human drugs and biologics, animal feed, food additives, and tobacco products, key aspects of administration to review may include: dosage, route and rate of administration, frequency of dosage, dose escalation increments, transition to next cohorts, stopping rules and decision making, allocation of responsibilities for decisions with respect to subject dosing and dose escalation; and timely communication of serious adverse findings or deviations related to administration to the sponsor; or

ii. For medical devices, key aspects of administration to review include: use according to manufacturer's directions and/or proper surgical techniques, as applicable.

h. Data collection:

i. Adherence to the protocol requirements on study data collection with attention to collection and assessment of primary endpoint data (i.e. efficacy and safety); and

ii. Completeness and accuracy of data listed on data line listings (e.g. site-level or subject-level data line listings provided by center POC for purposes of data verification) in comparison with original source of information (e.g., source documents), as applicable.

i. Any other information specific to the study (e.g., study-specific manuals, study-specific memoranda or newsletters) or specifically identified in the inspection assignment or by the center.

Review any deviations from the protocol. Determine whether the clinical investigator reported all protocol deviations to the IRB and the sponsor. Determine whether site level protocol deviations occurred, and how the clinical investigator and sponsor addressed the protocol deviations to resolve and prevent future deviations.

If any significant and/or unreported deviations from the approved protocol are observed, document the deviation as well as the following:

a. Dates of and reason for each deviation, including communication with the sponsor;

b. For investigational devices, prior approval from the sponsor for deviations from the investigational plan, except for emergency use (refer to 4.d. below);

c. Prior approval from the reviewing IRB, and for investigational devices, FDA, for deviations from the investigational plan that may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, except if for emergency use (refer to 4.d. below); and

d. If for emergency use of an investigational device, notification to the sponsor and reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject. In addition, for medical device studies, determine that this notice was given within five (5) working days after the emergency occurred. (21 CFR 812.150(a)(4))

F. INSTITUTIONAL REVIEW BOARD/INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE

For studies involving human drugs, biologics, devices, foods, color additives, food additives, and tobacco products, assess the clinical investigator's compliance with applicable regulations pertaining to obtaining institutional review board (IRB)[9] review and approval, and prompt reporting to an IRB of all changes in research activity and all unanticipated problems involving risk to human subjects or others. Refer to Part III Section S (International Inspections) of this CP for additional information regarding IRB approval for clinical studies conducted at a foreign clinical site under an IND.

For studies involving animal drugs: Review the inspection assignment to determine whether an institutional animal care and use committee (IACUC) reviewed and approved activities involving animal subjects. If required, assess the clinical investigator's compliance with regulations pertaining to obtaining IACUC review and approval of the identification and rationale of the species and approximate number of animal subjects to be used, the animal subjects' possible exposure to discomfort and pain, and the interaction with the owner or agent of the owner of the animal subject, or the legally-authorized representative (LAR) of the animal subject, as part of the establishment's informed (owner) consent process.

For all studies inspected:

1. Determine whether the clinical investigator assured that an IRB/IACUC provided initial and continuing review and approval of the study. If so, identify the name, address, and chairperson of the IRB/IACUC for the study.

[9] Refer to footnote 2.

2. Determine and describe whether the clinical investigator obtained IRB/IACUC approval for the items listed below before initiation of study-specific procedures on subjects. Obtain copies of the IRB or IACUC approvals for the following:

   a. Initial protocol and any changes to the protocol (e.g., amendments);

   b. Informed consent and/or assent documents, including all revised informed consent or assent documents; and

   c. Any recruitment protocols or promotional materials (e.g., advertising, social media, or phone recruitment scripts).

3. Describe the nature and frequency of communications with the IRB/IACUC. Determine whether the clinical investigator submitted information promptly to the IRB/IACUC, in compliance with the protocol, IRB/IACUC requirements, and applicable regulations, of all deaths, serious adverse experiences, and unanticipated problems involving risk to subjects or others.

4. Elements of Informed Consent

   For studies involving human subjects, review all approved versions of the informed consent documents and determine the following:

   a. Whether the written consent document(s) or oral consent complies with the eight (8) required elements in 21 CFR 50.25(a).

   b. Whether the written consent document(s) or oral consent complies with the additional elements of informed consent as outlined in 21 CFR 50.25(b). Prior to citing any of these additional elements of informed consent on the FDA 483, the ORA investigator should consult their supervisor and the center POC.

   c. Whether the informed consent document, for applicable clinical studies, includes the statement required by 21 CFR 50.25(c), “A description of this clinical trial will be available on https://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.”

G. SUBJECTS' RECORDS

In general, review subjects' records for completeness, accuracy, and compliance with applicable regulations.[10]

As described in Part III Section B (Inspection Procedures) of this CP, consult your supervisor and the center POC if there are questions related to significant inspectional observations that may have an impact on the safety of study subjects or the accuracy or reliability of the data. If falsification, fabrication or alteration of subjects' records is found during the inspection that may affect data reliability or endanger subject rights, safety, or welfare, immediately discuss the inspectional observations with your supervisor, ORA director of investigations, and the center POC to discuss expanding the scope of the inspection.

For studies involving animal subjects: Although regulatory requirements for studies involving animal subjects differ from studies involving human subjects, evaluate the adequacy of documentation and recordkeeping with the same standard for management of records as required for studies involving human subjects. The clinical investigator is responsible for recording any veterinary care and procedures, changes in animal health, or significant environmental changes.[11]

For all studies inspected:

1. Informed Consent and Assent Documentation and Process

   Review informed consent and assent documentation for all studies involving human subjects per Part III Section F (Institutional Review Board (IRB)/Institutional Animal Care and Use Committee (IACUC)) of this CP. For animal studies, only review if an IACUC requires informed consent of the animal subject's owner or agent of the owner, as current regulations do not require consent.

   The inspection assignment may include specific instructions regarding review of the informed consent process and documentation and the number of informed consent documents to review. Report the total number of subjects' informed consent documents reviewed and the number of subjects' informed consent documents exhibiting any observation, if applicable (e.g., clinical investigator failed to obtain consent from one or more subjects, consent was not obtained prior to subject

[10] Guidance for Industry: E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)
[11] Guidance for Industry (GFI #85): International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH GL9) Good Clinical Practice

enrollment in the study, clinical investigator failed to use the correct informed consent document). Contact your supervisor and the center POC with any questions and expand review of subjects' informed consent or assent documents to determine the extent of the observation.

a. Review the informed consent documents signed by the subjects or subject's legally authorized representative (LAR) (for animal studies, animal subject's owner or agent of the owner), including initial and revised informed consent documents. These may include, but are not limited to, written and electronic records.

   Determine the following:

   i. Whether the correct IRB-approved (or IACUC-approved, if applicable) version of the informed consent document was used for each subject prior to initiation of any study-related procedures and during participation in the study. If there is a question as to whether the correct informed consent document was used, collect a copy of each version of the informed consent document approved by the IRB/IACUC for the study or studies.

   ii. For studies involving human subjects: whether the subject or the subject's LAR signed the informed consent document prior to initiation of any study-related procedures. Describe how the clinical investigator determined that the person signing the informed consent document was the subject's LAR. If someone other than the subject or the subject's LAR signed the informed consent document, determine who signed it and that person's relationship to the subject.

   iii. For studies involving animal drugs: whether the clinical investigator obtained informed consent from each animal subject's owner or owner's agent, before their animal(s) participated in the study; and whether each owner or owner's agent received relevant information regarding such participation from the clinical investigator prior to giving their consent, including information regarding their obligations when animal subjects are housed off-site.

   iv. Determine whether each subject or the subject's LAR was given a copy of the informed consent document, or as appropriate, any revisions requiring reconsenting of the subject.

b. For studies involving human subjects, and for animal studies that an IACUC requires informed consent from the animal subject's owner or owner's agent, review the

process by which informed consent was obtained, and determine the following information:

i. Who (e.g., clinical investigator, nurse, study coordinator, or other study personnel) explained the investigational study and informed consent document to prospective subjects or subjects' LAR and whether the person obtaining informed consent was delegated this task by the clinical investigator;

ii. How and where the informed consent was obtained;

   a. Determine and describe by which means or combination of means informed consent was obtained (e.g., in-person; through electronic messaging, web-based portal, telephone or video conferencing, live chat at the subject's home or another venue where the subject reviews the informed consent document in the absence or presence of the clinical investigator or study personnel);

   b. Determine what other informed consent procedures were carried out specific to the study and the study population (e.g., use of translator or translating services, interactive electronic-based technology);

   c. Determine whether electronic informed consent (eIC)[12] was used to supplement or replace paper-based informed consent processes. If eIC is used, refer to Part III Section I (Electronic Records and Electronic Signatures) of this CP.

iii. Whether informed consent was provided in a language understandable by each subject or LAR;

iv. Whether the clinical investigator (or delegated personnel) was available to answer any questions about the subject's participation in the study during the informed consent process; and

v. If the IRB/IACUC specified any conditions for the informed consent process, determine whether the clinical investigator followed the IRB/IACUC's requirements.

c. For pediatric studies, review assent documents and determine whether assent was

[12] Guidance for Institutional Review Boards, Investigators, and Sponsors: Use of Electronic Informed Consent in Clinical Investigations – Questions and Answers

obtained from the subjects in addition to consent of the parent(s) or guardian(s), if required by the IRB (per 21 CFR 50, Subpart D). Determine whether and how assent was documented (e.g., written assent, or if oral assent is obtained, documented in the subject's study records).

d. For studies involving human subjects: If the short form was used as per 21 CFR 50.27(b)(2), determine whether the informed consent process was appropriately documented, including whether:

   i. The subject or the subject's LAR signed the short form;

   ii. A witness was present and signed the short form and a copy of the summary;

   iii. The person obtaining the consent signed a copy of the summary; and

   iv. Subject's records documented whether a copy of the summary and the short form were given to the subject or the subject's representative.

2. Source Records

   The source records (i.e., initial source of information) generally include original records or certified copies of original records.

   In some cases, data relating to patient health status and/or the delivery of health care collected[13,14] may also be submitted to support a marketing application. The original source of information for such data may include electronic health records (EHR), registries, and information gathered from other sources that inform on health status. If such data is to be reviewed during the inspection, it will be indicated in the inspection assignment.

   Review source records for completeness, accuracy, and compliance with applicable regulations. Report the total number of subjects whose source records were reviewed and specify the types of documents and records reviewed.

[13] 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.

[14] 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).

When data line listings are provided with the inspection assignment for purposes of data verification, review and compare the source records with the data line listings for completeness and accuracy.

If any discrepancies are noted between source documents and data line listings, compare source documents with CRFs for the source of the error and provide documentation in the EIR. Contact your supervisor and the center POC immediately if discrepancies between CRFs and data line listings are observed as this may suggest systemic data management issues. If data line listings are not provided with the inspection assignment, review and compare the original source records with CRFs.

a. Determine and review the original source records (including but not limited to, written and electronic records). Source records may include but are not limited to original records (electronic or paper) and certified copies of original records of clinical findings, inspectional observations, or other study activities used for reconstructing and evaluating the clinical investigation (e.g., case histories, progress notes, hospital or medical chart records, laboratory reports, nursing notes, barn sheets).

b. Describe the process for recording original source data. For source data contained on certified copies of original records, verify that the certified copies have the same attributes and information as the original records and were verified through a validated process or by dated signatures. Determine whether there are written procedures put in place to ensure consistency in the certification process.

c. Describe the clinical investigator's source records in terms of the types of records and their location, organization, condition, and completeness. Evaluate the quality of the records[15] (i.e., attributable, legible, contemporaneous, original, accurate, complete).

d. Determine whether there is adequate documentation to ensure that all subjects were alive and available for the duration of their stated participation in the study.

e. Determine whether the source records document the following:

    i. Subject’s eligibility for enrollment on the study (e.g., inclusion/exclusion criteria);

    ii. Protocol-required study visits and procedures, with attention to primary and key

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

secondary endpoint data, (e.g., efficacy and safety) as described in the inspection assignment;

iii. Any other data pertinent to the conduct of the clinical investigation, including supporting data (e.g., progress notes, hospital or medical chart records, nursing notes);

iv. Administration of investigational product (e.g., route and rate of administration, dose escalation increments, stopping rules);

v. Investigational product accountability; and

vi. Safety monitoring and reporting, including any unanticipated problems involving risk to subjects or others.

f. Determine whether the source records identify study personnel involved in obtaining and assessing data collected at the clinical site, with special attention to primary and key secondary endpoints. If there are any concerns about appropriate delegation, refer to Part III Section C (Authority and Administration) of this CP.

3. Case Report Forms

a. Describe the process for obtaining and recording information in case report forms (CRFs), including:

i. How data were entered into the CRFs, including the source of the information (e.g., manually transcribed from another record, recorded directly onto the CRFs, transmitted from digital health technology or other electronic systems).

ii. If manually entered by study personnel, whether the study personnel were appropriately delegated this task. If there are any concerns about appropriate delegation, refer to Part III Section C (Authority and Administration) of this CP.

iii. Whether corrections were made to the CRF data entries. If corrections were made, determine who made them, the reason(s) for the changes, and whether the clinical investigator was aware of these changes. If records are electronic, refer to Part III Section I (Electronic Records and Electronic Signatures) of this CP.

iv. Determine the status of the CRFs at the time of the inspection (e.g., data entry and query resolutions are ongoing, final changes to the CRFs have been made with final database lock, data entry access to the CRFs is restricted).

b. Verify that the information on the CRFs match the original source records and is complete and accurate, particularly with respect to primary efficacy and safety

endpoints, and to the following study-related procedures listed below.

As described in Part III Section G.2. (Source Records) of this CP, when data line listings are provided with the inspection assignment, review and compare data line listings with source records. If any discrepancies are noted between source documents and data line listings, compare the source documents with CRFs.

i. Subject selection (i.e., inclusion and exclusion criteria)

ii. Required study visits, procedures and evaluations (e.g., efficacy and safety assessments, blinding and emergency unblinding procedures, concomitant therapies and conditions)

iii. Administration of the investigational product

   a. For human drugs and biologics, animal feed, food additives, and tobacco products, key aspects of administration to review may include: dosage, route and rate of administration, frequency of dosage, dose escalation increments, transition to next cohorts, stopping rules and decision making, allocation of responsibilities for decisions with respect to subject dosing and dose escalation; and timely communication of serious adverse findings or deviations related to administration to the sponsor.

   b. For medical devices, key aspects of administration to review include: use according to manufacturer's directions and/or proper surgical techniques, as applicable.

iv. Safety monitoring, including documentation of adverse events (or other treatment-related safety concerns), assessment of the severity of the adverse event and relationship of the adverse event to the investigational product, and any changes to the subject's participation on the study related to the adverse events (e.g., study discontinuation/termination).

H. OTHER STUDY RECORDS

Study-related information may also be recorded in other documents. Determine if the clinical investigator maintains other study-related records (e.g., administrative study files, correspondence files, master subject list, appointment books, sign-in logs, screening lists, and MedWatch forms). Review these records to ensure that all pertinent information was reported to the sponsor.

I. ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES

Electronic systems, electronic records, electronic signatures, and handwritten signatures executed to electronic records used in clinical studies may be subject to regulations found in 21 CFR Part 11, Electronic Records and Electronic Signatures. In general, Part 11 requirements apply to electronic records and electronic signatures and to the electronic systems used in clinical studies to create, modify, maintain, archive, retrieve, or transmit them (e.g., 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) system), 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 the observation on an FDA 483 regarding noncompliance with Part 11, contact your supervisor and the center POC immediately for further guidance.

In general, the Agency intends to exercise enforcement discretion regarding certain Part 11 provisions for validation, record copying, record retention, and audit trails (refer to 21 CFR 11.10(a), (b), (c), and (e), respectively). Therefore, compliance with applicable regulatory requirements on recordkeeping, record copying, and record retention will be evaluated in accordance with appropriate predicate rules (e.g., 21 CFR 312.62, 21 CFR 812.140).

All study records should be evaluated for compliance with applicable regulatory requirements related to recordkeeping, record content, signatures, record retention, and

those related to access to records during an inspection. Refer to Part III Section G (Subjects' Records) of this CP.

If issues such as errors with programming, unblinding, record retention, and/or breach of subject's confidentiality are identified, consult with the center POC.

1. Identify what electronic systems, including software and hardware, are used to produce electronic records and obtain electronic signatures.

    a. Determine whether the clinical investigator utilized an electronic system that is owned and controlled by the clinical investigator or by the clinical site (e.g., EDC system, investigator site file).

    b. Determine if the clinical investigator or the clinical site has standard operating procedures or work instructions on the operational use of the electronic system that may include the following processes:

        i. System setup/installation;

        ii. Electronic system user training;

        iii. System or device operating instructions;

        iv. System security measures (e.g., back-up, firewalls, antivirus and anti-spy software);

        v. Alternative recording methods (in case of system unavailability);

        vi. Access controls and authorization checks for user's actions; and

        vii. Delegated roles and responsibilities of study personnel's use of the electronic system.

    c. Identify who authorizes and provides access to authorized users, how authorized users access the systems (e.g., use of username and password combinations, multifactor authentication, biometrics), and whether access rights (security credentials) are deactivated when a user is no longer involved with the study and communicated to the sponsor or CRO.

    d. Identify the authorized users (e.g., clinical investigator, delegated study personnel, study subject using study-specific mobile technology) of the electronic system or electronic records and determine the extent of their access, privileges, and restrictions (e.g., read-only access to data transmitted directly to the sponsor, CRO

or third-party). Determine whether there are reasons why the clinical investigator and study personnel should not have access to certain electronic data (e.g., potential for unblinding) and identify and document any instances in which the clinical investigator or study personnel had unauthorized access to this restricted information. Document any instances of attempted or confirmed unauthorized access to electronic systems or electronic records (e.g., unauthorized login, shared use of username and/or passwords), and whether the clinical investigator or other study personnel communicated the security breach to the sponsor.

Determine whether those who use the electronic systems are provided training and technical support to perform the specific operations before use, and what training and technical support was provided on an ongoing basis to ensure familiarity with the electronic system and any subsequent changes to the system (e.g., software or system upgrades).

2. Determine what the procedures are for creating, modifying, maintaining, archiving, retrieving, and transmitting electronic data and electronic records via electronic systems.

   a. Determine the location of source data.

   b. Determine the data originator, how electronic data are created, and how data are transmitted to the sponsor, CRO, or other third party, including frequency of data transfer. For example, determine if data are:

      i. Automatically captured electronically from the study subject (e.g., use of mobile app, ePROs or wearables) or transmitted via digital health technology to the clinical investigation site database, electronic health record (EHR) system, third-party database, or EDC system;

      ii. Manually entered into digital health technology by study subject or study personnel (e.g., via use of a mobile app/mobile platform) and electronically transmitted to the clinical investigation site database, EHR system, third party database, or EDC system; or

      iii. Manually entered by study personnel into the clinical investigation site database, EHR system, third-party database or EDC.

   c. Determine how changes or modifications are made to electronic data, including who is authorized to make changes, and determine whether the electronic system has a

means of tracking changes to electronic data, including information regarding the changes or modifications (e.g., date and time stamps, data originator, and reason for change).

d. Assess whether electronic records, source data, and all associated metadata are maintained in a manner that allows for assessment of study conduct and for verification of study data.

e. Determine the process or methods of 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 that the electronic signatures contain the following information associated with the signing:

   i. printed name of the signer;
   ii. date and time when the signature was executed; and
   iii. the meaning (e.g., review, approval, responsibility, authorship) associated with the signature.

f. Determine how the clinical investigator or delegated study personnel reviewed electronic data.

g. Determine the extent of the monitor's access to electronic data (e.g., were printouts or PDFs made of the data, was read-only access provided). If monitors were permitted to enter or modify eCRF data, determine who gave permission and what types of data were entered or modified.

h. Describe backup, disaster recovery, and/or contingency plans to protect against data loss, and whether these were put in use during the course of the investigation.

i. Document any instances in which the electronic system did not function as it was intended for the specific study protocol. Describe error messages or system failures that occurred and whether they were reported to the sponsor or CRO. Describe the corrective actions, if any, that were taken.

J. INTERVIEWS OF SUBJECTS/PERSONNEL

ORA investigators who observe or suspect significant deviations from applicable regulations that may require interviews with subjects or obtaining affidavits (Form FDA 463a) from study personnel (e.g., falsification) will immediately discuss the observation(s) with their supervisor and the center POC. The ORA investigator's supervisor and the center POC will promptly determine whether the ORA investigator should obtain an affidavit and provide any additional direction on appropriate documentation for the observation(s). For guidance, refer to IOM Chapter 5, Establishment Inspections, subchapter 5.2.9, Interviewing Confidential Informants.

K. FINANCIAL DISCLOSURE

For studies involving human subjects:

1. Verify whether and when the clinical investigator and all sub-investigators disclosed information about their financial interests, and the financial interests of spouse(s), and dependent children[16] to the sponsor, as required by 21CFR 54.4(b), 21 CFR 312.64(d), 21 CFR 812.110(d).

2. Determine whether and when the clinical investigator updated the information about such financial interests to report changes that occurred in the value of the financial interests during the clinical investigation or within one year following completion of the study and document the response.

For studies involving animal drugs, financial disclosure is not required.

Contact your supervisor and the center POC regarding any inspectional observations related to financial disclosure prior to citing on an FDA 483. Refer to FDA's Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure for Clinical Investigators.

L. CONTROL OF INVESTIGATIONAL PRODUCT

1. Review records that document shipment, receipt, disposition, return, and destruction of investigational product. Review any written procedures for investigational product accountability and evaluate investigational product accountability to determine

[16] 21 CFR 54.2(d).

compliance with applicable regulations (i.e. 21 CFR 312.62(a) and 21 CFR 812.140(a)(2)). Compare the amount of investigational product shipped, received, used, and returned or destroyed and obtain the information below.

For studies involving animal drugs: if a Notice of Claimed Investigational Exemption (NCIE) has been submitted to FDA, compare and reconcile drug inventory status of the investigational product with the NCIE. CVM will include this information as background materials. If the NCIE was not provided, follow the instructions described below, collect copies of records documenting the receipt and disposition of each investigational product shipment, and describe disposition in the EIR.

2. Determine how the investigational product arrived at the clinical site, and whether shipping records documented shipment dates, batch or lot numbers, and method of shipment to allow for adequate tracking of investigational product batches, shipping conditions (e.g., specific temperature controls), and accountability. Determine who received/accepted the shipment, and whether the shipment package was immediately inspected.

3. Determine how the investigational product was stored upon arrival to the clinical site, and whether the investigational product was stored under appropriate conditions.

4. Determine if the clinical investigator and/or study personnel were to be blinded to the contents of the investigational product, and if so, determine if blinding procedures were appropriately followed.

5. Determine if the investigational product requires preparation (e.g., specific reconstitution fluids and procedures, protection from light) before administration, where the preparation was performed, by whom and how this was documented. For studies involving animals, refer to Part III Section P (Food Animal and Laboratory Effectiveness Studies) of this CP.

6. Determine who is authorized to dispense or administer the investigational product.

7. Determine whether the investigational product was supplied to a person not authorized to receive it.

8. Determine whether the investigational product requires specific conditions for administration and whether such conditions were adhered to (e.g., specific device for infusion, infusion rate or times).

9. Compare the amount of investigational product shipped, received, dispensed, used, and returned or destroyed. Verify the following:

    a. Receipt date(s), quantity received, and the condition upon receipt;
    b. Date(s), subject number, and quantity dispensed;
    c. Date(s) and quantity returned to sponsor; and
    d. If not returned to sponsor, determine if the protocol or study documents outline destruction/disposition of the investigational product and describe the disposition of the investigational product.

10. If the investigational product is a controlled substance:

    a. Determine how it is secured and whether it is securely locked in a substantially constructed enclosure; and

    b. Determine who had access to the investigational product and/or the substantially constructed enclosure as per 21 CFR 312.69.

11. Inspect unused investigational product supplies, if available, and verify that the investigational product was appropriately labeled as per 21 CFR 312.6, 21 CFR 511.1(b)(1), and 21 CFR 812.5. If investigational product is not appropriately labeled, collect a copy or take a photograph of the label or labeling.

12. For studies involving animal drugs: Identify whether additional studies have been or are currently being conducted with the investigational product and determine drug accountability as per above. Obtain copies of final reports for these studies, if available.

M. RECORDS CUSTODY AND RETENTION

1. Determine whether study records are retained in accordance with the protocol and, applicable regulations (i.e. 21 CFR 312.62(c) and 812.140(d) and (e)).

2. Determine whether study records in all formats are stored securely to prevent unauthorized access, destruction, alteration, or removal from the designated storage location. Although there are no regulatory requirements for the nature or condition of the storage location, identify whether the study records are kept in a secure environment (e.g. password/code protected or key-locked rooms, locked file cabinets, fire-protected, protected and controlled access storage limited to authorized study personnel only).

3. Determine how the source records and CRFs are retained by the clinical investigator at the conclusion of the study. For example, determine in what format the electronic data are retained by the clinical investigator and if an electronic copy was provided by the sponsor or CRO. If a copy of the eCRF is provided to the clinical investigator, determine who provided it and how the clinical investigator ensured that the information in the eCRFs is representative of study data. Note, however, that there may be reasons why the clinical investigator should not have access to certain data (e.g., potential for unblinding).

N. REPORTS TO SPONSOR

Determine if required reports such as CRFs, progress reports, final reports, and safety reports (e.g., serious adverse event reports, unanticipated adverse device effect reports), were submitted to the sponsor in accordance with the study protocol and applicable regulations (i.e. 21 CFR 312.64 and 21 CFR 812.150).

Regarding Financial Disclosure reporting, refer to Part III Section K (Financial Disclosure) of this CP.

O. MONITORING

Sponsors may utilize a systematic, prioritized, risk-based approach in monitoring practices appropriate to a given clinical study.[17] No single approach to monitoring is appropriate or necessary for every clinical study. As such, the extent and nature of monitoring may vary.

1. Review monitoring plans/guidelines, if available, and determine whether the sponsor (via their own staff monitors, contracted monitors, or through a CRO) monitored the progress of the study to assure that the clinical investigator complied with the protocol, applicable regulations, and any IRB requirements and conditions. Document the name and address of the entity monitoring the study.

2. Describe any monitoring activities, including frequency, extent, and nature of monitoring (e.g., types of monitoring methods such as on-site, remote and centralized monitoring), that were performed and identify whether a risk-based monitoring approach was utilized. If evidence related to inadequate monitoring of the study is

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

found, collect documentation of this and describe in the EIR.

Examples of monitoring activities include, but are not limited to:

a. Pre-study contacts with the clinical investigator (e.g., who recruited the clinical site, use of a feasibility survey/questionnaire, site selection visits, protocol meetings, pre-study correspondence);

b. Site Initiation Visit (SIV) (e.g., onsite or via conference call, protocol training);

c. Routine monitoring visits (e.g., on-site visits, remote and/or centralized monitoring) throughout the course of the study or studies, and/or closeout monitoring visits. To support inspectional observations, collect copies of any monitoring logs and examples of monitoring visit follow-up letters and communications.

   i. Documentation of monitoring activities including written communications or other communications provided to the clinical investigator (e.g., documented telephone calls, facsimile, e-mail communications, and other electronic communication); and

   ii. Follow-up activities performed by the clinical investigator when the monitor or monitors found deficiencies or recommended changes or corrections (e.g., did the clinical investigator address and resolve the monitor's queries in a timely manner).

3. For sponsor-investigators, determine whether any monitoring was done for the study and, if so, describe as above. Obtain a copy of any written monitoring plan(s) and/or procedures, if available. Identify whether the sponsor-investigator utilized a systematic, prioritized risk-based approach to monitoring clinical studies. Collect copies of correspondence or other documentation that support inspectional observations in accordance with applicable sponsor requirements. Refer to CP 7348.810 Sponsors, Contract Research Organizations and Monitors.

P. FOOD ANIMAL AND LABORATORY EFFECTIVENESS STUDIES

In addition to issuing inspection assignments for companion animal studies, CVM may also issue assignments to cover food animal and laboratory effectiveness studies. The experimental design and the conduct of these studies are different from human and veterinary clinical studies discussed previously in this CP, and therefore, there are some

different considerations when conducting inspections of these studies. For example, these food animal and laboratory effectiveness studies are unique in that animal subjects are enrolled and assigned to study treatments at the same time (synchronously).

Given the unique nature of food animal and laboratory effectiveness studies, it is critically important to review the inspection assignment, which may include additional information regarding acceptable conduct of the study as agreed upon by CVM. As described in Part III Section B (Inspection Procedures) of this CP, contact the center POC prior to the beginning of the inspection to verify the focus and intent of the inspection.

Special instructions will be provided with the inspection assignment. For example, special instructions for food animal studies may include verifying performance characteristics (e.g., weight gain, milk production, feed consumption) used to assess the effectiveness of a new animal drug. The inspection assignment may also include specific instructions for verifying the conduct of studies using animal subjects artificially infected with a parasite for which the investigational product is administered.

In addition to the inspection procedures described throughout this CP, for food animal and laboratory effectiveness studies and other similarly designed synchronous animal studies:

1. Examine the facilities for compliance with the protocol and/or any written procedures (e.g., SOPs). Describe any failure to adhere to the protocol or written procedures and document discrepancies observed. If appropriate, take photographs of the research facilities.
2. Briefly describe the method used to identify animal subjects.
3. Briefly describe the condition of the animal subjects and adequacy of husbandry practices.
4. Determine the number of animal subjects by age, weight, sex, and breed. Compare to the protocol and describe any discrepancies.
5. Document the history of the animal subjects, including any prior and concomitant treatments of other drugs, vaccines, pesticides or other chemicals used on the animals.
6. Determine whether any of the study animals participated in another study. If so, determine and document whether an appropriate wash-out period was observed prior to initiation or after completion of the study.
7. Determine and document when animal subjects started and ended the study.

8. If the clinical investigator generated a final study report, collect a copy.

9. Determine and document whether scientific measurements are made on individual animal subjects or on groups of animals (e.g., herds, pens, or flocks). If measurements are taken on groups, determine whether the clinical investigator maintained records for these groups.

10. For studies involving drugs in animal feeds, review the drug mixing and feed allocation procedures. Determine where on the premises the medicated feed was mixed for the study. If it was performed at another location, document the name and address of the mill utilized. Determine if proper drug mixing procedures were followed and reconcile the amount of feed allocated during the study with the amount of feed mixed for each treatment group. Refer also to Part III Section L (Control of Investigational Product) of this CP.

11. Determine the method used to identify each lot of investigational product (e.g., drug or medicated feed). Determine the number of samples and types of assays run on the finished feed to verify dosage level. If investigational product is available for sampling, contact the center POC to determine if a sample should be collected. Refer to Part III Section T (Sample Collection) of this CP.

12. If the study involves food-producing animal subjects, determine whether the clinical investigator observed the time periods (e.g., withdrawal or discard periods) required for authorization to use edible products from such animals.

13. Reconcile the number of animal subjects allocated to the study with the number of animal subjects that completed, were removed, or died during the study. Describe any differences in the EIR.

14. Examine animal waste/carcass disposal records and determine if the methods of disposal were consistent with any protocol requirements.

15. Determine if the investigational product was used in additional studies. If so, determine drug accountability and obtain copies of final study reports for these studies, if available. Refer also to Part III Section L (Control of Investigational Product) of this CP.

16. Determine whether the clinical investigator has conducted or is conducting any nonclinical animal studies (i.e., studies subject to FDA's Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies requirements at 21 CFR 58), and if so, collect a copy of the master schedule.

Q. DEVICE STUDIES

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, the regulations pertaining to investigational devices do not contain all the provisions of the drug regulations. For example, there is no requirement that an FDA 1572 be used but there is a requirement for a signed Investigator Agreement.

1. Identify whether the clinical investigator has used the investigational product identified in the inspection assignment or any other investigational product under the emergency use or expanded access[18] provisions. If you identify emergency use or expanded access of any investigational product, contact your supervisor and the center POC for further guidance and briefly describe in the EIR.

2. Determine if the clinical investigator is involved in any nonsignificant risk (NSR) studies and, if so, identify these studies as NSR on the list of studies collected from the clinical investigator. Note: Unless FDA made an NSR determination for the study, there must be an NSR determination by an IRB. IRB approval is also required for NSR studies; Refer to 21 CFR 812.2(b)(1)(ii).

[18] Expanded access mechanisms for unapproved devices include emergency use and compassionate use. Emergency use is available when there is a serious disease or condition, no alternative, and no time to obtain FDA approval. Generally, FDA has considered this to be applicable when a patient is at risk for loss of life, limb, or eyesight. Compassionate use is available for a single patient or group of patients that do not meet the study inclusion criteria where there is a serious disease or condition, and no alternative. Patient protection measures are the same for both: informed consent, IRB/chairperson's approval; independent assessment; and institutional clearance. Compassionate use of a device under an approved IDE requires submission of an IDE supplement requesting approval of a deviation from the study protocol. 21 CFR 812.35(a). Refer to Expanded Access for Medical Devices.

3. Determine if the clinical investigator has been involved in any use of a custom device.[19] If so, first make sure the device meets the definition of a custom device (21 CFR 812.3(b)). Contact your supervisor and the center POC for further guidance and briefly describe in the EIR.

4. Determine if the clinical investigator has utilized a Humanitarian Use Device (HUD)[20] as provided by 21 CFR 814, Subpart H. If so, contact your supervisor and the center POC for further guidance.

R. ESTABLISHMENT INSPECTION REPORTS

The establishment inspection report (EIR), a detailed narrative with attachments and exhibits, and any related post-inspectional correspondence, are important in the decision-making process for research and marketing applications/submissions, general surveillance, and for evaluation of referrals (e.g., complaints, reports of noncompliance). Therefore, the EIR must clearly and completely document all inspectional observations that may have impact on the decision-making process. The endorsement to the EIR should provide a summary of the major inspectional observations.

The EIR package consists of the following: eNSpect cover sheet with endorsement, EIR narrative report, attachments, and exhibits.

Refer to IOM Chapter 5, Establishment Inspections, subchapter 5.10, Bioresearch Monitoring (BIMO), as well as subchapter 5.11, Reporting, for guidance on reporting inspectional findings.

The EIR for a clinical investigator inspection requires detailed information for every subsection listed below. ORA investigators are encouraged to add additional report headings as needed to communicate important information about the inspection, including relevance of inspectional observations that may impact public health, and/or to address specific instructions in the inspection assignment.

Required EIR elements:

[19] A custom device is a device that has been custom developed for use by an individual patient under the order of a physician or dentist; or is intended to meet the needs of a physician or dentist in the course of professional practice. Refer to 21 CFR 812.3(b) for a complete definition of custom device.
[20] A Humanitarian Use Device (HUD) 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).

- Summary
- Administrative Data
- History
- Interstate (I.S.) Commerce
- Jurisdiction
- Individual Responsibility and Persons Interviewed
- Clinical Site Training
- Authority and Administration
- Protocol
- Institutional Review Board (IRB)/Institutional Animal Care and Use Committee (IACUC)
- Subjects' Records
- Other Study Records
- Interviews of Subjects/Personnel
- Financial Disclosure
- Electronic Records and Electronic Signatures
- Control of Investigational Product
- Records Custody and Retention
- Reports to Sponsor
- Monitoring
- Animal Clinical Studies (as applicable)
- Device Studies (as applicable)
- Objectionable Conditions and Management's Response
    - Supporting Evidence and Relevance
    - Discussion with Management
- Refusals
- General Discussion with Management
- Additional Information
- Samples Collected
- Voluntary Corrections
- Exhibits Collected
- Attachments

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

S. INTERNATIONAL INSPECTIONS

1. Inspections of Clinical Investigators by Foreign Regulatory Authorities

   Regulatory authorities from countries in the European Union (EU) or other countries (e.g., United Kingdom's Medicine and Healthcare products Regulatory Agency [MHRA], Japan's Pharmaceutical and Medical Devices Agency [PMDA], Health Canada) may also conduct inspections of domestic or foreign clinical sites. On occasion, FDA may decide to observe these inspections or to conduct a joint inspection.

   If the ORA investigator becomes aware that a clinical site, domestic or foreign, 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. Inspections of Foreign Clinical Investigators

   As described in Part III Section B (Inspection Procedures) of this CP, the center POC provides background information and special instructions with the inspection assignment to the ORA BIMO international work planner via email at ORA BIMO FDA International BIMO, who will in turn provide these to the ORA investigator at the time of assignment. Contact the center POC prior to the beginning of the inspection to verify the focus and intent of the inspection. The ORA BIMO international work planner preannounces the inspection to the clinical investigator during the scheduling process; the ORA investigator will not need to preannounce. The ORA Division of Travel Operations (DTO) trip coordinator is responsible for coordinating the travel logistics and translation services. The ORA investigator is responsible for completing any necessary travel documentation (e.g., passport and visa applications, traveler profile).

   Consider the following when inspecting foreign studies:

   a. Inspections of Foreign Clinical Investigators – Human Drugs and Biologics

      When inspecting a clinical study conducted at a foreign clinical site, first confirm whether the clinical site conducted the study under a US IND.

Inspections of clinical studies conducted at foreign clinical sites, whether or not conducted under IND, should be conducted as usual following the instructions in Part III (Inspectional) of this CP.

i. Foreign studies not conducted under an IND

When a clinical study 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 Good Clinical Practice (GCP) and if FDA is able to validate the data from the study through an onsite inspection, if necessary.[21] The GCP requirements at 21 CFR 312.120 help ensure that studies conducted at foreign clinical sites not under IND are conducted in a manner comparable to that required for IND studies.

Per 21 CFR 312.120(b), if the inspection involves a clinical study conducted at a foreign clinical site that is not under an IND, the sponsor is required to submit documentation to FDA that may also need to be verified on-site during the inspection. 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 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 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:

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

a. A sponsor wishing to conduct a foreign study under an IND may seek a waiver of the IRB requirements so that it may conduct the study using an Independent Ethics Committee operating in accordance with GCP.[22,23]

b. A sponsor may also seek a waiver from the FDA 1572 signature requirement for clinical investigators at foreign clinical sites conducting studies under IND.[24] 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 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.

Upon arrival at the inspection site determine whether FDA has granted a waiver of the requirements for studies conducted at foreign clinical sites under an IND. Except to the extent the waiver applies, conduct the inspection as usual following the instructions in Part III (Inspectional) of this CP. If available, 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.

b. Inspections of Foreign Clinical Investigators – Devices

Effective February 21, 2019, 21 CFR 812.28 imposed new regulatory requirements for FDA acceptance of clinical data from foreign clinical 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 February 21, 2019 (as indicated by the first subject

[22] Information Sheet Guidance for Sponsors, Clinical Investigators and IRBs: Waiver of IRB Requirements for Drug and Biological Product Studies.
[23] Information Sheet Guidance for Sponsors, Clinical Investigators and IRBs: Waiver of IRB Requirements for Drug and Biological Product Studies Frequently Asked Questions – Statement of Investigator (Form FDA 1572).
[24] Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions – Statement of Investigator (Form FDA 1572)

signing informed consent documents) would be subject to the requirements under 21 CFR 812.28.[25]

Clinical studies that began before the effective date of February 21, 2019, would be subject to the prior version of 21 CFR 814.15[26]:

> For clinical studies conducted wholly or in part OUS and began prior to 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 studies 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.

[25] 83 FR 7366 at 7368, February 21, 2018
[26] Id.

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

3. Translation to English Language

For clinical studies where study-related documents are not in English and/or the study personnel may be non-English speaking, having an independent qualified translator present during the inspection is necessary to explain and assist inspectional procedures (e.g., interviews, affidavits) and to translate study records in foreign languages. Translation services will be arranged prior to the inspection by the ORA Division of Travel Operations (DTO) trip coordinator.

View the records with the translator present to assist in requesting and verbally translating the records. If study records used to document cited FDA 483 inspectional observations are in a foreign language, request handwritten translations of the study records. Request the specific language supporting the observation be translated directly onto the exhibit, if possible, as long as the translation does not obscure any original source data. In most cases, such translation need not be more than the sentence or two that relates directly the observation. Request the signature of the translator and date of translation be placed on the translated document.

T. SAMPLE COLLECTION

Collect samples of the investigational product during clinical investigator inspections only if directed by the center. For instance, the center may request samples of an investigational product (usually one (1) package of each investigational product) to be collected if irregularities in the product are suspected (e.g., if, in an investigational drug study, there is a noticeable difference in color, size, shape, dosage form, route of administration, etc.,

between the investigational drug and the placebo or control). Contact your supervisor and the center POC prior to collecting a sample.

PART IV - ANALYTICAL

Centers will provide specific instructions if sample analysis of investigational product is needed. Contact your supervisor and the center POC for additional guidance. Refer to Part III Section T (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) to determine the ORA BIMO division recommended classification and center final classification of inspections of clinical investigators.

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 the Agency 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 clinical investigator 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 BIMO 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 also responsible for drafting, developing, and issuing all regulatory and enforcement letters for OAI inspections. Post-inspectional correspondence for VAI inspections may identify significant issues and, when needed, state that FDA expects prompt, voluntary corrective action by the clinical investigator. 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 applicable regulations. FDA can invoke other legal

sanctions under the Federal Food Drug and Cosmetic Act (FFDCA) and/or Title 18, U.S.C., where appropriate. FDA may pursue the following based on inspectional observations:

1. An Untitled Letter (UL) may be considered when the violations 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 clinical investigator (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. A Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) may be considered when the inspectional findings meet the criteria for OAI above, indicating that a clinical investigator has:
    a. Repeatedly or deliberately failed to comply with the requirements of 21 CFR 312, 511, and/or 812, as appropriate, and/or 21 CFR 50 or 56; or
    b. Repeatedly or deliberately submitted false information to FDA or to the sponsor in any required report.
4. Rejection of data
5. Seizure of investigational product
6. Injunction
7. Civil Money Penalties
8. Prosecution under the FFDCA 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, withdrawal of approval of IDE application for studies subject to 21 CFR 812, regulatory meetings, device detention) based on the inspectional observations. Refer to FMD-86 (Establishment Inspection Report Conclusions and Decisions) and Regulatory Procedures Manual (RPM).

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

For sponsor-investigators, additional administrative/enforcement actions that may be applicable. Refer to Sponsors, Contract Research Organizations and Monitors Compliance Program (CP 7348.810).

Follow-up Inspections:

1. ORA BIMO 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 (e.g., IRB, sponsor, CRO, monitor, other clinical investigators).

2. Following the issuance of a Warning Letter, centers should periodically review their clinical investigator databases for entries indicating that a Warning Letter recipient is actively conducting other clinical studies. If such entries are found, the center should issue a follow-up inspection assignment to verify the clinical investigator is fulfilling the terms of any corrective action plans and complying with applicable human subject protection and GCP regulations.

PART VI – REFERENCES AND PROGRAM CONTACTS

A. References

1. FDA Laws

   Federal Food Drug and Cosmetic Act (FFDCA)

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 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 71	Color Additive Petitions
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 or Antibiotic Drug
Part 514	New Animal Drug Applications
Part 570	Investigational Use of Food Additives (Animal Feed and Pet Food)
Part 601	Licensing (Applications for FDA Approval of a Biologic License)
Part 814	Premarket Approval of Medical Devices
Part 1100	Tobacco Products

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.

Guidance documents, including information sheets, and notices pertaining to good clinical practice (GCP) and the conduct of clinical studies are accessible on FDA's website at this link: Guidance Documents (Including Information Sheets) and Notices. (This is a limited list. All guidance documents and information sheets can be found here under the topic of "Good Clinical Practice (GCP)".)

Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors: FDA Inspections of Clinical Investigators. June 2010.

Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions – Statement of Investigator (Form FDA 1572). May 2010.

Compliance Policy Guides (CPG)

Compliance Policy Guide (CPG) Section 120.100. Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities. July 1991.

Compliance Policy Guide (CPG) Section 130.300. FDA Access to Results of Quality Assurance Program Audits and Inspections. June 2007.

Memoranda of Understanding

MOU 225-82-8400: FDA's continuing MOU with the Veterans Administration (VA)

MOU 225-16-010: FDA's continuing MOU with the USDA Animal and Plant Health Inspection Service (APHIS) and NIH Office of Laboratory Animal Welfare (OLAW)

Electronic Systems and Data

Guidance for Industry: Use of Electronic Health Record Data In Clinical Investigations. July 2018.

Guidance for Institutional Review Boards, Investigators, and Sponsors: Use of Electronic Informed Consent Questions and Answers. December 2016.

Guidance for Industry: Electronic Source Data in Clinical Investigations. September 2013.

Guidance for Industry: Computerized Systems Used in Clinical Investigations. May 2007.

Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application. August 2003.

General Principles of Software Validation; Final Guidance for Industry and FDA Staff. January 2002.

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. August 2017.

Framework for FDA's Real-World Evidence Program. December 2018.

B. Program Contacts

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

2. For operational questions, contact:

   Office of Regulatory Affairs (ORA)
   Office of Medical Products and Tobacco Operations (OMPTO)
   Office of Bioresearch Monitoring Operations (OBIMO)
   ORA BIMO Inspection POC

3. 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 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 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 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

4. For crosscutting questions about GCP policy and program issues impacting the Agency's BIMO Programs for GCP, or suggestions to improve this CP, contact:

   Office of Good Clinical Practice (OGCP)
   Office of Clinical Policy and Programs (OCPP)
   (301) 796-8340, FAX (301) 847-8640
   gcp.questions@fda.hhs.gov

5. For information about inspection warrants and final issuance of Notice of Opportunity of Hearing (NOOH) letters for clinical investigator disqualifications, 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 - CENTER RESPONSIBILITIES

A. CENTERS

Center Personnel:

1. Identifies the clinical investigators to be inspected (from information in research or marketing applications), issues inspection assignments with background materials (e.g., protocols, correspondence, data line listings) to ORA.
2. Communicates specific concerns, if any, to the ORA investigator prior to inspection.
3. Addresses inquiries regarding clinical investigator inspection assignments and compliance issues.
4. Participates in 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 BIMO divisions.
7. Submits regulatory recommendations 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 clinical investigator and FDA to the ORA BIMO division.
12. Notifies center review divisions, as appropriate, of significant violations.

B. OFFICE OF REGULATORY AFFAIRS

1. OFFICE OF BIORESEARCH MONITORING OPERATIONS (OBIMO) Headquarters

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

    b. Maintains liaison with centers, ORA BIMO divisions, and OGCP, and resolves operational questions.

    c. Receives and reviews all clinical investigator inspection assignments from the centers via ORAHQ BIMO Inspection POC email (domestic inspections) or ORA BIMO FDA International BIMO email (foreign inspections) 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.

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. For disqualification actions, reviews and issues the Notice of Opportunity of Hearing (NOOH) letter with the signature of the Associate Commissioner for Regulatory Affairs (ACRA), and coordinates actions related to the clinical investigator's initial response to the NOOH.

    c. Reviews and issues Notice of Noncompliance Letters related to ClinicalTrials.gov with the signature of the 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

1. Coordinates cross-cutting clinical BIMO policy program activities.
2. Provides expert technical guidance, advice, information, interpretation, and analysis relevant to FDA's human subject protection and GCP 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 of Human Research Protections, VA) for coordination of clinical BIMO and human subject protection issues.