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Change History

Item	Change	Date
Update	Updated administrative, organizational and computer systems information	04/16/2018

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., Suite 574
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., Suite 574
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