CHAPTER 48: Bioresearch Monitoring

SUBJECT: Institutional Review Boards	IMPLEMENTATION DATE: 09/26/2018
DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
FACTS/eNSpect does not require product codes for Bioresearch Monitoring inspections.	09809: Foods
	41809: Biologics- Human Cellular, Tissue and Gene Transfer
	42809: Biologics- Blood and Blood Products
	45809: Biologics- Vaccines and Allergenic Products
	48809: Human Drugs
	83809: Medical Devices
	98809: Tobacco Products

FIELD REPORTING REQUIREMENTS:

Copies of all establishment inspection reports (EIRs) complete with attachments, exhibits, and any related correspondence are to be submitted promptly to the Center (usually the reviewer in the Center's Bioresearch Monitoring (BIMO) program identified in the assignment).

All EIRs should be completed in accordance with FMD No. 86, Establishment Inspection Report (EIR) - Inspection Conclusions and District Decisions (https://www.fda.gov/downloads/ICECI/Inspections/FieldManagementDirectives/UCM382035.pdf) and the Investigations Operation Manual (IOM), Chapter 5, Establishment Inspections. (http://www.fda.gov/downloads/ICECI/Inspections/IOM/UCM150576.pdf).

When a Form FDA 483, "Inspectional Observations" (483), is issued, a copy should be forwarded to the Center contact (by facsimile or e-mail, or filed in a shared folder, as agreed to with the Center), as soon as possible, generally within 3 business days after being issued.

Contents

Change History

Item	Change	Date
Update	Updated administrative, organizational and computer systems information	04/16/2018
Update	Updated VA address for notification to remove Suite 574 at their request.	09/26/2018

PART I – BACKGROUND

Since the Investigational New Drug (IND) Regulations went into effect in 1963, the Food and Drug Administration (FDA) has exercised oversight of the conduct of clinical studies involving FDA-regulated products. The Bioresearch Monitoring Program (BIMO) was established in 1977 by a task force that included representatives from the drug, biologic, device, animal drug, and food areas.

Compliance programs (CP) were developed to provide uniform guidance and specific instructions for inspections of Clinical Investigators (CP 7348.811), Sponsors (CP 7348.810), In-Vivo Bioequivalence facilities (CP 7348.001), Institutional Review Boards (CP 7348.809), and Nonclinical Laboratories (CP 7348.808).

The Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act (the FD&C Act) increased FDA's regulatory authority over the clinical testing of new drugs. With the passage of the Kefauver-Harris Amendments, the Medical Device Amendments of 1976, and other legislation, FDA has been provided additional safeguards to protect the rights, safety and welfare of human subjects who participate in investigational trials involving FDA-regulated articles.

Congress has given a mandate to institutional review boards (IRBs) to oversee research involving human subjects that is being conducted using FDA-regulated articles. FDA has published regulations that set forth standards and procedures for IRBs in 21 CFR Part 56, which became a final rule in the Federal Register (FR) on January 27, 1981 (46 FR 8958 – "Protection of Human Subjects; Standards for Institutional Review Boards for Clinical Investigators"). The requirements for informed consent, which are found in 21 CFR Part 50,[1] were published as a final rule in the Federal Register (FR) on the same date (46 FR 8942, January 27, 1981; "Protection of Human Subjects; Informed Consent").

The above regulations require IRB review of all clinical investigations using test articles regulated by FDA under sections 505(i) and 520(g) of the FD&C Act, as well as clinical investigations conducted in support of applications for research or marketing permits for other articles regulated by the agency. The rewrite of the investigational new drug (IND) application regulations on March 19, 1987, includes informed consent and IRB review as conditions for exempting from the IND requirements certain studies involving marketed drugs (21 CFR 312.2(b)(1)(iv)). Similar conditions are included in the IDE regulations (21 CFR 812.2(b)) for abbreviated requirements of certain categories of device investigations.

On June 18, 1991, the Federal Policy for the Protection of Human Subjects; Final Rule (Common Rule) was published in the Federal Register (FR) (56 FR 28003). [2] These regulations set forth requirements for the protection of human subjects involved in

[1] www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm113818.htm
[2] www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm118862.htm

research conducted or funded by 15 Federal departments and agencies, including the Department of Health and Human Services (DHHS). In the same issue of the FR (56 FR 28025), amendments to the FDA regulations on IRBs and on informed consent requirements were published; these amendments bring 21 CFR Parts 50 and 56[3] into conformity with the above Federal Policy. Existing FDA regulations governing the protection of human subjects share a common core with the Federal Policy, and implement the fundamental principles embodied in that policy. The Federal Policy and the FDA amendments of 21 CFR Parts 50 and 56 became effective on August 19, 1991.[4]

Please note that there are some differences between the Department of Health and Human Services (DHHS) human subject protection regulations found at 45 CFR 46 and the FDA human subject protection regulations found at 21 CFR Parts 50 and 56. IRB written procedures that are compliant with the DHHS requirements will not necessarily be compliant with FDA regulations, i.e., IRBs that are subject to 45 CFR Part 46 will need to ensure that their SOPs are in compliance with both sets of regulations. FDA inspections, however, should only focus on FDA's regulations.

[3] www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm118296.htm

[4] http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm118893.htm

PART II - IMPLEMENTATION

1. **Objective**

The objectives of the BIMO Program are:

A. To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials;
B. To verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications; and
C. To assess compliance with FDA's regulations governing the conduct of clinical trials.

The purpose of this compliance program is to provide instructions to the field and Center personnel for conducting inspections of IRBs and recommending associated regulatory and/or administrative actions.

2. **Program Management Instructions**

A. Coverage -- This program provides for the inspection of domestic IRBs that review and approve investigational studies involving human subjects and FDA-regulated articles (e.g., drugs including biologics, food or color additives, and medical devices).

B. Types of IRBs -- There are many types of IRBs. They can be categorized as government, independent, hospital, academic, or central.

C. Due Dates -- All assignments will be issued by the Centers and will have a ninety (90) day completion date unless otherwise indicated.

D. Centers should give consideration to the following factors when selecting IRBs for inspection:

i. IRBs for which the previous inspection was classified Official Action Indicated (OAI) (e.g., sanctions imposed, Warning letter issued). These IRBs should be re- inspected within one year (i.e., soon after the last Warning Letter correspondence was issued);
ii. IRBs that have never been inspected before; and
iii. IRBs that were recently established or have limited experience reviewing FDA- regulated research (for example, an IRB that previously only reviewed social behavioral research begins to review investigations of FDA-regulated articles).

E. Centers may pursue special IRB inspection initiatives, for example, inspecting IRBs that review particular types of studies, such as first-in-human trials, studies involving an exception from informed consent, or studies involving vulnerable populations (e.g., Alzheimer's patients, pediatric populations). Any unique focus of an inspection will

generally be discussed in the assignment.

3. **Types of Inspections**

FDA will periodically inspect each IRB that reviews research involving FDA-regulated articles. The inspections will be either routine or directed.

A. Routine Inspections

The assigning Center will provide evidence of FDA jurisdiction over the IRB by consulting the IRB Registration database maintained by the Office for Human Research Protections (OHRP) for the name and address of the institution, and when available, the name of a contact person at the IRB. The assigning Center may provide a specific protocol to review during the inspection, when available.

Those IRBs found to have no objectionable conditions (NAI classification) or objectionable conditions that do not meet the threshold for regulatory action (VAI classification) will usually be assigned for reinspection in 5 years.

B. Directed Inspections

A directed inspection may be assigned when the assigning Center receives information that calls an IRB's practices into question. A directed inspection may be limited to one area of concern or assigned to cover the entire compliance program.

IRBs found to have major deficiencies (OAI classification) will usually be assigned for reinspection within one year to confirm that adequate corrections have been made.

C. Inspection Assignments

i. Center BIMO units issue inspection assignments of IRBs. The Centers will identify IRBs to be inspected from sources such as the IRB's Official Establishment Inventory (OEI) file maintained by ORA BIMO Division offices, Center files (including complaints), the IRB Registration database[5] maintained by the Office for Human Research Protections (OHRP), Web searches, journal articles, research permits, and marketing applications submitted to the Center.

[5] https://ohrp.cit.nih.gov/search/irbsearch.aspx?styp=bsc

ii. To ensure the appropriate and efficient use of FDA resources, IRB assignments will follow Field Management Directive (FMD) No. 17, ORA Field Assignments - Guidelines for Issuance by Headquarters, whether from an ORA headquarters unit or a Center. (http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/UCM056651).

iii. The assignment should identify:

a. The program assignment code (PAC), Field Accomplishments and Compliance Tracking System (FACTS) number or eNSPect number, and Firm Establishment Identification (FEI) number, if known;

b. The name, address and phone number of the IRB, when available, to be inspected;

c. The type and purpose of the inspection (e.g., routine or directed inspection). Occasionally, some Centers will designate sub-types (e.g., Surveillance, For Cause, Complaint, or OAI follow-up);

d. The background materials that are being sent from the Center to facilitate the inspection (e.g., information obtained from OHRP's IRB registry);

e. Specific issues or concerns (if applicable) that need to be addressed during the inspection;

f. The due date for the Center contact to receive the completed EIR;

g. The headquarters address where the EIR should be sent; and

h. The name, telephone number, fax number, and email of the Center contact(s).

Note: For any inspection attempt where it is determined the IRB is out of business or it is been determined that FDA does not have jurisdiction (e.g., IRB is not reviewing FDA-regulated studies), please contact the Center that issued the assignment in order to discuss converting the inspection request (Operation 12) to an Operation 13 designation.

iv. Inspection of the Department of Veterans Affairs (VA) as the IRB of FDA-regulated clinical trials.

a. Pre-Inspection

1. **Center.** The BIMO unit in the assigning Center will provide the VA's office of Research Oversight (ORO) with written notification of FDA's intention to inspect a VA IRB program at the time an assignment is being issued to the field. Information on the VA's ORO is at: http://www.va.gov/ORO/about_us.asp#sthash.ABGMdXOR.dpuf.

The notice should be sent to:

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

2. **Field.** The field investigator will contact the VA IRB program before the inspection, as they would any other IRB they are assigned to inspect.

b. Post-Inspection

1. The Center will provide the VA's ORO redacted copies of post-inspection correspondence issued to VA IRB programs that include a discussion of deficiencies noted during the inspection (including the Form FDA 483). Such materials should be sent to:

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

c. If, following receipt of the FDA correspondence, the VA-ORO requests a copy of the EIR, a redacted copy of the report will be provided to VA-ORO by the ORA BIMO Division offices.

v. All headquarters and field personnel who become aware of complaints or problems related to an IRB are encouraged to refer them to the

appropriate Center contact with a recommendation for inspection. All recommendations should include the following:

a. The name and address of the IRB;
b. If available, the name(s) of the test article(s) being investigated, and the application for research or marketing permit number(s); and
c. The basis for the recommendation and any relevant documentation.

4. **Communication between the Centers and the ORA BIMO Divisions**

Inspectional observations documenting that an IRB is not operating in compliance with the regulations in 21 CFR Parts 50 and 56 may be used as evidence for taking appropriate administrative and/or enforcement actions. Ensuring that the evidence collected to support such actions is both appropriate and adequate requires that communication lines between the ORA BIMO Division offices and the Center be established early and maintained throughout the entire process, i.e., until post-inspectional correspondence is issued by the Center.

i. Prior to an inspection

a. The Center issues an assignment that includes contact information for the BIMO reviewer.

b. The field investigator contacts the BIMO reviewer:

1. Upon receipt of the assignment, to establish initial contact and/or provide an inspection start date;
2. When the inspection date is firmly set, to alert the BIMO reviewer and/or a back-up to be available and to establish the most appropriate means of contact for both the investigator and the BIMO reviewer/back-up;
3. To obtain any new information that may change the focus of the inspection; and
4. To coordinate inspection arrangements if Center personnel plan to participate in the inspection.

ii. Special Considerations

a. In particular cases, the Center may arrange for a consultative teleconference immediately prior to the inspection(s) if, for example, the complexity of issues, urgency of feedback, compliance history, etc., trigger the need to discuss issues further. Such conference calls are most likely when the agency encounters special situations (e.g., directed inspections where pertinent information is either complex or needs discussion between the Center and the field). Unless information necessitating this discussion emerges after the assignment is issued, the assignment will usually include information as to when this teleconference will occur.

b. These teleconferences may include the following participants, as warranted and feasible:

1. BIMO reviewer (and supervisor/division director or other staff, as appropriate);

2. Lead application reviewer (along with branch and division chiefs, if appropriate) or other application reviewers as needed; and

3. ORA Field investigator(s) assigned to the inspection(s), the ORA BIMO Program Expert (PE) (when not yet specifically assigned), and ORA BIMO management and staff, as appropriate.

iii. During an Inspection

a. The BIMO reviewer contacts the field investigator if significant new information becomes available.

b. The field investigator contacts the BIMO reviewer or designated back-up person if the field investigator:

1. Needs advice or clarification. The BIMO reviewer and field investigator should strive to be accessible to one another as much as possible during the time that the inspection is ongoing.

2. Uncovers other evidence of concern warranting discussion with Center staff.

iv. After an Inspection

a. As soon as possible but within three (3) business days after conclusion of the inspection, the field investigator forwards to the BIMO reviewer (by facsimile, e- mail, or placement in the appropriate shared drive folder) any Form FDA 483 (commonly referred to as a “483”) that is issued.

b. The field investigator/ORA BIMO Division will forward as soon as possible to the BIMO reviewer a copy of any written response to the 483 by the inspected party. The BIMO reviewer will forward to the field investigator, a copy of any response to a 483 that does not appear to have been shared with the inspecting ORA BIMO Division. If desirable, the field investigator provides Center contact information so that the response to the 483 can be sent directly to the Center for review in addition to sending it to the field inspector/ORA BIMO Division.

c. The BIMO reviewer consults with the field investigator and their supervisor as needed when reviewing the EIR.

d. If the Center’s final classification is different from the one recommended by the field, the Center should ensure that ORA BIMO Division personnel are aware of the change and reasons for the change. The Center promptly forwards to the field investigator and other appropriate ORA BIMO Division management by e-mail, if possible, copies of post-inspectional correspondence issued to the inspected party.

e. The Center enters the final classification.

5. **Responsibilities of Field Investigators, Inspection Team Leaders, and Headquarters Participants**

i. Solo inspections

When conducting solo inspections, the field investigator’s responsibilities include, but are not limited to, the following:

a. Scheduling and conducting the assigned inspection;

b. Discussing with ORA BIMO Division management the need to adjust the workload in order to meet specific deadlines or goals (e.g., goals established as part of the Prescription Drug/Medical Device User Fee Acts);

c. Communicating inspectional observations with the institutional officials and IRB staff during the course of the inspection, as appropriate;

d. Communicating inspectional observations and issues with the Center contact during the course of the inspection and review, as appropriate;

e. Preparing, issuing, and discussing the items listed on the 483 with the IRB at the close of the inspection;

f. Preparing and submitting an EIR within FDA timelines; and

g. When appropriate, participating in discussions with the Center regarding potential changes in the EIR classification.

ii. When conducting team inspections

When inspections are conducted by a team, a field investigator serves as inspection Team Leader who is responsible for the cooperative conduct of the inspection. The Team Leader's responsibilities include, but are not limited to the following (see also Investigations Operations Manual (IOM) at http://www.fda.gov/ICECI/Inspections/IOM/default.htm, Chapter 5, section 5.1.2.5- Team Inspections):

a. Scheduling and coordinating the participation of team members;

b. Discussing inspection plans and objectives with team members;

1. Assuring that team members understand their roles and responsibilities in conducting the inspection, taking

notes, collecting documentation, preparing sections of the inspection report and exhibits, and signing the report;

c. Setting team policy regarding communications with institutional officials and/or the IRB staff;

d. Discussing personal conduct with team members as necessary; and

e. Resolving disputes or differences of opinion among team members, including items to be listed on the 483. If an agreement cannot be reached during the inspection, the final items included on a 483 will be decided by the ORA field investigator.

iii. Headquarters Participants

A headquarters participant is a member of the inspection team who serves in a compliance or scientific advisory capacity to the Team Leader. The headquarters participant's responsibilities include, but are not limited to, the following:

a. Obtaining training on inspection conduct and behavior prior to participating in inspections;

b. Obtaining inspection credentials from the FDA Office of Security Operations by completing Form FDA 2115) available at
i. http://inside.fda.gov:9003/downloads/Administrative/Forms/FDA/UCM030799.pdf;

c. participate in field inspections and submitting the completed Inspection Participation Request Form;

d. Providing information pertinent to the inspection;

e. Attending pre-inspection discussions, if and when requested by the Team
i. Leader;

f. Participating in the on-site inspection as permitted by agency priorities; and

g. Providing guidance and expertise during the inspection and completing inspection tasks as directed by the Team Leader (e.g., auditing documents, preparing inspection notes and specific sections of the establishment inspection report within guidelines and timeframes).

6. **Resolution of Disagreements**

If there is disagreement among members of the inspection team, the issue should be discussed off-site and resolved cooperatively. Any difficulties in conducting team inspections should be discussed with both ORA BIMO Division management and the assigning Center, and, if not resolved, immediately referred to the ORAHQ BIMO Inspection POC.

PART III - INSPECTIONAL

1. **Operations**

ORA BIMO Divisions are encouraged to identify IRBs that have not been recently inspected (e.g. no inspection within the past 5 years). The ORA BIMO Division should make efforts to determine the type of studies that are being reviewed by the IRB and notify the program contact for the appropriate Center.

Inspections involve an evaluation of the IRB's written procedures and records to determine the IRB's compliance with 21 CFR Parts 50 and 56. In general, assignments are issued from Headquarters and may identify several studies (generally no more than three) for inspection (in order to establish that FDA-regulated research has been reviewed by the IRB). The field investigator should evaluate these studies during the inspection unless otherwise directed by the assignment.

A. Criteria for Selecting Studies

If the assignment does not specify specific studies for inspection, the field investigator should select studies that reflect current IRB practices, preferably ones that were initially approved within the previous three years and are presently ongoing. Additionally, it might be beneficial for the field investigator to choose one study that has been through a continuing review cycle. Generally, the studies should be selected using the following priority:

i. Studies specified in the inspection assignment, if any;
ii. Studies employing novel regulatory mechanisms, such as exploratory IND studies[6], or involving cutting edge technologies (e.g., cell, gene, and tissue-based therapies);
iii. Studies involving vulnerable populations (e.g., pediatric studies, studies involving an exception from informed consent under 21 CFR 50.24);
iv. Device studies that involve the IRB's determination as to whether a device study is significant risk (SR) or non-significant Risk (NSR);
v. Other safety and efficacy studies of investigational new drugs, devices and/or biologics performed under IND, IDE, or Biologic-IND applications;
vi. Studies where privacy/confidentiality protections may be of particular concern (e.g., HIV studies, etc.);
vii. Studies for which no FDA research permit is required, e.g., certain marketed drugs and non-significant risk devices; and
viii. Comparison studies of one or more marketed products with an investigational product.

[6] www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078933.pdf

B. Time Period

Selection of studies reviewed by the IRB during the 3 years prior to the inspection would generally assure that the IRB's records for those studies (e.g., meeting minutes, membership rosters, continuing review records) are available and that the inspection covers the IRB's "current" review procedures and practices. However, if an IRB has revised its written procedures within the past 3 years, only studies reviewed by the IRB since the date the procedures were revised should be included in the inspection in order to avoid citing the IRB for procedures that are no longer applicable. For very small IRBs that presently have no active FDA-regulated protocols, the field investigator may need to evaluate protocols that have been closed within the last 3 years.

If an IRB inspection assignment includes studies that are linked to specific marketing applications or studies that have been placed on clinical hold, and which were reviewed prior to a revision in the IRB's procedures, the field investigator should consult with the Center as to whether a particular study should be included in the inspection

2. **Reporting**

A. The ORA BIMO Divisions are responsible for conducting inspections and preparing EIRs. All reports, including copies of exhibits, are to be submitted directly to the Center initiating the assignment.

B. When a duplicate IRB assignment has been issued or an inspection was recently completed, ORA BIMO Divisions should contact the assigning Center for instructions prior to initiating the inspection.

C. The EIR should contain the headings as prescribed in the Investigations Operations Manual (IOM). [7] Centers encourage submitting electronic inspectional documents, if possible. Any adverse findings should be fully explained and documented in the EIR.

D. A 483 should be issued under this program when deviations from the requirements in 21 CFR Parts 50, 56, 312, 812, (and 814 when applicable) are observed.

NOTE: Reports must include the name and address of the IRB Chairperson and should include the name and address of the head of the institution at which the IRB is located.

E. Documents that should be collected are:

[7] http://www.fda.gov/ICECI/Inspections/IOM/default.htm

i. IRB written procedures

ii. IRB membership rosters for the time period covered by the inspection

iii. Copies of IRB minutes which show

- Recent practices
- Violative procedures
- Approval and follow-up on tracked studies

iv. Records of tracked studies

- Protocol and Investigator Brochure - routine collection of protocols and investigators brochures is not necessary, unless there are 483 observations involving these areas.
- Consent form
- Correspondence between the IRB and the clinical investigator
- Correspondence between the IRB, FDA, and appropriate institutional officials that report any unanticipated problems involving risk to human subjects or others and any instances of serious or continuing noncompliance with these regulations.

Note: Record collection requirements vary from Center to Center. **Please contact the BIMO reviewer before collecting records for the inspection.**

F. For an inspection recommended to be No Action Indicated (NAI), please follow the guidelines outlined in the inspection assignment for collecting records and documents.

G. Please remember to collect records and documents related to all 483 observations to support the violations noted on the form.

3. **Establishment Inspections**

The inspections should be guided by the regulations found in 21 CFR Parts 50, 56, 312, 812, and 814.

4. **Prior Notification of Intent to Inspect**

The FDA field investigator shall contact the institution to confirm the name and location of the IRB Chairperson to determine appropriate time for the inspection to assure that responsible individuals are present and that IRB records are available. The field investigator shall confirm that the IRB oversees FDA-regulated research. The primary purpose of such prior notice is efficient use of the field investigator's time.

ORA BIMO Division management may elect to conduct unannounced inspections with approval of the assigning Center, if conditions warrant.

Participation in an IRB meeting (Optional). FDA field investigators may consider whether to ask the IRB to allow them to attend a regularly scheduled meeting of the IRB. The IRB would be expected to follow the agenda for the meeting and the IRB's customary procedures. Attendance at the IRB's scheduled meeting would be for purposes of observing the IRB's processes and procedures, not to answer questions. If the IRB has questions about FDA regulations or policy, the IRB should be referred to the Center contact or to the Office of Good Clinical Practice.

5. Refusal to Inspect

If the institution refuses to permit either the inspection, access to records, or copying of records, or if delays instituted by the inspectee are such that they constitute a de facto refusal, inform your supervisor so he/she can advise the assigning Center promptly. Send a follow-up INFO FAX to the listed Center and ORAHQ BIMO Inspection POC. IOM 5.2.5 provides additional guidelines.

6. Subsequent Related Sponsor/Investigator Inspections

An IRB inspection may reveal significant regulatory deviations which may lead to clinical investigator and/or sponsor inspections. ORA BIMO Divisions may carry out such inspections after obtaining the necessary instructions from the appropriate Center. The Center may issue these assignments as directed inspections.

7. IRB Registration

Effective September 14, 2009, every IRB that reviews FDA-regulated research is required to register and/or update the IRB's information on the registration Web site maintained by OHRP at least every three (3) years (see 21 CFR 56.106).

Information at this site includes the organization with which they are registered (OHRP, FDA, or both) and their present registration status.

A. **Determine** whether the IRB has registered or updated its information (https://ohrp.cit.nih.gov/search/irbsearch.aspx?styp=bsc) as required by 21 CFR 56.106.

   BIMO headquarters staff also has access to the full registration information which includes:

   i. Contact information (such as addresses and telephone number
   ii. The numbers of active protocols involving FDA-regulated products reviewed during the preceding 12 months; and
   iii. A description of the types of FDA-regulated products involved in the protocols reviewed.

This information should be included in the assignment or can be requested as needed.

The IRB registration requirements will make it easier for FDA to inspect IRBs and to convey information to IRBs[8].

8. **IRB Membership**

A. Determine whether the IRB membership has the representation required by 21 CFR 56.107.

Each IRB shall have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members.

i. An IRB must possess the professional competence to review the research activities it considers;
ii. An IRB may not be made up of members of one profession;
iii. An IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in non-scientific area; and
iv. An IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution

If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration should be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects. In addition to possessing the professional competency necessary to review the specific research activities, the IRB should be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice.

B. Determine that no IRB member participates in the deliberation or voting during the initial or continuing review of any study in which that IRB member has a conflicting interest except to provide information requested by the IRB (21 CFR 56.107(e)).

C. Determine if, except when an expedited review procedure was used, the IRB reviewed proposed research at convened meeting when a majority of the IRB members were present, including at least one member whose primary concerns are in non-scientific areas (21 CFR 56.108(c)).

[8] Final Rule IRB Registration Requirements - http://edocket.access.gpo.gov/2009/pdf/E9-682.pdf

i. Any IRB member with a conflict of interest should not be counted towards the majority for any agenda item for which the member has a conflict.
ii. The total number of eligible voting members present may change from one agenda item to the next. Majority may be lost if:

a. the total number of IRB members voting on a particular agenda item falls below the required number of members that must be present for the IRB to conduct business; or
b. at least one of the IRB members counting towards majority does not have primary concerns in non-scientific areas.

iii. Although 21 CFR 56.107(a) does not explicitly address the use of alternate members, the regulations allow an IRB to use alternate members in case one or more of the regular members is absent or is not eligible for considering a proposal because of a conflict of interest. FDA recommends that the names of any alternate members be included on the list of IRB members required by 21 CFR 56.115(a)(5).

iv. Although not regulatory requirements, FDA recommends that, if alternate members are used:

b. Alternate members should be appointed in advance and should possess the same area of expertise as primary IRB members, e.g., cardiology, oncology, or endocrinology specialties
c. Alternate members should be listed on the IRB roster and identified as to the primary IRB members for whom they may substitute at convened meetings.
d. IRB minutes should record when alternate members act in the absence of primary members.
e. Alternate members should receive the same information as primary members.

9. **Meetings**

A. 21 CFR 56.108(c) requires that, except when an expedited procedure is used (see 21 CFR 56.110), the IRB must review research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in non-scientific areas. For research to be approved, the research must receive the approval of a majority of those members present at the meeting.

Majority (often referred to as quorum) is the minimum number and type of IRB members that must be present for the IRB to conduct business. IRBs often calculate majority by using the “half-plus-one” technique. This technique works well for IRBs with an even number of IRB members. For example, if the total IRB membership is 10, then majority is 6 (half of 10 is 5 +1 = 6).

However, if the IRB has an odd number of members, then majority should be calculated by taking half of the total number of IRB members, then rounding up to the next whole number. For example, if the IRB membership is 15, then majority is 8 (half of 15 is 7.5, and rounding up to the next whole number is 8).

A majority must be maintained at all times throughout the meeting in order for the IRB to conduct business

For the selected studies, determine:

i. whether the IRB's written procedures address how a majority is calculated.

ii. whether the IRB's meeting minutes document that a majority of voting IRB members were present at each meeting, and that the majority was maintained throughout the meeting for each vote taken on FDA-regulated studies.

iii. 21 CFR 56.107(e) prohibits a member from participating in the initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

For the selected studies, determine:

a. conducting its initial and continuing review of research and for reporting findings and actions to the investigator and institution;
b. if a member has a conflict of interest, it is up to the IRB to decide whether that member needs to leave the room during the IRB's deliberations and voting.

B. 21 CFR 56.107(e) prohibits a member from participating in the initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

For the selected studies, determine:

i. whether the IRB's meeting minutes indicate whether any IRB member counted towards the majority on projects for which the member had a conflicting interest (if a member was determined to have a conflict of interest, that member may not vote on any action related to the study in which they have a conflict); and
ii. if a member has a conflict of interest, it is up to the IRB to decide whether that member needs to leave the room during the IRB's deliberations and voting.

10. **Written Procedures**

A. Determine whether the IRB has written procedures for:
   i. conducting its initial and continuing review of research and for reporting findings and actions to the investigator and institution;
   ii. determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review;
   iii. ensuring prompt reporting to the IRB of changes in research activity; and
   iv. ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to human subjects.

B. Determine whether the IRB has written procedures for ensuring prompt reporting to the appropriate institutional officials and the FDA by the IRB, and to the IRB by the clinical investigator of:
   i. any unanticipated problems involving risk to human subjects and others;
   ii. any instance of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB; and
   iii. any suspension or termination of IRB approval.

C. IRB review of Humanitarian Use Devices (HUDs) and Humanitarian Device Exemptions (HDEs).

As defined in 21 CFR 814.3(n), a HUD is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. An HDE is an application similar to a premarket approval (PMA) application, but is exempt from the reasonable assurance of effectiveness standard. HDE approval is based, in part, on evidence that the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit from use of the device outweighs the risk of injury or illness. The decision must take into account the probable risk and benefits of currently available devices and alternative forms of treatment. FDA approval of a HDE authorizes an applicant to market a HUD, subject to certain profit and use restrictions. Specifically, HUDs cannot be sold for profit, except in narrow circumstance [9] and they can only be used in a facility after an IRB has approved their use in the facility, except in certain emergencies.

There is a distinction between “use” of a HUD and “investigational use/clinical

[9] See section 520(m)(6) of the FD&C Act, https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM345931.pdf

investigation" of a HUD.

i. Prior to approval of an HDE application, any studies using the device must be conducted in compliance with the applicable IDE regulations (see 21 CFR Part 812).

a. Determine if the IRB is reviewing any such studies. If so, verify that the study, if it is considered a significant risk device study, is conducted under an approved IDE. The study must have both IDE approval from FDA and IRB approval before the study may begin (21 CFR 812.42). If it is a non-significant risk device study under 21 CFR 812.2(b), or is exempt from the IDE requirements under 21 CFR 812.2(c), determine if the study has IRB approval.

ii. "Use" of a HUD that has an approved HDE, requires IRB approval before use in a facility, with the exception of emergency use (see 21 CFR 814.124). The HDE holder is responsible for maintaining records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing IRBs, and any other information requested by the reviewing IRB or FDA (21 CFR 814.126(b)(2)).

The IRB should have written procedures addressing the initial and continuing review of a HUD used under an HDE. Written procedures for HUDs may include information as to whether the IRB will require an informed consent document for the use of a HUD.

a. Determine if the IRB reviews the use of HUDs that have an approved HDE. If so, determine if the IRB has written procedure(s) for initial and continuing review of a HUD. If the IRB does not have such procedures, FDA recommends that the IRB have policies and procedures in place for the review and approval, including whether the IRB requires a consent document for the use of the HUD.

iii. An HDE holder may collect safety and effectiveness data in a clinical investigation for the HDE-approved indications(s) without an IDE. IRB approval (21 CFR Part 56) and informed consent of the subjects (21 CFR Part 50) are still required for the clinical investigations, as defined in these regulations.

a. Determine if the IRB approved such a study and verify if it is in compliance with the applicable requirements of 21 CFR Parts 50 and 56.

iv. Clinical investigations of a HUD for an indication different from the HDE-approved indication(s) must be conducted in compliance with the applicable IDE regulations (21 CFR Part 812), in addition to complying with the applicable requirements for IRB approval and informed consent. If the study is a significant risk study, an FDA- approved IDE is required (21 CFR 812.20(a)(1)).

a. Determine if the IRB approved a study of a HUD for a different indication

than the HDE approved indication. If so, verify that the study is in compliance with 21 CFR Parts 812, 50, and 56. NOTE: IRBs may reference the following link on FDA's Web site for additional guidance on IRB review of a HUD. [10] For questions regarding a HUD/HDE, please contact the BIMO reviewer or CDRH's, HDE contact at 301-796-5640.

D. IRB responsibilities in making significant risk (SR) and non-significant risk (NSR) device determinations

IRB responsibilities for SR/NSR device determinations are found in 21 CFR 812.66. The IRB serves as FDA's surrogate for NSR investigations, including initial and continuing review.

i. Definition – Under 21 CFR 812.3(m), the definition of a SR device is one that is:
   a. Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
   b. Purported or represented for supporting or sustaining human life and presents a potential for serious risk to the health, safety, and welfare of a subject;
   c. For a use of substantial importance in diagnosing, curing, mitigating, or treating disease and presents a potential for serious risk to the health, safety, or welfare of a subject; or
   d. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

   Examples of SR devices are dental lasers for hard tissue applications, vascular hemostasis devices, biliary stents, and collagen and bone replacements.

ii. NSR devices are devices that do not pose a significant risk to human subjects. FDA does not have a specific definition for an NSR device.

NOTE: NSR should not be confused with minimal risk; a term used to identify certain studies that IRBs may approve through an expedited review procedure. For a device study to be eligible for expedited review, it must be an NSR study AND present no more than minimal risk to the subject (21 CFR 56.110). Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (21 CFR 56.102(i)).

[10] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm

Examples of NSR devices are external monitors for glucose monitoring, digital mammography, transcutaneous electric nerve stimulators (TENS) for treatment of pain (except for chest pain/angina), and conventional gastroenterology and urology endoscopes and/or accessories.

The risk determination is based on the proposed use of a device in an investigation, and not the device alone. SR studies are those that present a potential for serious risk to the health, safety, or welfare of a subject. IRBs should consider the potential harm of any associated procedure as well as the potential harm caused by the device. A device may be determined to be NSR in one case, while for another indication it may be considered SR.

iii. Risk Determination – The IRB is required to make a risk determination when the sponsor or clinical investigator presents a device for investigation as NSR. Unless FDA has already made a risk determination for the investigation, the IRB must review the sponsor's NSR determination for each investigational device study reviewed. If the IRB determines that an investigation involves a significant risk device, presented by the sponsor or clinical investigator as NSR, the IRB must notify the investigator and where appropriate, the sponsor of the SR determination. (21 CFR 812.66)

a. **Determine** whether the IRB has and follows written procedures for making the SR/NSR determination for investigational devices. Although not required by the regulations, FDA recommends that IRBs have policies and procedures in place that explain how the IRB makes the SR/NSR determination and that the decision should be documented.
b. **Determine** if the sponsor made the initial risk determination of NSR and presented this information to the IRB.
c. **Determine** if the IRB has made a determination of NSR for any device studies. The IRB should make the NSR determination by reviewing relevant information at the convened meeting and document the results in the meeting minutes.
d. **Identify** if the IRB informed the clinical investigator and/or sponsor when the IRB determined the study submitted as NSR has been determined to be a SR.
e. **Determine** if the IRB documented in meeting minutes the risk determination for each NSR study reviewed. (Note: 21 CFR 56.115(a)(2) requires a written summary of the discussion of controverted issues and their resolution).

Where a device study is determined to be SR, the sponsor may not begin the investigation except as provided in 21 CFR 812.30(a), requiring approval by FDA of an IDE application.

If the IRB agrees with the sponsor that the study is NSR, the IRB reviews the study using the criteria in 21 CFR 56.111. The study may begin without submission of an IDE application to FDA and is considered to have an approved IDE.

iv. Non-Significant Risk (NSR) Device Studies

Although not required by the regulations, FDA recommends that IRBs have written procedures that explain how the IRB makes SR/NSR determinations. The IRB should document its SR/NSR determination in the IRB meeting minutes.

a. **Describe** the IRB's written procedures that explain how the IRB makes the NSR determination. FDA considers this determination to be part of the IRB's responsibilities for conducting its initial and continuing review of the investigation.

Requirements for NSR device studies are located in 21 CFR 812.2(b) -- abbreviated requirements, which include labeling (21 CFR 812.2(b)((1)(i)); IRB approval (21 CFR

812.2(b)((1)(ii)); informed consent (21 CFR 812.2(b)((1)(iii)); monitoring (21 CFR 812.2(b)((1(iv)); record keeping and reports (21 CFR 812.2(b)((1)(v) and (vi)); and, prohibitions against promotion and other practices (21 CFR 812.2(b)((1)(vii)).

Guidance: See Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Non-significant Risk Medical Device Studies. [11]

Note: For additional information on SR or NSR determination, please see section 21 of this document.

11. **Initial IRB Review of Research**

A. **Determine** whether the IRB has the authority to approve, modify, or disapprove proposed studies, and to modify or suspend or terminate approval of ongoing studies
B. **Determine** whether the IRB provides a system for receiving and distributing the materials submitted by the clinical investigators.
C. **Determine** whether the IRB ensures that the clinical investigator has the necessary experience, research staff, and facility to conduct the clinical investigation.
D. **Determine** that each IRB member receives at a minimum, a copy of the consent document and a summary of the protocol.
E. **Determine** that all IRB members have access to copies of the complete submission to the IRB.

[11] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

An acceptable package for initial review would contain the proposed protocol, the consent form, and the investigator's brochure provided by the sponsor. When an investigator's brochure is not available or not required, the protocol should contain an appropriate description of the previous animal and human experience associated with use of the test article. Copies of the clinical investigator, sub-investigator, and/or any necessary study staff curricula vitae (CVs) should be submitted to demonstrate the experience and resources necessary for the IRB to assess the study team's qualifications to perform the study. Any payment schedules, information sheets or instruction summaries given to human subjects should be included. When advertising is to be used for recruiting subjects, a copy of the advertisement should be submitted for IRB review.

F. **Determine** whether the IRB has reviewed proposed and continuing studies at convened meetings. A majority of the IRB members must be present, including at least one member whose primary concerns are in non-scientific areas, except when the expedited procedures described in 21 CFR 56.110 apply.
G. **Determine** whether IRB-approved research received the approval of a majority of the IRB members present at the meeting.
H. **Determine** whether the written procedures describe how the IRB ensures that clinical investigators make all initially required modifications prior to enrollment of research subjects.
I. **Determine** whether the written procedures describe the IRB actions for determining when projects require review more often than once a year. It is recommended that the review frequency be recorded in the minutes, and be included in the notice of approval sent to the clinical investigator.
J. **Review** whether the IRB's records reflect the IRB determination that risks to subjects were minimized in relation to anticipated benefit.

   The IRB should ensure that the test article was adequately described and appropriate preclinical testing was conducted with the results included in the submission. Typically, a summary and assessment of the preclinical testing (e.g., study types, outcomes, and considerations for potential risks, if any, to human subjects) to support the investigation phase and duration is included in the investigator's brochure or study protocol. Without results from preclinical testing, a determination of risk to subjects cannot be made.

   Note: Please contact the BIMO reviewer for clarification on observations of missing or minimal preclinical testing and assessments thereof, as provided by the IRB in the submission.

K. **Review** the IRB's records regarding the IRB determination that the proposed research was acceptable in terms of applicable law, regulations, and standards of professional conduct and practices, i.e., an IRB member was assigned the responsibility for an in- depth evaluation of the investigational proposal, the consent form, and when applicable, the investigator's brochure or agreement. Also,

determine if the IRB assessed the adequacy of the site facilities for conducting the research. The IRB should evaluate the adequacy of the facilities to execute the protocol requirements (e.g., whether the site is appropriately staffed and equipped to conduct the proposed research and is able provide the appropriate emergent or specialized care, if required).

An IRB should perform an evaluation of the clinical investigator qualifications to determine if she/he is qualified by training and experience to oversee and perform the research, i.e., curricula vitae, current medical license, if applicable, professional references, and/or research training and experience. For research involving novel technologies and/or the potential for increased risk of mortality and/or morbidity, the IRB should evaluate any additional information documenting the clinical investigator's previous specific experience in this field (e.g., as demonstrated by recent presentations or publications) and with the test article. Should questions arise regarding clinical investigator qualifications during an inspection, please contact the BIMO reviewer.

12. **Continuing IRB Review of Research**

When the IRB reviews and approves research at a convened meeting ***without*** conditions, the effective date of the initial approval is the date of that IRB meeting.

When the IRB reviews and approves research ***with*** conditions at a convened meeting without requiring further review at a subsequent convened meeting, the effective date of the initial approval is the date on which the IRB chairperson (or any other individual(s) designated by the IRB) has reviewed and accepted as satisfactory all changes to the protocol or informed consent documents, or any other responsive materials, required by the IRB.

In either circumstance, the expiration date of the initial approval period, which is the date by which the **first** continuing review must occur, may be as late as one year after the effective date of initial IRB approval (see 21 CFR 56.109(f)).

A. **Determine** whether the clinical investigator promptly submits progress reports.
B. **Determine** whether each member has access to progress reports.
C. **Determine** whether at least one member is assigned responsibility for appropriate review of each progress report.
D. **Determine** how progress reports are evaluated to determine whether the study should be amended, terminated or allowed to continue as originally approved.
E. **Determine** whether the protocols and consent forms approved by the IRB are those used by the clinical investigator.
F. **Determine** whether unanticipated problems involving risk to subjects or others are promptly submitted and reviewed by the IRB.

G. **Determine** whether the IRB files contain documentation that appropriate continuing review procedures were completed and the IRB followed the criteria for approval of research as outlined in 21 CFR 56.111.
H. **Determine** that the review for ongoing studies is performed by the IRB at the assigned frequency and before the approval expiration date.

13. **Adverse Event Reporting**

FDA regulations use different terms when referring to an adverse event (AE). For example, "adverse device effect" is used in 21 CFR 812.46; "adverse drug event" is used in 21 CFR 312.32; and "unanticipated problems" is used in 21 CFR 312.66. For device studies, Part 812 uses the term "unanticipated adverse device effect" as defined in 21 CFR 812.3(s).

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and therefore reported to the IRB, **only** if the AE were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related change in the protocol, such as revising inclusion/exclusion criteria, including a new monitoring requirement, or modifying the informed consent or investigator's brochure). [12] An individual AE *ordinarily* does not meet these criteria because, as an isolated event, its implications for a study cannot be understood. [13]

Examples of AEs that FDA considers "unanticipated problems" include :[14]

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Steven-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals a higher rate in the drug treatment arm versus a control).

[12] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf

[13] Guidance for Clinical Investigators, Sponsors, and IRBs, *Adverse Event Reporting to IRBs -- Improving Human Subject Protection* (Jan. 2009) at 3.

[14] Guidance for Clinical Investigators, Sponsors, and IRBs, *Adverse Event Reporting to IRBs -- Improving Human Subject Protection* (Jan. 2009) at 4-5. There are additional examples in this guidance.

A. Determine if the IRB has written procedures in place for clinical investigator reporting of AEs to the IRB (21 CFR 56.108(b)). The written procedures should also address how unanticipated problems are reported to the IRB, appropriate institutional officials, and FDA. The written procedures should include reporting of serious AEs observed during the conduct of an in vitro bioavailability or bioequivalence study in humans (21 CFR 320.31(d)(3)) that is exempt from the IND requirements under Part 312 (21 CFR 320.31(d)). [15]

B. **Determine** if the IRB has written procedures for notifying subjects of changes in a protocol or informed consent triggered by an adverse event.

C. For device studies, **determine** if unanticipated adverse device effect (UADE) reports were submitted to the IRB as soon as possible, but in no event later than 10 working days after the investigator first learned of the event. (21 CFR 812.150(a)(1))

The investigational device exemption (IDE) regulations define an UADE as "… any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects." (21 CFR 812.3(s))

14. **IRB Reporting to the Clinical Investigator and the Institution**

A. **Determine** whether the IRB notifies clinical investigators and the institution in writing of the IRB decisions to approve or disapprove a proposed research activity, or of modifications required to secure IRB approval of the research activity in accordance with 21 CFR 56.109(e).

B. **Determine** whether the IRB notifies clinical investigators of the IRB's continuing review and the investigators' responsibility to promptly report and obtain IRB approval of proposed changes in a research activity, and to report unanticipated problems regarding risks to human subjects or others, any instance of serious or continuing noncompliance with applicable regulations, and any suspension or termination of IRB approval. (21 CFR 56.108(a) and (b))

The IRB should ensure that clinical investigators are made aware of their responsibilities for complying with the IRB written procedures. Some methods for informing clinical investigators may include, but are not limited to, the following:

15 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplic

i. Handbooks or Informational Sheets for clinical investigators which describe their responsibilities.
ii. Letters of approval to clinical investigators which describe their responsibilities. For the latter method, a sample copy of the approval letter should be referenced in and attached to the written procedures.
iii. The IRB procedures given to the clinical investigators or posted electronically by the IRB for access by clinical investigators.

Clinical investigators must be provided with an opportunity to respond in person or in writing to the IRB for any disapproval of their proposed research (21 CFR 56.109(e)). IRB files should contain copies of both the IRB notifications and subsequent responses from the clinical investigator.

C. **Determine** whether the IRB maintains records to document that both the IRB and the clinical investigator have met their responsibilities.
The IRB written procedures should describe how the IRB reports its findings and actions to the clinical investigator and the institution. Notifications of IRB actions are to be in writing. IRB requests for additional information and/or modifications of the proposed research should be fully described in the notices to the clinical investigators.

15. **Expedited Review**

A. **Determine** whether the IRB's use of expedited review procedures meets the requirements of 21 CFR 56.110, and that these actions are documented in the IRB records.

The list of categories of research that may be approved through expedited review is found in the Federal Register Notice published in 1998. (http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm118099.htm).

B. **Determine** that expedited review procedures are not used for circumventing the convened meeting requirements. Examples of such misuse may be any of the following actions:
i. Interim approval granted by the chairperson pending review of the proposed study at a later convened meeting.
ii. Approval granted for the one-patient nonemergency use in a protocol which does not meet the requirements of 21 CFR 56.110
iii. Expedited approval based on IRB approval of the protocol at another institution for which no cooperative agreement exists
iv. Expedited review of a claimed emergency use when the circumstances do not meet the requirements of 21 CFR 56.102(d).

C. **Ensure** that the IRB adopted a method for keeping all members advised of research proposals which have been approved via expedited review.

16. **Exception from Informed Consent**

A. Exception from general requirements for informed consent (21 CFR 50.23).

i. **Determine** whether all uses of FDA-regulated articles exempted from prior IRB review on the basis of "emergency use" meet the requirements of 21 CFR 50.23(a) and (b), and 56.102(d) and 56.104(c).

ii. **Determine** whether the clinical investigator's documentation of emergency use, consistent with 21 CFR 50.23(a) and (b), was submitted to the IRB within 5 working days after the use of the test article as required by 21 CFR 50.23(c).

iii. **Determine** whether subsequent use is subject to IRB review.

iv. **Determine** if the IRB written procedures contain procedures for emergency use and that the IRB followed its procedures.

B. Exception from informed consent requirements for emergency research (21 CFR 50.24).

Studies involving an exception from informed consent requirements for emergency research under 21 CFR 50.24:

i. **Determine** if the IRB's written procedures contain information for reviewing clinical investigations with the exception from informed consent requirements and that the IRB followed its procedures.

ii. **Determine** if the IRB, with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation, found and documented whether the investigation satisfies the criteria in 21 CFR 50.24(a)(1):

a. Determine if the IRB's written procedures contain information for reviewing clinical investigations with the exception from informed consent requirements and that the IRB followed its procedures.

b. Determine if the IRB, with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation, found and documented whether the investigation satisfies the criteria in 21 CFR 50.24(a)(1):

i. The human subjects were in a life-threatening situation that necessitated urgent intervention;

ii. Available treatments were unproven or unsatisfactory;

iii. Collection of valid scientific evidence was necessary to determine the safety and effectiveness of the intervention;

iv. Obtaining informed consent was not feasible because the subjects were not able to give their informed consent as a result of their medical condition;

v. Participation in the research held out the prospect of direct benefit to the subjects;

vi. The clinical investigation could not practicably be carried out without the waiver;

vii. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a Legally Authorized Representative (LAR) for each subject within that window of time and, if feasible, to asking the LAR contacted for consent within that window rather than proceeding without consent;
viii. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25; and
ix. Additional protections of the rights and welfare of the subjects will be provided (e.g., community consultation and public disclosure).

c. **Assure** that an IRB-approved informed consent was available in the event it became possible to obtain informed consent from a prospective subject or their legally authorized representative (LAR).
d. **Determine** if the IRB reviewed the proposed plan and procedures for attempting to contact the LAR or family member within the therapeutic window (protocol-specified period of time during which the test article must be administered.)

Determine if the IRB assured that an independent data monitoring committee was established by the sponsor to provide oversight of the clinical investigation. Note: Community consultation and public disclosure to communities are an “additional protection” of the rights and welfare of the subjects.

e. **Determine** if the IRB:
i. **Reviewed** and requested appropriate modifications in the plans for and contents of the community consultation and public disclosure prior to initiation of the clinical investigation.
ii. **Evaluated** the adequacy of the community consultation:
1. Whether the IRB considered the community concerns and incorporated the feedback, as appropriate, into the IRB’s review of the protocol and informed consent document.
2. Whether IRB meeting minutes reflected consideration of the community consultation.
3. Whether IRB meeting minutes reflected sufficient detail to show attendance at the meetings, actions taken by the IRB, the vote on these actions, the basis for requiring changes in or disapproving research, and a written summary of the discussion of controverted issues and their resolution.
4. Whether the IRB reviewed plans for and contents of public disclosure following completion of the clinical investigation.

17. **Informed Consent**

The IRB is responsible for ensuring that each consent document provides the required information in readily understandable wording (see 21 CFR 50.20 and 50.25).

A. **Determine** whether the consent form contains the required elements in 21 CFR 50.25(a) and any of the elements of 21 CFR 50.25(b) that are relevant to the study.
B. **Determine** if the IRB reviewed and approved the consent form(s), including changes and revisions to the informed consent document.
C. When the research is expected to involve potential subjects who do not speak English, the IRB should review and approve a translated consent form. **Determine** the IRB's instructions to clinical investigators for obtaining translations of informed consent documents.
D. **Determine** if the IRB has SOPs for dealing with a change in the protocol or informed consent if an interim analysis changes the treatment assignments of the protocol or the informed consent. (21 CFR 50.25(b) requires that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation in the research will be provided to the subject.)
E. **Determine** if the IRB has ever waived informed consent requirements for FDA-regulated studies, i.e., permitted subjects to participate in a study without obtaining informed consent. FDA regulations only allow the exception from informed consent under two circumstances: 21 CFR 50.23 and 21 CFR 50.24, discussed above.
F. **Determine** if the IRB has approved a waiver of the requirement to sign a written consent form. Obtain any written procedures and document each instance where this occurred. Collect any minutes during which the board approved and granted the exception. Include the documents that the IRB reviewed to make its determination. As noted in 21 CFR 109(c)(1), the IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds:

    i. that the research presents no more than minimal risk of harm to subjects, and
    ii. involves no procedures for which written consent is normally required outside the research content.

    If applicable, **determine** if the IRB waived the requirement that the subject, or the subject's legally authorized representative, signed a written consent form.

G. As a result of Public Law 105-115, known as the Food and Drug Administration Modernization Act of 1997, the National Library of Medicine (NLM) within the National Institutes of Health (NIH) developed an Internet-based registry and results data bank for clinical trials of drugs, including biological products, for serious or life-threatening conditions. The Food and Drug Administration Amendments Act of 2007 (FDAAA) broadened the scope of the ClinicalTrials.gov (CT.gov) registry to "applicable clinical trials" (ACTs) for all diseases and conditions and outlined requirements for submitting registration, summary results, and adverse events information for ACTs of drug products (including biological products) and device products, as well as pediatric post market surveillances of device products, to the clinical trial databank. FDA published regulations implementing the CT.gov submission requirements at 42 CFR Part 11 in the Federal Register (81 FR 64982) on September 21, 2016. FDAAA also requires that a certification

form (Form FDA 3674) accompany certain human drug, biological, and device product applications made to FDA. (The certification requirement went into effect on December 26, 2007.)

For additional information regarding the CT.gov registration and reporting requirements see the CP 7348.810 for Sponsors, Contract Research Organizations and Monitors.

Applicable clinical trials, as defined in 42 CFR Part 11, are:

i. For drugs, including biological products:

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

A clinical trial of a combination product with a drug primary mode of action under 21 CFR Part 3 is also an ACT, provided that it meets all other criteria of the definition under this part. [16]

ii. For device products:

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

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

A clinical trial of a combination product with a device primary mode of action under 21 CFR Part 3, is also an ACT, provided that it meets all other criteria of the definition under this part. [17]

When examining informed consent documents related to an applicable clinical trial registered on ClinicalTrials.gov, **determine** if the appropriate required statement referencing ClinicalTrials.gov is included. 21 CFR 50.25(c). The statement is:

[16] See 42 CFR 11.10(a). See also ClinicalTrials.gov Protocol Data Element Definitions for Interventional and Observational Studies (February 7, 2017) for a complete list of the required elements for registration.
[17] See footnote 16.

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

18. **Pediatric Studies – General**

A. If a study involves children as subjects, 21 CFR 56.109(h) requires the IRB to determine that the research study complies with 21 CFR Part 50 Subpart D – Additional Safeguards for Children in Clinical Investigations (Subpart D). Subpart D requires that the IRB review each clinical investigation involving children as subjects and approve only those investigations that meet the criteria with respect to the level of risk posed by the study (see 21 CFR 50.51, 50.52, and 50.53). Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient, if consistent with State law, for clinical investigations conducted under 21 CFR 50.51 or 50.52. Where clinical investigations are covered by 21 CFR 50.53 or 50.54, permission is to be obtained from both parents unless one parent is deceased, unknown, incompetent, or not reasonably available.

Additionally, when the IRB determines that assent from the child is required, it must also determine whether and how assent must be documented. The IRB must also assure that adequate provision is made to obtain the assent of the children (if in the IRB's judgment the children are capable of agreeing to participate in the study) and to obtain the permission of the children's parents or guardians, in order for these studies to be approved. There are also specific requirements if the children are wards of the State. See below.

For research involving children as subjects, the IRB must find and document one of the following:

i. 21 CFR 50.51 -- Clinical investigations not involving greater than minimal risk.

The IRB may approve a clinical investigation involving pediatric subjects provided that the study does not pose more than minimal risk to the children and adequate provision is made to solicit the assent of the children and the permission of their parents or guardians, as described in 21 CFR 50.55.

Determine if the IRB approved any studies under 50.51 and how the board documented its decision.

ii. 21 CFR 50.52 -- Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

The IRB may approve a clinical investigation involving pediatric subjects if the study involves more than minimal risk that holds out

the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds and documents that:

1. The risk is justified by the anticipated benefit to subjects;
2. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
3. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as described in 21 CFR 50.55.

Determine if the IRB approved any studies under 50.52 and how the board documented its decision.

iii. 21 CFR 50.53 -- Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

The IRB may approve a clinical investigation involving more than minimal risk to children by an intervention or procedure that does NOT hold out the prospect of direct benefit to the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, only if the IRB finds and documents that:

1. The risk represents a minor increase over minimal risk;
2. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situation;
3. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
4. Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as described in 21 CFR 50.55.

Determine if the IRB approved any studies under 50.53 and how the board documented is decision.

iv. 21 CFR 50.54 -- Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Determine if the IRB approved and documented any clinical investigations that present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children according to 50.54.

Note: Before the IRB could approve a study under this provision, the Commissioner of Food and Drugs, after consultation with a panel of experts, must have determined either:

1. That the clinical investigation in fact satisfies the conditions of 21 CFR 50.51, 50.52, or 50.53 as applicable; or

2. That the following conditions are met: (i) the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) the clinical investigation will be conducted in accordance with sound ethical principles; and (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 21 CFR 50.55.

B. If an IRB regularly reviews research that involves pediatric studies:

i. **Determine** if the IRB has written procedures describing how to review a pediatric study and how to make the special determinations required by 21 CFR Part 50 Subpart D.

For meetings at which a pediatric study was reviewed, **determine** if the IRB considered including in the membership "…one or more individuals knowledgeable about and experienced in working with [pediatric] subjects". (21 CFR 56.107(a)) If the membership of the IRB does not include such individuals, **determine** if the IRB utilized consultants or invited individuals with appropriate pediatric expertise to assist the IRB in reviewing the study. (21 CFR 56.107(f))

ii. **Determine** if meeting minutes at which the IRB reviewed a pediatric study document the discussion about the level of risk posed by the study.

iii. **Determine** if meeting minutes document the risk determination for the particular type of pediatric study as described in 21 CFR 50.51, 50.52, or 50.53 made by the IRB and the rationale.

iv. **Determine** if the IRB found and documented that the clinical investigation presents a reasonable opportunity to further the

understanding, prevention, or alleviation of the serious problems affecting the health, welfare of children.

C. 21 CFR 50.56 – Wards

Determine if the IRB approved clinical investigations under 21 CFR 50.53 or 50.54 that are for children who are wards of the State or any other agency, institution, or entity. If so, **determine** whether the IRB's actions conformed to 21 CFR 50.56.

19. **Electronic Records and Electronic Signatures**

Computerized systems are more commonly being used by IRBs to collect and preserve records as required by 21 CFR 56.115.

Computerized systems range from a desktop or laptop personal computer using an internal network to different systems located at multiple sites which use an Internet connection (e.g., a Web-based system managed by an independent software vendor to which the IRB, the sponsor and clinical sites have controlled access).

Regardless of the type of system used by the IRB, an important principle to understand when evaluating IRB records is that the regulatory requirements for adequate documentation of IRB activities do not change whether the documentation is captured on paper, electronically, or using a hybrid approach.

21 CFR Part 11 (Part 11) describes the technical and procedural requirements that must be met if a firm chooses to maintain records electronically and/or use electronic signatures. Part 11 is a companion regulation to other FDA regulations and laws. It is within these other regulations and laws, called predicate rules, where specific requirements for issues such as recordkeeping, record content, signatures, and record retention are addressed.

A. Guidance for Industry -- Part 11, Electronic Records; Electronic Signatures – Scope and Application [18]

Section III. B. 2 of the Part 11 guidance document [19] states that Part 11 is applicable to the following electronic records and electronic signatures:

i. Records that are required to be maintained under the predicate rules and that are maintained in electronic format in place of paper format.
ii. Records that are required to be maintained under the predicate rules, that are maintained in electronic format in addition to paper format, and

[18] https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm125125.pdf
[19] https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm125125.pdf, Page 5

are relied on to perform regulated activities.

iii. Records that are required to be submitted to FDA under predicate rules and that are in electronic format.

iv. Electronic signatures that are intended to be the equivalent of handwritten signatures, initials or other general signings that are required by the predicate rules and/or the IRB's written procedures.

In Section III. C. of the Part 11 guidance document,[20] specific requirements for which the agency intends to exercise enforcement discretion include the:

i. validation of computerized systems;
ii. use of computer-generated, time-stamped audit trails;
iii. use of legacy systems;
iv. generation of copies of records; and
v. protection of records (i.e., record retention and availability). [21]

B. Inspectional Guidelines

The field investigator should consult with the Center contact and/or the ORA national computer expert for guidance on the depth to which Part 11 should be covered during an inspection.

C. Equipment, Procedures, Processes

i. **Describe** any computerized system(s) used at the IRB site(s) to generate, collect, or preserve documented IRB activities (e.g., stand-alone personal computer, Web- based system, hand-held computers).

ii. **Determine** whether electronic records or reports are defined in the IRB's written procedures.

iii. **Explain** how the IRB determines which records (e.g., meeting minutes, voting logs, etc.) are collected and stored in electronic format (i.e., does the IRB prescribe any off-the-shelf program or follow any written procedures which describe selection of records for electronic formatting).

iv. **Determine** whether electronic records are available for inspection and have been retained for the required period of time (i.e., at least 3 years after completion of the research) (see 21 CFR 56.115(b)).

v. **Determine** whether the IRB's electronic system has operating instructions, user- manuals, access policies and procedures, training policies, or management controls to create, modify, maintain, or transmit electronic records.

vi. **Determine** whether individuals who develop, maintain or use the

[20] https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm125125.pdf, page6
[21] https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm125125.pdf

computerized systems have the necessary training to perform their assigned tasks.

D. Maintenance of Electronic Records

i. **Determine** whether the IRB is able to ensure adequate electronic and human readable copies of electronic records suitable for review and copying. (If you are unable to gain access to records from the computerized system following the procedures outlined in IOM 5.3, contact the Center immediately).

NOTE: ORA investigators and the inspection team are not to be independently accessing a firm's electronic files.

ii. **Determine** whether electronic records and documentation meet the requirements applicable to IRB records maintained in paper format.

iii. **Describe** how records, reports, or correspondence are transmitted from the IRB to the sponsor, clinical investigator, institutional official, FDA, etc., and vice-versa.

iv. **Determine** how the computerized system allows changes to be made. (e.g., is it based on individual access privileges? Are all changes to electronic source data accompanied with write-protected audit trails to include the name, date, and reason for change?)

E. Security

i. **Determine** who is authorized to access the system.

ii. **Describe** how the computerized systems are accessed (e.g., password protected, access privileges, user identification).

iii. **Determine** how information is captured related to the creation, modification, or deletion of electronic records (e.g., audit trails, date/time stamps).

iv. **Describe** whether there is a backup, disaster recovery, and/or contingency plan to protect against record loss. Were there any installed software upgrades, security or performance patches, or new instrumentation that affected the electronic records?

v. **Describe** how error messages or system failures are reported to the IRB, including the corrective actions taken, if any.

20. **Central IRBs/ Independent IRBs**

Under 21 CFR 56.114, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

For multicenter studies, a central IRB may conduct reviews on behalf of all study sites that agree to participate in the centralized review process. For sites at institutions that have an IRB that would ordinarily review research conducted at the site, the central IRB

should institute a written agreement with the individual institutions participating in centralized review identifying apportionment of the review responsibilities between local IRBs and the central IRB.

A. If an institution, its IRB, and a central IRB agree to participate in a centralized IRB review process, **determine** whether the action agreed upon is documented and signed by the appropriate parties. Collect a copy of the agreement.

B. If the written agreement apportions IRB review responsibilities between a central IRB and the institution's IRB, **determine** whether the agreement delineated the specific responsibilities of the central IRB and the institution's IRB for the initial and continuing review of the study.

C. When an institution and an institution's IRB rely on review by a central IRB, both IRBs must have written procedures in place to implement the centralized IRB review process (see 21 CFR 56.108, 56.114). For example, procedures should address the following:
   i. How the institution's IRB determines that the central IRB is qualified to review and approve research conducted at the institution.
   ii. How the central IRB intends to communicate with the relevant institutions, the institution's IRBs, and investigators regarding its review.
   iii. How the central IRB ensures that it provides meaningful consideration of relevant local factors for communities from which research subjects will be drawn.
   iv. How the central IRB assesses the ability of a geographically remote site to participate in the study (e.g., whether the site has medical services appropriate for the complexity of the study.)

   When an institution, an institution's IRB, and a central IRB agree to apportion IRB review responsibilities between the two IRBs, each IRB must have written procedures describing how it implements its responsibilities under the agreement (see 21 CFR 56.108, 56.115(a)(6)).[22]

21. **Investigational New Drug (IND) Application / Investigational Device Exemption (IDE) Status**

A. For Investigational Device Studies:

As discussed previously in Section J.4. *IRB Responsibilities in Making SR and NSR Device Determinations,* the IRB is required to make a risk determination when the sponsor or clinical investigator presents a device for investigation as NSR. Unless FDA has already made a risk determination for the investigation, the IRB must review the sponsor's NSR determination for each investigational device study reviewed. If the IRB determines that an investigation involves a significant

[22] http://www.fda.gov/RegulatoryInformation/Guidances/ucm127004.htm

risk device, presented by the sponsor or clinical investigator as NSR, the IRB must notify the investigator and where appropriate, the sponsor of the SR determination. (21 CFR 812.66)

Although not required by the regulations, FDA recommends that the IRB have written procedures that explain how the IRB makes SR/NSR determinations.

i. **Determine** whether the IRB has and follows written procedures for significant risk and non-significant risk determinations for investigational devices.
ii. **Determine** if the sponsor made the initial risk determination of NSR and presented this information to the IRB.
iii. **Determine** if the IRB has made a determination of NSR for any device studies. The IRB should make the NSR determination by reviewing relevant information at the convened meeting and document the results in the meeting minutes.
iv. **Identify** if the IRB informed the clinical investigator and/or sponsor when the IRB determined the study submitted as NSR has been determined to be a SR.
v. **Determine** if the IRB documented in meeting minutes the risk determination for each NSR study reviewed. (Note: 21 CFR 56.115(a)(2) requires a written summary of the discussion of controverted issues and their resolution).

B. For Investigational New Drug Applications:

FDA regulations require sponsors and clinical investigators to determine whether an IND is necessary for a particular study (see 21 CFR 312.50, 312.60). However, FDA regulations require that, in order to approve research, an IRB shall determine that the risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. (21 CFR 56.111(a)(1))

Prior to research being approved by the IRB, the IRB should obtain (for example):

i. Published literature about the chemistry, manufacturing, and control of the drug substance and product;
ii. A summary of previous human experience with the drug product;
iii. Sufficient information regarding the source, purity, quality, and method of preparation and delivery of the drug used in the research; and
iv. Information regarding the pharmacology and toxicity of the drug product in animals.

Determine if the IRB obtained the information needed to be able to make the determinations required under 21 CFR 56.111(a)(1) and questioned, for

example, the need for an IND for any studies submitted for review and approval.

If, during an IRB's initial review of a study, the IRB questions whether an IND is necessary, but is unable to obtain to resolve this issue, the IRB should follow its written procedures for resolving controverted issues, e.g., by notifying the CI of the IRB's concerns and delaying approval of the study until the matter is resolved.

PART IV - ANALYTICAL

No analytical activities are planned under this program.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

1. **Administrative Guidance**

A. ORA BIMO Division EIR Classification Authority

The ORA BIMO Division must follow the procedures for assigning Division inspection conclusions and decisions to an Establishment Inspection Report (EIR) within established timeframes as defined in Field Management Directive #86, Establishment Inspection Report Conclusions and Decisions (FMD #86).

B. Center EIR Classification Authority

The Center has final classification authority for all EIRs generated under this compliance program. If the Center is considering a classification that differs from the ORA BIMO Division's recommended classification, the Center will contact the ORA BIMO Division to discuss the issues as soon as possible to avoid delays in the final classification process. In addition, the Center will provide the ORA BIMO Division with notice of all final classifications, including the rationale for any classification that differs from the ORA BIMO Division's initial classification.

C. EIR Classifications

The following guidance is to be used in conjunction with the instructions in FMD-86 for initial ORA BIMO Division and Center classification of EIRs generated under this Compliance Program:

i. NAI - No Action Indicated -- No objectionable conditions or practices were found during an inspection (or the objectionable conditions found do not justify further regulatory action);
ii. VAI - Voluntary Action Indicated -- Objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action; and
iii. OAI – Official Action Indicated – Regulatory and/or administrative actions will be recommended.

D. Administrative/Civil/Criminal Actions will be in accordance with 21 CFR Parts 50, 56, 312, and 812. FDA can invoke other legal sanctions under the FD&C Act and/or Title 18, USC, where appropriate.
   i. Administrative Actions for noncompliance -- If apparent noncompliance with FDA regulations (21 CFR 56.120), the FDA can move forward with the following regulatory actions:

1. Untitled Letters
2. Warning Letters
3. Reinspection to verify corrective actions
4. Regulatory meetings
5. Withhold approval of new studies that are conducted at the institution or reviewed by the IRB
6. Direct that no new subjects may be recruited for ongoing studies
7. Terminate ongoing studies
8. Refer pertinent matters, with headquarters concurrence, to other Federal, State, or local agencies for such action as that agency deems appropriate

ii. Disqualification of an IRB or institution (21 CFR 56.121)

If an IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under 21 CFR 56.120(a), FDA may institute proceedings in accordance with the requirements for a regulatory hearing set forth in Part 16 (21 CFR 56.121(a)).

Disqualifications may occur if:

1. the IRB has refused or repeatedly failed to comply with any of the regulations set forth in 21 CFR Part 56 (21 CFR 56.121(b)(1)), and
2. the noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation (21 CFR 56.121(b)(2)).

FDA will issue an order that explains the basis for the determination and will send a notice of disqualification to the IRB or institution. FDA will not approve an application for a research permit for a clinical investigation that is to be under the review of a disqualified IRB or that is to be conducted at a disqualified institution, and may refuse to consider in support of a marketing permit the data from a clinical investigation that was reviewed by a disqualified IRB.

E. Communications

The ORA BIMO Division should promptly inform Headquarters/Centers about any written or oral communication from the institution following the inspection. Similarly, Headquarters/Centers should promptly inform the ORA BIMO Division of communication (including any written correspondence) with the institution following the inspection, including any judicial/administrative actions. Copies of any written communications should be shared.

2. **Regulatory Guidance**

The following criteria are relevant to FDA's classification of inspections of IRBs:

A. No Action Indicated (NAI): No objectionable conditions or practices (e.g., violations of 21 CFR Parts 50, 56, 312, and 812) were found during the inspection, or the significance of the documented objectionable conditions found does not justify further FDA action.
   i. Any post-inspectional correspondence acknowledges the IRB's basic compliance with pertinent regulations.

B. Voluntary Action Indicated (VAI): Objectionable conditions were found and documented, but the Center is not prepared to take or recommend any further regulatory (advisory, administrative, or judicial) action because the objectionable conditions do not meet the threshold for regulatory action (i.e., regulatory violations uncovered during the inspection are few and do not seriously impact subject safety or data integrity).
   i. Post-inspectional correspondence may identify the issues and, when needed, state that FDA expects prompt, voluntary corrective action by the IRB.

C: Official Action Indicated (OAI): An OAI recommendation is appropriate when regulatory violation(s) uncovered is/are significant/serious and/or numerous, and the scope, severity, or pattern of violations(s) support a finding that:

   i. Subjects participating in studies approved by the IRB would be or have been exposed to an unreasonable and significant risk of illness or injury; or
   ii. Subjects' rights would be or have been seriously compromised; or
   iii. Data integrity or reliability is or has been compromised.

Once an OAI decision is reached, additional information (e.g., previous inspectional findings, correspondence, or other information about the IRB) may assist the Center in determining the type of post-inspectional correspondence that is appropriate. If the Center chooses to issue a Warning Letter and allow the IRB to submit a detailed corrective action plan or alternate approach that is acceptable to FDA, the Center should nevertheless be prepared to initiate disqualification proceedings should the IRB not respond appropriately (i.e., fails to respond, fails to develop an adequate corrective action plan, or is found, during a subsequent inspection, to have failed to comply with a corrective action plan).

A Warning Letter may be considered when the violations can be corrected through specific action(s) by the IRB (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.

EXAMPLES:

The following are examples of violations that, alone or in combination, would be considered significant and may warrant an OAI classification. This list is not all inclusive; other circumstances may also merit an OAI classification.

When applying the classification criteria, Center reviewers will generally evaluate the impact of the IRB's actions (number, scope, and severity of the regulatory violations) on subjects' rights, safety and welfare. There are gradations in the severity of each example, and the specific observation(s) should support the seriousness of the violation(s) and the effect(s) on subjects' safety and welfare and/or the reliability and acceptability of data for FDA decision-making purposes. The Center should also consider whether FDA has cited the IRB for the same or similar violations during a previous inspection.

Inadequate Human Subject Protection	
Violation/Related Citation	**Examples**
Failure of the IRB to register with OHRP (http://ohrp.cit.nih.gov/efile) *21 CFR 56.106*	IRB is not registered on OHRP's Registration Web site. The initial IRB registration must occur before the IRB begins to review clinical investigations and must be updated as required by the regulation.
Failure to conform to membership criteria listed in *21 CFR 56.107*	• IRB has fewer than 5 members • IRB fails to have an unaffiliated member OR at least one member whose primary concerns are scientific OR at least one member whose primary concerns are non-scientific • IRB is composed entirely of one sex or members of one profession • Conflicted member votes on his/her own study • Invited consultant votes on study
Failure to conform to meeting participation criteria as listed in *21 CFR 56.107(e)*	IRB has a member participate in the IRB's initial and continuing review of a project in which the member has a conflicting interest
Failure to follow written procedures *21 CFR 56.108(a)*	IRB does not follow written procedures that state the IRB will conduct continuing review at least annually. For example, if a clinical investigator failed to submit a periodic report, the IRB did not detect the omission.
Failure to have minutes of IRB meetings in sufficient detail to show attendance at the meetings *21 CFR 56.115(a)(2)*	IRB records of meetings (e.g., minutes) are missing or do not have sufficient detail to show who attended, actions taken, and the votes, including the number of members for and against, and abstentions. *Note:* Please contact the BIMO reviewer for clarification on the frequency of the missing minutes to warrant an OAI classification.
Failure to have records of continuing review activities *21 CFR 56.115(a)(3)*	Records of continuing review activities are missing or incomplete. *Note:* Please contact the BIMO reviewer for clarification on the frequency of the missing or incomplete records to warrant an OAI classification.

Inadequate Human Subject Protection (con't)	
Violation/Related Citation	**Examples**
Failure to make a risk determination regarding an investigation presented for approval as NSR *21 CFR 812.66*	The IRB failed to determine whether an investigation presented for approval as NSR is a SR or NSR study.
Failure to determine that the research study is in compliance with 21 CFR Part 50 Subpart D when some or all of the subjects in a study are children *21 CFR 56.109(h)*	The IRB failed to determine at the time of initial review that studies involving children were in compliance with 21 CFR Part 50 Subpart D -- "Additional Safeguards for Children in Clinical Trials"
Failure to conduct continuing review of research at intervals appropriate to the degree of risk *21 CFR 56.109(f)*	The IRB failed to conduct continuing review of research at intervals of not less than once per year

Inadequate Human Subject Protection (con't)	
Violation/Related Citation	**Examples**
Failure to evaluate that all conditions for exception of informed consent and requirements for emergency research were satisfied. *21 CFR 50.24*	The IRB failed to determine and document that: • The human subjects were in a life-threatening situation that necessitated urgent intervention • Available treatments were unproven or unsatisfactory • Collection of valid scientific evidence was necessary to determine the safety and effectiveness of the intervention • Informed consent was not feasible • Participation in research held out the prospect of direct benefit to the subjects • The clinical investigation could not practicably be carried out without a waiver • The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a LAR for each subject within that window of time and, if feasible, to asking the LAR contacted for consent within that window rather than proceeding without consent • The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25 • Additional protections of the rights and welfare of the subjects will be provided (e.g., community consultation and public disclosure)

3. **Follow-Up Inspections**

A. 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., sponsor, CRO, monitor, clinical investigator(s)).

B. Following issuance of a Warning Letter, Centers should schedule a follow-up inspection to verify if the IRB is fulfilling the terms of any corrective action plan and is in compliance with applicable regulations. Such follow-up inspections should take place within one year after the date of the last Warning Letter correspondence, depending on the nature of the violations.

4. **Post-Inspection Information Sharing**

Per the April 27, 2015, agreement between the Department of Veterans Affairs (VA) and the FDA Office of Regulatory Affairs (ORA) and upon the written request by the Office of Research Oversight, VA, the Center contacts are authorized to provide to the Office of Research Oversight, VA, and its staff, redacted copies of FDA-reviewed EIRs and any post-inspection correspondence issued to VA facilities or employees following any inspection (including the 483s).

Post inspection documents should be sent to:

Executive Director

Office of Research Oversight
(10R) Veterans Health
Administration Department of
Veterans Affairs

810 Vermont Avenue, N.W.
Washington, D.C. 20420

Responses are subject to FDA priority and available resources, and are pursuant to ORA, VA's June 18, 2010, non-disclosure agreement.

PART VI REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

1. **References**

A. FDA Laws
   b. Federal Food, Drug, and Cosmetic Act (FD&C Act)

B. Most Relevant 21 CFR Regulations
   i. Part 50 – Protection of Human Subjects
   ii. Part 56 – Institutional Review Boards
   iii. Part 312 – Investigational New Drug Application
   iv. Part 812 – Investigational Device Exemptions

C. Other 21 CFR Regulations
   i. Part 11 - Electronic Records; Electronic Signatures
   ii. Part 814 - Premarket Approval of Medical Devices (includes HDE Requirements in 814.100)
   iii. Part 320 – Bioavailability and Bioequivalence Requirements

D. FDA Guidelines, Guidance, and Inspection Guides
   i. Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRB—Improving Human Subject Protection (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf)
   ii. Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf)
   iii. Guidance for Industry: IRB Review of Stand-Alone HIPPA Authorizations Under FDA Regulations (http://www.fda.gov/downloads/RegulatoryInformation/sGuidances/UCM126952.pdf)
   iv. FDA Information Sheet Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors (http://www.fda.gov/oc/ohrt/irbs/default.htm)
   v. Guidance for Clinical Investigators, Institutional Review Boards, and Sponsors: Process for Handling Referrals to FDA under 21 CFR 50.54 – Additional Safeguards for Children in Clinical Investigations (Guidances>ProcessforHandlingReferralsto FDAUnder21CFR50.54-AdditionalSafeguardsforChildreninClinical Investigations)

vi. Guidance for Industry: International Conference on Harmonization (ICH) E6, Good Clinical Practice: Consolidated Guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf)
vii. Guidance for Industry: Computerized Systems Used in Clinical Investigations (http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdl0002.pdf)
viii. Guidance for Industry: Part 11: Electronic Records, Electronic Signatures -- Scope and Application (http://www.fda.gov/ohrms/dockets/98fr/5667fnl.pdf)
ix. Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review after Clinical Investigation Approval (https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm294558.pdf)
x. Humanitarian Device Exemption (HDE) Regulation: Questions and Answers; Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators and FDA Staff (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110203.pdf)
xi. Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors — Frequently Asked Questions About Medical Devices (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf)
xii. Investigations Operational Manual (IOM) (http://www.fda.gov/ICECI/Inspections/IOM/default.htm)
xiii. General Principles of Software Validation; Final Guidance for Industry and FDA Staff (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085281.htm)
xiv. Guidance for Industry: Protecting the Rights, Safety, and Welfare of Study Subjects – Supervisory Responsibilities of Investigators (http://www.fda.gov/OHRMS/DOCKETS/98fr/07d-0173-gdl0001.pdf)
xv. Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127013.pdf)
xvi. Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors -- Significant Risk and Nonsignificant Risk Medical Device Studies (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf)

2. **Program Contacts**

When medical, technical or scientific questions or issues arise from a specific assignment or if additional information is required about a specific assignment, consult the Center contact identified in the assignment.

A. For operational questions, contact:

Office of Regulatory Affairs (ORA)

Office of Medical Products and Tobacco Operations (OMPTO)

Office of Bioresearch Monitoring Operations (OBIMO) - ORAHQ BIMO Inspection POC

B. For questions about GCP and Compliance program issues, specific to a Center product area, contact:

Center for Drug Evaluation and Research (CDER) Office of Scientific Investigations: 301-796-3510, FAX 301-847-8748
Center for Biologics Evaluation and Research (CBER) Bioresearch Monitoring Staff: CBERBIMONotification@fda.hhs.gov; 240-402-9161.
Center for Devices and Radiological Health (CDRH) Division of Bioresearch Monitoring: 301-796-5490, FAX 301-847-8137
Center for Food Safety and Applied Nutrition (CFSAN) Bioresearch Monitoring Program 301-402-1757; CFSANBIMO@FDA.HHS.GOV
Center for Tobacco Products (CTP) Office of Compliance and Enforcement (OCE) 877-287-1373

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

Office of Good Clinical Practice
Office of Special Medical Programs
Office of the Commissioner
301-796-8340, FAX 301-847-8640

PART VII - HEADQUARTERS RESPONSIBILITIES

1. **Centers**

Each Center:

A. Identifies Institutional Review Boards to be inspected and forwards inspection assignments and background material (e.g., protocols, correspondence, complaint, and Center concerns) to the ORAHQ BIMO Inspection POC and enters into the appropriate electronic data system such as FACTS or eNSPect.

B. Reviews and makes final classifications of EIRs, and enters the classification into the appropriate electronic data system.

C. Issues correspondence to the inspected institution after EIR review. This letter will typically be addressed to the most responsible individual in the institution along with a copy to the IRB chairperson and will state the Center's assessment of the IRB's performance. Copies of letters will be sent to the appropriate ORA BIMO Division Office.

D. Conducts follow-up regulatory and/or administrative actions. Promptly provides copies of relevant correspondence between the institution or IRB and FDA to the ORA BIMO Division Offices.

E. Provides expert technical guidance, advice, information, interpretation, analysis, and support related to implementation of the clinical BIMO Program for internal and external constituents.

2. **ORA/OFFICE OF ENFORCEMENT AND IMPORT OPERATIONS (OEIO)/DIVISION OF ENFORCEMENT (DE)**

D. Serves as the Agency clearance point and coordinator for inspection warrants.

E. For disqualification actions, reviews and issues the letter with the signature of the Associate Commissioner for Regulatory Affairs (ACRA, and coordinates actions related to the IRB or IRB's parent institution initial response.

3. **ORA/OFFICE OF BIORESEARCH MONITORING OPERATIONS (OBIMO)**

A. Provides inspection quality assurance, training of field personnel, and operational guidance.

B. Maintains liaison with Centers and ORA BIMO Divisions and resolves operational questions.

C. Coordinates and schedules independent and team inspections.

4. **Office of Good Clinical Practice, Office of the Commissioner**

A. Coordinates crosscutting clinical BIMO program activities including modifications of this compliance program.

B. Provides expert technical guidance, advice, information, interpretation, and analysis relevant to clinical BIMO Program implementation to internal and external program constituents to assure program consistency.

C. Serves as agency liaison to other Federal Agencies (e.g., OHRP, VA) for coordination of clinical BIMO and human subject protection issues.