CHAPTER 48: Bioresearch Monitoring FINAL

SUBJECT: INSTITUTIONAL REVIEW BOARDS	IMPLEMENTATION DATE: 04/04/2025
DATA REPORTING	
PRODUCT CODES: Bioresearch Monitoring inspections do not require product codes	
PROGRAM ASSIGNMENT CODES	
09809: Food and Color Additives	
41809: Biologics (Human Cellular, Tissue and Gene Therapies)	
42809: Biologics (Blood and Blood Products)	
45809: Biologics (Vaccines, Allergenic, and Live Biotherapeutic Products)	
48809: Human Drugs	
83809: Medical Devices	
98809: Tobacco Pre-Market Activities	

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 Point of Contact (Center POC).

All EIRs should be completed in accordance with Office of Inspections and Investigations (OII) SOP: *Establishment Inspection Report Classification Process* (former FMD No. 86) and the Investigations Operations Manual (IOM)[1], Chapter 5 (Establishment Inspections).

A preliminary summary of inspectional findings, as well as any Form FDA 483 Inspectional Observations (FDA 483), should be emailed to the Center POC, as agreed to with the center, as soon as possible, but generally no later than three business days after the inspection has completed.

[1] https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual

Contents

PART I – BACKGROUND 4
PART II - IMPLEMENTATION 6
1. Objective 6
2. Program Management Instructions 6
A. Coverage 6
B. Inspection Assignments 6
C. Remote Regulatory Assessment 6
D. Communication Between the Centers and OII 7
E. Responsibilities of OII Investigators, Inspection Team Leaders, & Center Participants 7
F. Inspections of Facilities under the Jurisdiction of the Veterans Affairs 9
PART III - INSPECTIONAL 10
1. General 10
2. IRB Registration 11
3. IRB Membership 12
4. Meetings & Meeting Minutes 12
5. Written Procedures 13
6. Criteria for Selecting Studies/Time Frame 14
7. Initial IRB Review of Research 14
8. IRB Review of Research Involving Medical Devices 16
9. IRB Review of HUDs - Clinical Use and Use in Research 17
10. Studies Involving Children 18
11. Continuing IRB Review of Research 21
12. Expedited Review 21
13. Unanticipated Problems Involving Risks to Human Subjects or Others 22
14. IRB Reporting to the Clinical Investigator and Institution 23
15. Informed Consent (21 CFR 50.20, 50.25 & 50.27) 23
16. Exception and/or Waiver of Informed Consent 24
17. Emergency Use of a Test Article (21 CFR 56.104(c)) 26
18. Electronic Records and Electronic Signatures 26
19. Cooperative Research 28
PART IV - ANALYTICAL 30
PART V - REGULATORY/ADMINISTRATIVE STRATEGY 31
1. Classification 31

2. Administrative Actions for Noncompliance. 31
3. Follow-Up Inspections 32
PART VI REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS 34
1. References 34
A. FDA Laws 34
B. FDA Guidelines, Guidance and Inspection Guides 34
C. Relevant FDA Information Sheets 36
2. Program Contacts 37
PART VII – FDA CENTER AND OFFICE RESPONSIBILITIES 38
1. CENTER 38
2. OFFICE OF INSPECTIONS AND INVESTIGATIONS 38
3. OFFICE OF CLINICAL POLICY 39

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
Update	Full Revision	03/21/2025

PART I – BACKGROUND

In 1977, the Food and Drug Administration (FDA or Agency) established the Bioresearch Monitoring (BIMO) program to ensure the protection of the rights, welfare, and safety of human subjects involved in FDA-regulated studies; to verify the quality, integrity, and reliability of clinical study data submitted to FDA in support of research or marketing applications; and to assess compliance with statutory requirements and FDA's regulations governing the conduct of clinical studies, including those for informed consent and ethical review.

Title 21 of the Code of Federal Regulations (21 CFR), parts 50 and 56, provide FDA's regulations for the protection of human subjects. These regulations require, among other things, IRB review of all clinical investigations using FDA-regulated products 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 and authorizations for other FDA-regulated products.

FDA's Office of Inspections and Investigations (OII) conducts inspections of clinical investigators, sponsors, sponsor-investigators, contract research organizations (CROs), institutional review boards (IRBs), radioactive drug research committees (RDRCs), nonclinical (animal) laboratories, bioavailability and bioequivalence studies, post-marketing adverse drug experience reporting, and risk evaluation and mitigation strategies reporting. These inspections are conducted in support of preapproval, licensing, premarket, and marketing applications submitted to the agency for products regulated by FDA product centers as part of the BIMO program, among other activities.

The BIMO program is implemented through multicenter compliance programs (CPs)[2] to ensure regulated entities are operating in accordance with applicable statutes and regulations to verify if clinical trials follow applicable ethical and quality standards. These CPs were developed to establish a framework that outlines instructions and expectations for BIMO inspections.

Section 704(a)(5)(D)(i) of the FD&C Act underscores that those subject to BIMO inspection must provide FDA with access to the information to be inspected (including access to all paper and electronic records and access to electronic information systems used to hold, analyze, process, or transfer that information), and permit FDA to inspect relevant facilities and equipment used in generating that information. At the same time, section 704(a)(5)(D)(ii) makes clear that existing safeguards against disclosure of confidential commercial information and trade secrets continue to apply.

In addition to its inspectional authority, section 704(a)(5), FDA may initiate or request to conduct remote regulatory assessments (RRAs), whenever FDA determines an RRA is appropriate to help fulfill the Agency's regulatory responsibilities and protect human and animal health. An RRA is an examination of an FDA-regulated establishment and/or its records, conducted entirely remotely, to evaluate compliance with applicable FDA requirements. RRAs assist in protecting human health, informing regulatory decisions, and verifying certain information submitted to the Agency.[3]

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[2] https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring-program-bimo-compliance-programs

[3] See the revised draft guidance for industry Conducting Remote Regulatory Assessments: Questions and Answers (January 2024). When final, this guidance will represent FDA's current thinking on this topic. Also see section 704 of the Federal Food, Drug, and Cosmetic Act.

Requests for records or other information from establishments subject to section 704(a)(4) of the FD&C Act, are a type of RRA. Section 704(a)(4) gives FDA the authority to request (and requires establishments to provide) any records or other information that FDA may inspect under section 704 of the FD&C Act, in advance of or in lieu of inspections of such establishments that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or device, or a site or facility that is subject to inspection under section 704(a)(5)(C) (i.e., sites, entities, or facilities subject to BIMO) inspections.

PART II - IMPLEMENTATION

1. Objective

The objectives of the BIMO program are:

- To protect the rights, welfare, and safety of subjects involved in FDA-regulated clinical trials[4];
- To verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications; and
- To assess compliance with FDA's regulations governing the conduct of clinical trials.

The purpose of this CP is to provide instructions to OII 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 clinical investigations involving human subjects and FDA-regulated products.

B. Inspection Assignments

1) Centers, on an annual basis, will select IRBs for surveillance inspections and send OII a list of IRBs selected for surveillance inspections.

2) Centers issue IRB for-cause inspection assignments, with a comprehensive or directed approach, including background materials.

3) Inspection assignments should be issued with due dates according to pre-defined timeframes.

4) Once an inspection assignment has been issued, any requested change in the due date by the center will be routed through the OII Office of Bioresearch Monitoring Inspectorate (OBMI) point of contact (POC) and the appropriate OII OBMI division director(s). The inability of OII OBMI to meet a due date should be immediately communicated to the appropriate OBMI division director and center POC.

5) If the inspection involves a U.S. Department of Veterans Affairs (VA) facility, refer to Part II Section 2.F. (Inspections of Facilities under the Jurisdiction of the Veterans Affairs) of this CP for additional instructions.

C. Remote Regulatory Assessment

As part of the IRB surveillance inspection program, centers may select a number of IRBs for an RRA. The center IRB liaison will identify those IRBs for which the center requests an RRA be conducted in lieu of an inspection.

[4] The terms *research, clinical research, clinical study, study,* and *clinical investigation* are deemed to be synonymous with *clinical trials* for purposes of this CP.

D. Communication Between the Centers and OII

1) Prior to an Inspection

a) The OII investigator contacts the center POC to notify them that they have been assigned to conduct the inspection, provide the inspection start date, contact information for communication during the inspection, obtain special instructions, and coordinate the logistics of center personnel participation if needed.

b) A pre-inspection meeting may be arranged by the center or OII to discuss the assignment.

2) During an Inspection

a) The center POC and OII investigator should strive to be accessible to one another during the inspection.

b) The OII investigator contacts the center POC if advice or clarification of the inspection assignment is needed, or if evidence is uncovered that warrants discussion with the OII investigator's supervisor and center personnel.

3) After an Inspection

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

b) As soon as possible, OBMI forwards a copy of any written response to the FDA 483 by the inspected party to the center POC. The center POC forwards a copy of any response to FDA 483 that does not appear to have been shared with the inspecting OII OBMI Division.

c) The center POC consults with the OII investigator and their supervisor as needed when reviewing the EIR.

d) The center determines the final classification and enters the final classification decision into the appropriate information technology system(s).

e) If the center's final classification is different from the one recommended by OII, the center should ensure that OII OBMI Division personnel are aware of the change and reasons for the change.

f) The center promptly forwards documentation of the final classification decision and copies of post-inspectional correspondence issued to the inspected party to the appropriate OII OBMI division's correspondence box email address.

E. Responsibilities of OII Investigators, Inspection Team Leaders, & Center Participants

1) OII Investigator

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

- Reviewing inspection instructions and attending pre-inspection meetings (as needed) prior to the start of the inspection;

- Discussing with OII OBMI Division management the need to adjust the workload in order to meet specific inspection due dates;
- Scheduling domestic inspections and conducting the assigned inspection;
- Communicating inspectional observations/issues with institutional officials and IRB staff during the course of the inspection, as appropriate;
- Communicating inspectional observations and issues to the OII investigator's supervisor and the center POC;
- Preparing and issuing any FDA 483; discussing with institutional officials and IRB staff any inspectional observations listed on the FDA 483 and/or any discussion items at the close of the inspection, informing the IRB that they may submit a written response to the FDA 483;
- Preparing and submitting an EIR within established timeframes; and
- Participating in post-inspectional discussions with the center, when appropriate.

2) Inspection Team Leader

When inspections are conducted by a team, an OII investigator serves as Inspection Team Leader and is responsible for the cooperative conduct of the inspection. In addition to the responsibilities listed above, the Inspection Team Leader's responsibilities include but are not limited to those listed in the IOM Chapter 5 (Establishment Inspections-Team Inspections).

3) Center Participant

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

- Obtaining OII OBMI approval for participation in an inspection and obtaining FDA credentials through OII OBMI Immediate Office;
- Attending pre-inspection discussions, if and when requested by the Inspection Team Leader;
- Participating in and providing information pertinent to the inspection;
- Providing guidance and expertise during the inspection and completing inspection tasks as directed by the Inspection Team Leader if the center participant is serving as a subject matter expert (SME) (e.g., auditing documents, preparing inspection notes and specific sections of the EIR within guidelines and timeframes); and
- Providing their written portion of the EIR to the Inspection Team Leader within timeframes.

4) Resolution of Disagreements

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

F. Inspections of Facilities under the Jurisdiction of the Veterans Affairs[5]

1) Pre-Inspection

The center may provide the Veterans Affairs Office of Research Oversight (VA-ORO) with written notification of FDA's intention to inspect an institutional review board at a VA facility at the beginning of the fiscal year for IRB surveillance inspections or at the time that the assignment is issued to OII for for-cause IRB inspections.

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

Executive Director, Office of Research Oversight (10R)
Veterans Health Administration
U.S. Department of Veterans Affairs
810 Vermont Avenue, N.W.
Washington, D.C. 20420
Telephone: (202) 632-7620
Email: vha10rresearchoversightaction@va.gov

2) Post-Inspection

The center will make available, upon request, a copy of any post-inspectional correspondence with the inspected entity to the VA Office of Research Oversight.

[5]Memorandum of Understanding Between the U.S. Department of Veterans Affairs, Veterans Health Administration and the U.S. Department of Health and Human Services, Food and Drug Administration, MOU 225-82-8400, https://www.fda.gov/about-fda/domestic-mous/mou-225-82-8400

PART III - INSPECTIONAL

1. General

The following instructions apply to inspections of IRBs:

A. The primary focus of an IRB inspection is to evaluate IRB practices and procedures to determine compliance with the applicable regulations, specifically 21 CFR 50 and 56 and, as applicable, 21 CFR 312, 812, and 814 to ensure human subject protection. These regulations apply to clinical investigations of products regulated by FDA. These inspections may include, but are not limited to, IRB's written procedures, membership, registration, initial and continuing IRB review of research.

B. Inspections under this program will be preannounced unless otherwise instructed in the inspection assignment or a determination is made not to preannounce by OII. The OII investigator should keep the time span between initial contact and start of the inspection as short as possible. The OII investigator should immediately report to the OII investigator's supervisor, OII division director, and center POC, any attempt by the IRB to delay an inspection without sufficient justification.

C. The OII investigator contacts 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 IRB records are available. The OII investigator shall confirm that the IRB is providing oversight of FDA-regulated research as the IRB of record. For any inspection attempt where it is determined that the IRB is out of business or it is determined that FDA does not have jurisdiction (e.g., IRB is not reviewing FDA-regulated research or is not serving as the IRB of record), the OII investigator will contact the center POC to discuss converting the inspection (Operation 12) to an investigation (Operation 13).

D. IRB records must be retained for at least three years after the completion of the research, and accessible for inspection and copying by FDA (21 CFR 56.115(b)). If the OII investigator encounters a refusal to permit entry or inspection, or a refusal of information, including a refusal to permit access to or copying of requested records, the appropriate section of IOM Chapter 5 (Establishment Inspections) and applicable regulatory requirements should be consulted, and current policy/procedures followed.

E. If the OII investigator observes or suspects regulatory or statutory deviations that may endanger subject rights, welfare, or safety, they will immediately contact their supervisor, OII division director, and center POC, and then continue the inspection.

F. If possible, OII investigators should attend a convened meeting of the IRB to observe the IRB's processes and procedures under 21 CFR 56. The OII investigator may address questions from the IRB outside of the IRB meeting as part of the inspection.

G. The OII investigator issues a FDA 483 at the conclusion of the inspection when deviations from applicable regulations are observed. Those inspectional observations that do not reach the level of significance to be included on the FDA 483 will be discussed during the closeout discussion with management and reported in the EIR. OII investigators should collect all records necessary to fully support all FDA 483 observations and discussion items.

H. The OII investigator informs the IRB that they may submit a written response to the FDA 483 within 15 business days of the end of the inspection to the appropriate OII OBMI division correspondence email address. Refer to IOM Chapter 5 (Establishment Inspections).

I. OII investigators are responsible for conducting inspections and preparing EIRs. The EIR must include content required by this compliance program and specific assignment instructions, where applicable. This content should be included by utilizing the headings that are listed in the CP and the headings as prescribed in the IOM. The EIR must include the name and address of the IRB Chairperson and should include the name and address of the head of the institution or Institutional Official at which the IRB is located.

J. Documents to be collected and included as an exhibit in each EIR:

1) IRB written procedures required by 21 CFR 56;

2) Current IRB membership list;

3) Examples of IRB meeting minutes to illustrate initial review and approval of studies for each type of FDA regulated product reviewed, e.g., drugs, biologics, and medical devices;

4) Protocol or protocol summary for each study reviewed including documentation of IND, IDE, or HDE #, if available; and

5) List of FDA-regulated studies for which the IRB is providing oversight as the IRB of record, if available.

Note: The OII investigator should contact the center POC if it is not feasible to collect the records identified above.

K. If during the inspection of IRB, the OII investigator becomes aware of complaints or problems related to a clinical investigator, sponsor, or CRO, they should promptly forward the information to the appropriate center for evaluation, in accordance with current complaint handling procedures. The referral should be documented in the endorsement.

2. IRB Registration

Every IRB in the United States that reviews FDA-regulated research is required to register and/or update the IRB's information on the registration website maintained by the Office for Human Research Protections (OHRP) at least every three years (21 CFR 56.106).

Determine whether the IRB has registered[6] or updated its information as required by 21 CFR 56.106(c) or as described in 21 CFR 56.106(e).

A. Change in IRB's Contact: If there is a change in the IRB's contact or chairperson, verify that the IRB revised its registration information within 90 days of the change.

B. Change in Types of FDA-Regulated Products: If the IRB decides to review clinical investigations involving new types of FDA-regulated products or to discontinue reviewing clinical investigations regulated by FDA, verify that the IRB updated its registration information within 30 days of the change.

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

C. Change in Status: When the IRB decides to disband, verify that the IRB updated its registration to reflect the change in its status within 30 days of permanent cessation of the IRB's review of research.

D. Change in Name: If the IRB has a name change, identify whether the IRB has updated its registration information.

3. IRB Membership

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

B. **Determine** whether any 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, other than to provide information requested by the IRB (21 CFR 56.107(e)).

C. **Identify** whether the IRB has a process for appointing alternate members as substitutes for primary members for an entire meeting (e.g., when the primary member is not able to attend the meeting), or at any time during a meeting (e.g., when the primary member has a conflicting interest and is recused from review of a particular study).

1) **Identify** whether alternate members are listed on the IRB membership list and identified as to the primary IRB member(s) or representative capacity (e.g., scientific, non-scientific, non-affiliated) for whom they may substitute at convened meetings.

2) **Identify** whether an alternate member is included in the meeting minutes when the alternate member replaces a primary member at a convened meeting and whether the minutes identify the name of the primary member for whom the alternate member is substituting, and the reason for the substitution.

D. **Determine** if the IRB maintains a list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution as required by 21 CFR 56.115(a)(5).

4. Meetings & Meeting Minutes

21 CFR 56.108(c) requires that, except when an expedited procedure is used (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.

A. 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. For example, if the total IRB membership is 10 (even number of IRB members), then majority is 6 (half of 10 is 5 +1 = 6). If the IRB membership is 15 (odd number of IRB members), then majority is 8 (half of 15 is 7.5, and rounding up to the next whole number is 8). **Identify** whether the IRB’s written procedures address how a majority is calculated.

B. **Determine** whether the IRB meeting minutes include attendance at the convened meeting of

the IRB (21 CFR 56.115(a)(2)).

C. Except when an expedited review procedure was used, **determine** if the IRB reviewed proposed research at a convened meeting when a majority of the IRB members were present, including at least one member whose primary concerns are in non-scientific areas and that the required membership was maintained throughout the meeting for each vote taken on FDA-regulated studies (21 CFR 56.108(c)).

   The total number of eligible voting members present may change from one agenda item to the next agenda item. Majority may be lost if:

   1) 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

   2) At least one of the IRB members counting towards majority does not have primary concerns in non-scientific areas.

D. **Determine** whether actions voted on during a convened meeting received approval of a majority of the IRB members present.

E. **Determine** whether the IRB has reviewed proposed and ongoing studies at convened meetings.

F. **Determine** whether the IRB minutes include sufficient detail that shows the actions taken by the IRB, a vote on these actions including the number of members voting for, against or abstaining (21 CFR 56.115(a)(2)).

G. **Determine** whether the IRB meeting minutes include sufficient detail to show the basis for requiring changes in (to secure approval) or disapproving research (21 CFR 56.115(a)(2)).

H. **Determine** whether the IRB meeting minutes include a summary of the discussion of controverted issues and its resolution (21 CFR 56.115(a)(2)).

I. **Review** the IRB's meeting minutes to ascertain whether any IRB member participates in the initial or continuing review of any project for which the member has a conflicting interest (21 CFR 56.107(e)). Identify whether the IRB maintained quorum if an IRB member is recused from voting on a specific study because of a conflicting interest.

5. Written Procedures

A. **Determine** whether the IRB maintains and follows written procedures as required by 21 CFR 56.108(a) for:

   1) Conducting initial and continuing review of research and for reporting findings and actions to the clinical investigator and institution;

   2) Determining which projects require review more often than annually and which projects need verification from sources other than the clinical investigator that no material changes have occurred since previous IRB review;

   3) Ensuring prompt reporting to the IRB of changes in research activity; and

4) Ensuring that changes in approved research, during the period for which IRB approval has already been given, are not initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to human subjects.

B. **Determine** whether the IRB maintains and follows written procedures as required by 21 CFR 56.108(b) for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of:

1) Any unanticipated problems involving risk to human subjects and others;

2) Any instance of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB; and

3) Any suspension or termination of IRB approval.

6. Criteria for Selecting Studies/Time Frame

A. The OII investigator should select FDA-regulated studies that reflect current IRB practices, preferably ones that were initially approved within the previous three years and are presently ongoing, including study(ies) that have undergone a continuing review. During the inspection, OII investigators prioritize selection of clinical studies, based on the following criteria:

1) Studies specified in the for-cause inspection assignment if any;

2) Safety and efficacy studies of investigational new drugs, devices and/or biologics or combination products performed under IND (drug or biologic), or IDE application;

3) Studies employing novel or cutting-edge technologies (e.g., cell, gene, and tissue-based therapies);

4) Studies involving vulnerable populations (e.g., pediatric studies, refer to 21 CFR 56.107 (a));

5) Studies involving an exception from informed consent under 21 CFR 50.24;

6) Sponsor-investigator initiated clinical trials;

7) Device studies that involve the IRB's determination as to whether a device study is significant risk (SR) or non-significant risk (NSR); and

8) Studies for which an IND or IDE is not required, e.g. certain marketed drugs and devices, and NSR devices.

Document the protocol number, full protocol title, sponsor, clinical investigator, IND/IDE/HDE number, if available, and initial IRB approval date for studies reviewed during the inspection.

7. Initial IRB Review of Research

A. **Determine** whether the IRB has the authority to approve, require modifications in (to secure approval), or disapprove proposed research (21 CFR 56.109(a)).

B. **Determine** whether officials of the institution approved research that has not been approved by the IRB (21 CFR 56.112).

C. **Identify** whether the IRB provides a system for receiving and distributing the materials submitted to the IRB.

D. **Identify** if the written procedures describe the method of review utilized by the convened IRB (e.g., full board review, primary reviewer(s)).

1) If the IRB uses a primary reviewer system, **identify** if the written procedures outline the role of the primary reviewer, for example, attendance at the IRB meeting, leading the discussion, etc.

2) **Identify** if the written procedures describe what documents are routinely distributed to all IRB members and those that may be distributed to specific IRB members (e.g., primary reviewer(s)). If so, **identify** what each IRB member receives prior to the convened IRB meeting.

3) **Identify** if all IRB members have access to copies of the complete submission to the IRB. If so, describe the mechanism utilized by the IRB members to access the copies of the complete submission.

A submission package for initial review may include:

- Protocol(s)/amendment(s);
- Written informed consent document(s) and consent form updates that the clinical investigator proposes for use in the trial;
- Subject recruitment procedures (e.g., advertisements);
- Written information to be provided to subjects;
- Information about payments and compensation available to subjects; and
- Information sheets or instruction summaries given to human subjects, and if applicable, the clinical investigator’s brochure that includes, but is not limited to, the summary of information relating to safety and effectiveness in humans obtained from prior clinical studies, and a description of the drug product.

E. **Identify** if the written procedures describe how the IRB ensures that clinical investigators make all modifications initially required by the IRB prior to enrollment of research subjects.

F. **Determine** whether the IRB ensures the requirements set forth in 21 CFR 56.111, Criteria for IRB Approval of Research, were met prior to approving the research.

G. **Describe** the IRB's written procedures for determining the effective date of initial approval, including when the IRB reviews and approves research with conditions without requiring further review at a subsequent meeting.

H. **Identify** if the IRB has a mechanism to assess whether the investigator and/or sponsor has made a determination about whether an IND or IDE is/is not required for a proposed study, if

applicable, and the basis for this determination.[7]

FDA regulations require sponsors and sponsor-investigators to obtain an IND or IDE when necessary for a particular study (21 CFR 312.20,312.50, and 812.20).

8. IRB Review of Research Involving Medical Devices[8]

The IRB is responsible for making a SR/NSR determination for research involving medical devices (21 CFR 812.66) unless FDA has already made the risk determination, i.e., an IDE has been approved or FDA has determined that the study is SR, NSR, or exempt. For NSR medical device research conducted under 21 CFR 812.2(b)(1)(ii), the IRB serves as FDA's surrogate for the review, approval, and continuing review of NSR investigations.

A. Under 21 CFR 812.3(m), the definition of a SR device is one that is:

1) Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

2) 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;

3) 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

4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

FDA does not have a specific definition for an NSR device.

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.

The NSR designation 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)).

[7] Guidance for IRBs, Clinical Investigators and Sponsors IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed (2013), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/irb-responsibilities-reviewing-qualifications-investigators-adequacy-research-sites-and

[8] Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors Significant Risk and Nonsignificant Risk Medical Device Studies (2006), http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

B. Risk Determination

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

1) If the IRB reviews research involving medical devices, **identify** whether the IRB has and follows written procedures for making the SR/NSR determination for investigational device research. FDA recommends that IRBs have procedures in place that explain how the IRB makes the SR/NSR determination and how that determination should be documented.

2) **Determine** if the sponsor made the initial risk determination of NSR and presented this information to the IRB. 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 abbreviated IDE. The requirements for abbreviated IDEs can be found at 21 CFR 812.2(b).

3) **Identify** if the IRB has made a determination of SR/NSR for any device studies and describe how the IRB documented the risk determination. The IRB should make the SR/NSR determination by reviewing relevant information at a convened meeting and document the results in the meeting minutes.

4) **Determine** 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 (21 CFR 812.66).

9. IRB Review of HUDs - Clinical Use and Use in Research[9]

As defined in 21 CFR 814.3(n), a humanitarian use device (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 no more than 8,000 individuals in the United States per year. A Humanitarian Device Exemption (HDE) is a marketing application for a HUD, which is exempt from effectiveness requirements and subject to certain profit and use restrictions. HUDs can only be used in a facility after an IRB has approved its use in the facility, except in certain emergencies. Full board approval is required to authorize the HUD's use under the HDE at the institution initially, but expedited review may be used for oversight thereafter.

The use of an HUD itself does not constitute research. However, research may be performed using the HUD without an IDE when the HUD is used within the approved labeling. Research on uses of the HUD outside of the approved labeling must follow the IDE regulations.

[9]Humanitarian Device Exemption Program Guidance for Industry and FDA Staff (2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/humanitarian-device-exemption-hde-program

A. **Determine** if the IRB reviews the use of HUDs in the facility that have an approved HDE. If so, **determine** if the IRB has written procedure(s) for initial and continuing review of a HUD including whether the IRB requires a consent document for the use of the HUD (21 CFR 814.124). 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.

1) A physician in an emergency situation may determine that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient. In this case, a HUD may be used without prior approval. The physician must provide notification of the use to the chairperson of the IRB, and the notification must include the identification of the patient involved, the date of the use, and the reason for the use (FD&C Act, Section 520(m)(4)). FDA regulations require that physicians provide such notification to the chairperson of an IRB in writing within 5 days of the emergency use of the device (21 CFR 814.124 (a)). **Determine** if the IRB has received notifications of the emergency use of an HUD that has not been approved for use in the facility.

2) 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 56) and informed consent of the subjects (21 CFR 50) are still required for the clinical investigations, as defined in these regulations. **Determine** if the IRB approved such a study and verify compliance with the applicable requirements of 21 CFR 50 and 56.

3) Investigational use for an indication different from the HDE- approved indication(s) must be conducted in compliance with the applicable IDE regulations (21 CFR 812), in addition to complying with the applicable requirements for IRB approval and informed consent. If the study is a SR study, an FDA- approved IDE is required (21 CFR 812.20(a)(1)). **Determine** if the IRB approved a study investigating use of a HUD for a different indication than the HDE approved indication. If so, verify compliance with 21 CFR 812, 50, and 56.

10. Studies Involving Children

If a study involves children as subjects, the IRB must determine that the research study complies with 21 CFR 50 Subpart D – Additional Safeguards for Children in Clinical Investigations (Subpart D) (21 CFR 56.109(h)). Subpart D requires that the IRB approve only those clinical investigations that meet the criteria described in 21 CFR 50.51, 50.52, 50.53, or 50.54. The IRB must also assure that adequate provisions are 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 the permission of the children's parents or guardians as set forth in 21 CFR 50.55 (21 CFR 50.51-50.55). When the IRB determines that assent from the child is required, it must also determine whether and how assent must be documented (21 CFR 50.55(g)).

Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for clinical investigations covered by 21 CFR 50.51 or 50.52 (21 CFR 50.55(e)(1)). Where clinical investigations are covered by 21 CFR 50.53 or 50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child (21 CFR 50.55(e)(2)).

If children that are wards of the State are included in the clinical investigation, the study must meet the requirements in 21 CFR 50.56.

For research involving children as subjects, the IRB must find that the research fits into one of the following[10]:

- 21 CFR 50.51 -- Clinical investigations not involving greater than minimal risk;
- 21 CFR 50.52 -- Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects;
- 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; or
- 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.

A. If an IRB reviews research that involves children:

1) **Determine** if the IRB has written procedures describing the IRB's responsibilities for the additional safeguards for children involved in clinical research including the determinations required by 21 CFR 50 Subpart D.

2) **Determine** if the IRB considered including in the membership one or more individuals knowledgeable about and experienced in working with children as subjects (21 CFR 56.107(a)).

3) **Identify** if the IRB chose to invite individuals with appropriate expertise in studies involving children to assist the IRB in reviewing the study (21 CFR 56.107(f)).

4) If the IRB approved any studies under 21 CFR 50.51, 50.52, and/or 50.53, **determine** if the IRB found that the criteria set forth in the applicable regulations were met prior to approval of the research. For example, that adequate provisions were made for soliciting the assent of children and permission of their parents or guardians as required in 21 CFR 50.55. **Identify** where the IRB documented this finding.

5) If the IRB approved any studies under 21 CFR 50.54, **determine** if the IRB found that the conditions set forth in the regulations were met prior to approval of the research. For example, that adequate provisions were made for soliciting the assent of children and permission of their parents or guardians as required in 21 CFR 50.55. **Identify** where the IRB documented this finding.

[10] Ethical Considerations for Clinical Investigations of Medical Products Involving Children Draft Guidance for Industry, Sponsors, and IRBs (2022), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ethical-considerations-clinical-investigations-medical-products-involving-children

6) For the studies conducted under Subpart D, **determine** if the IRB found that permission of the child's parent(s) or guardian(s) was granted in accordance with (21 CFR 50.55(e)-(f). **Identify** where the IRB documented this finding.

7) For the studies conducted under Subpart D, **determine** if the IRB found that the children were capable of providing assent (21 CFR 50.55(a)-(b)). **Identify** where the IRB documented this finding.

8) If the IRB concluded that assent is not necessary for proceeding with the clinical investigation, **determine** if the IRB found that the following criteria under 21 CFR 50.55(c) were met:

   a) That the capability of some or all of the children is so limited that they cannot reasonably be consulted; or

   b) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.

   Identify where the IRB documented these findings.

9) If the IRB waived assent for children participating in research, **determine** if the IRB found and documented that the following criteria under 21 CFR 50.55(d) were met:

   a) The clinical investigation involves no more than minimal risk to the subjects;

   b) The waiver will not adversely affect the rights, welfare, or safety of the subjects;

   c) The clinical investigation could not practicably be carried out without the waiver; and

   d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

B. 21 CFR 50.56 Wards

Children who are wards of the state or any other agency, institution or entity may participate in clinical investigations under 21 CFR 50.51 and 50.52. Children who are wards may only participate in clinical investigations under 21 CFR 50.53 or 50.54 if the clinical investigation meets the criteria included in the 21 CFR 50.56.

If children who are wards of the state or any other agency, institution, or entity may be included in a clinical investigation approved by the IRB under 21 CFR 50.53 or 50.54, **determine** if the IRB ensured the regulatory requirements included in 21 CFR 50.56 were met.

11. Continuing IRB Review of Research

A. **Determine** if the IRB has the authority to approve, require modifications in (to secure approval), disapprove all research activities, and/or suspend or terminate approval of ongoing studies (21 CFR 56.109(a) and 56.113).

B. **Determine** if the IRB conducts continuing review of research at intervals appropriate to the degree of risk, but not less than once per year in accordance with 21 CFR 56.109(f).

C. **Determine** whether the IRB followed its written procedures for conducting continuing review of research (21 CFR 56.108(a)(1)).

1) **Identify** whether the clinical investigator submits reports (e.g., progress reports) to facilitate continuing review of research as required by the IRB's written procedures.

2) **Identify** if IRB members have access to the information required by the IRB's written procedures in order to conduct its continuing review of research.

D. **Determine** if the IRB was provided with sufficient information to determine whether the study should be allowed to continue, modified in order to continue, suspended, or terminated.

E. **Determine** whether the IRB followed the criteria for approval of research as outlined in 21 CFR 56.111 when considering if a study should be allowed to continue.

F. **Describe** how the IRB verifies that the clinical investigator addressed the modifications required by the IRB to continue the study.

G. **Identify** how changes in research (protocol amendments, informed consent form changes, and other revisions) are reviewed and approved by the IRB.

H. **Determine** if the IRB prepares and maintains adequate documentation of records of continuing review activities, including copies of progress reports submitted by clinical investigators and copies of all correspondence between the IRB and the clinical investigators (21 CFR 56.115(a)(1)(3) and (4)).

I. **Determine** if actions by the IRB on continuing review activities are documented in the meeting minutes (21 CFR 56.115(a)(2) and (3)).

J. **Identify** where the study approval period, i.e., frequency of review, is documented.

12. Expedited Review

A. **Determine** whether the IRB's use of expedited review procedures meets the requirements of 21 CFR 56.110. **Determine** if the IRB adopts a method for keeping all members advised of research proposals which have been approved under the expedited review procedure (21 CFR 56.110(c)).

The list of categories of research that may be approved through expedited review is found in the Federal Register Notice, Categories of Research That May Be Reviewed by the

Institutional Review Board (IRB) Through an Expedited Review Procedure.[11]

B. **Determine** whether expedited review procedures are used to approve research other than the types of research described in 21 CFR 56.110.

13. Unanticipated Problems Involving Risks to Human Subjects or Others

The IRB must follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any unanticipated problems involving risks to human subjects or others (21 CFR 56.108(b)(1)). To fulfill its oversight obligations during the conduct of a clinical study, an IRB must have, among other things, information concerning unanticipated problems involving risk to human subjects in the study, including adverse events (AEs) that are considered unanticipated problems.

For IND studies, clinical investigators are required to "promptly report to the IRB . . . all unanticipated problems involving risk to human subjects or others" (21 CFR 312.66).

For IDE studies, investigators are required to submit a report of an unanticipated adverse device effect (UADE) to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)).

A. **Determine** if the IRB follows written procedures for ensuring prompt reporting to the IRB, the appropriate institutional officials, and the FDA of any unanticipated problems involving risks to human subjects or others (21 CFR 56.108(b)(1)).

B. **Identify** if the IRB's written procedures include information about who is responsible for promptly reporting to each of the three entities (the IRB, appropriate institutional officials, and the FDA), the timeframes for reporting, and whether such reports are being submitted in accordance with the IRB's written procedures.

C. **Identify** if the IRB's written procedures include information about what might qualify as an unanticipated problem involving risks to human subjects or others, such as types of AEs (e.g., serious and unexpected AEs) that may be considered unanticipated problems, the type of information to submit to the IRB regarding an unanticipated problem, and the type of IRB review for such reports (e.g., full board review vs. expedited review).

D. **Describe** the IRB's actions when the IRB reviews an unanticipated problem involving risks to subjects or others that requires prompt reporting to the IRB under 21 CFR 56.108(b). If the IRB's written procedures specify full board review of the unanticipated problem, determine whether the IRB meeting minutes document the IRB's action, if any, resulting from that review (21 CFR 56.115(a)(2)).

[11] Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure (1998), https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/categories-research-may-be-reviewed-institutional-review-board-irb-through-expedited-review

14. IRB Reporting to the Clinical Investigator and 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. **Identify** how the IRB notifies clinical investigators of their responsibility to promptly report and obtain IRB approval of proposed changes in a research activity, except where necessary to eliminate apparent immediate hazards to human subjects; and to report unanticipated problems regarding risks to human subjects or others, any instance of serious or continuing noncompliance with applicable regulations or the requirements or determinations of the IRB, and any suspension or termination of IRB approval.

C. **Identify** whether the IRB has a mechanism for ensuring that clinical investigators are made aware of their responsibilities for complying with the IRB written procedures (e.g., handbooks or informational sheets for clinical investigators which describe their responsibilities; letters of approval to clinical investigators which describe their responsibilities; copy of the IRB written procedures given to the clinical investigators or posted electronically by the IRB for access by clinical investigators).

D. If the IRB disapproved proposed research, **determine** if the IRB provided a statement of the reasons for its decision and gave the clinical investigator an opportunity to respond in person or in writing (21 CFR 56.109(e)).

E. **Determine** if the IRB maintains copies of all correspondence between the IRB and clinical investigator (21 CFR 56.115(a)(4)).

15. Informed Consent (21 CFR 50.20, 50.25 & 50.27)

The IRB is responsible for reviewing research protocols and related materials, including informed consent documents, to ensure the protection of the rights, welfare, and safety of human subjects participating in research and the requirements of 21 CFR 50 are met. **Determine** if the IRB has written procedures for reviewing the informed consent document and the informed consent process, and whether these written procedures were followed.

For the studies selected for review during the inspection:

A. **Determine** if the IRB reviewed and approved the informed consent document, that includes the required elements for informed consent under 21 CFR 50.25(a), any of the elements of 21 CFR 50.25(b) that are relevant to the study, and changes and revisions to the informed consent document.

B. For applicable clinical trials, **determine** whether the informed consent document includes the statement required by 21 CFR 50.25(c), “A description of this clinical trial will be available on https://ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.”

C. **Determine** if the IRB reviewed and approved an informed consent document that is in a language understandable to the prospective subject or legally authorized representative (21 CFR 50.20), e.g., when the research is expected to involve potential subjects who do not understand English.

D. **Determine** if the IRB requires documentation of informed consent in accordance with 21 CFR 50.27 (21 CFR 56.111 (a)(5)).

E. **Identify** whether the IRB has written procedures for determining whether the additional elements of informed consent (found at 21 CFR 50.25(b)) are material to prospective subjects' decision to participate and to be included in the informed consent.

F. **Identify** whether the IRB has written procedures to determine the need and method to inform currently enrolled subjects of new information that arises during the conduct of the clinical investigation that could affect a subject's willingness to continue participation in the clinical trial.

16. Exception and/or Waiver of Informed Consent

A. Exception from Informed Consent Requirements for Minimal Risk Investigations (21 CFR 50.22)

The IRB responsible for the review, approval, and continuing review of the clinical investigation may approve an informed consent procedure that does not include or that alters some or all of the elements of informed consent set forth in the regulations at 21 CFR 50.25(a) and (b), or may waive the requirement to obtain informed consent, provided the IRB finds and documents certain criteria are met.

1) **Determine** whether the IRB reviewed and approved a waiver or alteration of informed consent for any clinical investigations.

2) If so, **determine** whether the IRB found and documented that the following criteria for waiver or alteration were met:

a) The clinical investigation involves no more than minimal risk to the subjects;

b) The clinical investigation could not practicably be carried out without the requested waiver or alteration;

c) If the clinical investigation involves using identifiable private information or identifiable biospecimens, the clinical investigation could not practicably be carried out without using such information or biospecimens in an identifiable format;

d) The waiver or alteration will not adversely affect the rights, welfare, and safety of the subjects; and

e) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

3) **Determine** whether the IRB found that subjects or legally authorized representatives were to be provided with additional pertinent information after participation.

4) **Identify** whether the IRB has written procedures for waiver or alteration of informed consent. If so, **determine** whether the IRB followed its written procedures.

B. Exception from General Requirements for Informed Consent (21 CFR 50.23)

21 CFR 50.23 allows for the use of a test article with an exception from the requirements of informed consent in certain situations.

1) Prior to the use of the test article

If informed consent is not obtained before the use of the test article, **determine** if the IRB confirmed that the clinical investigator and a physician who is not participating in the clinical investigation certify in writing all of the following:

a) The subject was in a life-threatening situation necessitating the use of the test article;

b) Informed consent could not be obtained from the subject due to an inability to communicate with or obtain legally effective informed consent from the subject;

c) Time was not sufficient to obtain consent from the subject's legal representative; and

d) There was no available alternative method of approved or generally recognized therapy that provided an equal or greater likelihood of saving the life of the subject.

2) After the use of the test article

If the immediate use of the test article is required to preserve the life of the subject and time is not sufficient to obtain an independent determination as required in 21 CFR 50.23(a) before the use of the test article, verify that the determination was made by the clinical investigator and within five working days after the use of the article was reviewed and evaluated in writing by a physician who is not participating in the clinical investigation (21 CFR 50.23(b)).

3) If the test article is used without informed consent in accordance with 21 CFR 50.23(a) and (b), **determine** if it was reported to the IRB within five working days after the use of the test article (21 CFR 50.23(c)). If it was not reported within five working days, what action did the IRB take?

4) If the IRB has written procedures for the use of a test article per 21 CFR 50.23(a) and (b), **determine** if the IRB follows its written procedures.

C. Exception from Informed Consent Requirement for Emergency Research (21 CFR 50.24) [12]

1) If the IRB has written procedures for review and approval of clinical investigations involving exception from informed consent for emergency research under 21 CFR 50.24, **determine** whether the IRB follows its written procedures.

2) If the IRB responsible for the review, approval, and continuing review of the clinical investigation involving an exception from informed consent approved the clinical investigation without requiring informed consent, **determine** if the IRB:

[12]Exception from Informed Consent Requirements for Emergency Research (2013), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exception-informed-consent-requirements-emergency-research

a) Included 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; and

b) Found and documented that each of the requirements in 21 CFR 50.24(a)(1-7) are met.

3) **Determine** if the IRB has addressed procedural requirements in 21 CFR 50.24 (b, c, & e).

17. Emergency Use of a Test Article (21 CFR 56.104(c))

Emergency use means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)).

In accordance with the regulations at 21 CFR 56.104(c), emergency use of a test article is exempt from the requirements of IRB review provided that such emergency use is reported to the IRB within five working days. Any subsequent use of the test article at the institution is subject to IRB review.

A. **Determine** if the IRB ensured that the emergency use of the investigational product met all of the conditions in 21 CFR 56.102(d).

B. **Determine** if the emergency use of the investigational product was reported to the IRB within five working days.

C. **Determine** if the IRB is aware of any subsequent use of the investigational product at the institution without its review and approval.

D. **Identify** if the IRB has established written procedures for the emergency use of investigational products and confirm whether the IRB follows these procedures in emergency use situations.

18. Electronic Records and Electronic Signatures[13]

Electronic systems, electronic records, electronic signatures, and handwritten signatures executed to electronic records used by an IRB may be subject to regulations found in 21 CFR Part 11, Electronic Records and Electronic Signatures. In general, 21 CFR 11 requirements apply to electronic records and electronic signatures and to the electronic systems used by IRBs to create, modify, maintain, archive, retrieve, or transmit records required by 21 CFR 56.115.

Regardless of the type of electronic 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.

[13] See the Draft Guidance for Industry Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers (March 2023).See also Guidance for Industry Part 11, Electronic Records; Electronic Signatures - Scope and Application (August 2003).

In general, as stated in the 2003 Part 11 guidance[14], the Agency intends to exercise enforcement discretion regarding certain Part 11 provisions for validation, record copying, record retention, and audit trails (refer to 21 CFR 11.10(a), (b), (c), and (e), respectively). Therefore, compliance with applicable regulatory requirements on recordkeeping, record copying, and record retention will be evaluated in accordance with appropriate predicate rules (e.g., 21 CFR 56.115). Prior to noting an observation on an FDA 483 regarding non-compliance with Part 11, discuss the issue with your supervisor and the center POC.

A. **Identify** what electronic systems, including software and hardware, if any, are used by the IRB to create, modify, maintain, archive, retrieve, or transmit electronic records and obtain electronic signatures documenting IRB activities.

   1) **Explain** how the IRB determines which records (e.g., IRB submission records, meeting minutes, membership lists, notifications to an investigator and institution, etc.) are created, modified, maintained, archived, retrieved, or transmitted in electronic format.

   2) **Identify** if the IRB has written procedures, user-manuals, access policies and procedures on the operational use of the electronic system that may include the following processes:

      a) System setup/installation and maintenance;

      b) Electronic system user training;

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

      d) Alternative recording methods (in case of system unavailability);

      e) Access controls and authorization checks for user's actions; and

      f) Delegated roles and responsibilities of authorized users.

   3) **Determine** if the IRB limits access to authorized individuals and uses authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

   4) **Describe** the extent of the authorized individual's access, privileges, and restrictions (e.g., read-only access to IRB communications to the investigator, etc.). Include how authorized users access the systems (e.g., use of username and password combinations, multifactor authentication, biometrics), and whether access rights (security credentials) are deactivated when a user is no longer required or permitted to use the IRB or institution’s electronic system.

   5) **Determine** whether individuals who develop, maintain, or use the electronic system have the education, training, and experience to perform their assigned tasks.

[14] See the Draft Guidance for Industry Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers (March 2023).See also Guidance for Industry Part 11, Electronic Records; Electronic Signatures - Scope and Application (August 2003).

6) **Identify** backup, disaster recovery, and/or contingency plans to protect against record loss. Were there any installed software upgrades, security or performance patches, or new instrumentation that affected the electronic records?

7) **Document** any instances in which the electronic system did not function as it was intended. **Describe** any system failures or error messages that resulted in loss of electronic records and whether the incident was reported (for example, to the IRB, appropriate institutional official, and FDA). **Describe** the corrective actions, if any, that were taken.

19. Cooperative Research[15]

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, an institution's IRB may serve as a central IRB, an institution's IRB may rely on the review of research by a centralized IRB (in whole or in part) in place of its own IRB review of the study, or it can conduct its own review of the study.

A. **Identify** whether the IRB's policies outline under what circumstances the institution's IRB may participate in a centralized review process and the role of the institution's IRB in that process.

1) Institution's IRB **serving** as the central IRB (IRB of record)

a) **Identify** whether a signed agreement exists between the institution, its IRB, and participating IRBs in the multi-institutional research.

b) **Identify** if the IRB provided a copy of the agreement to the institution and the clinical investigator.

c) **Describe** the specific responsibilities of the central IRB for conducting initial and continuing review of the research.

d) **Identify** if the institution's IRB serving as the central IRB has written procedures in place to implement the centralized review process. For example, procedures on how the central IRB intends to communicate with relevant institutions, the institutions' IRB, and clinical investigators regarding its review and how the central IRB ensures that it provides meaningful consideration of relevant local factors for communities from which the research subjects are drawn.

e) **Identify** if IRB meeting minutes or other records document whether relevant local community issues were considered in the review of the research.

f) **Identify** if the signed agreement apportions IRB review responsibilities between the central IRB and local IRBs where the multicenter studies are conducted. Identify if the IRB serving as the central IRB has written procedures describing how it will implement its responsibilities under the agreement.

2) Institution's IRB **relying** on the review of research by a central IRB (IRB of record)

[15] Using a Centralized IRB Review Process in Multicenter Clinical Trials (2006), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/using-centralized-irb-review-process-multicenter-clinical-trials

a) **Identify** whether a signed agreement exists between the institution, institution's IRB relying on the central IRB, and the central IRB.

b) **Identify** if the institution's IRB provided a copy of the agreement to the institution and the clinical investigator.

c) **Describe** the specific responsibilities of the institution's IRB when relying on the central IRB's conduct of initial and continuing review of the research.

d) **Identify** how the institution's IRB determines that the central IRB is qualified to review and approve research conducted at the institution.

e) **Identify** if the institution's IRB relying on the central IRB has written procedures in place to implement the centralized review process.

f) **Identify** if the signed agreement apportions IRB review responsibilities between the central IRB and institution's IRB for the multicenter studies conducted at the site. **Determine** if the institution's IRB has written procedures describing how it will implement its responsibilities under the agreement.

PART IV - ANALYTICAL

No analytical activities are planned under this program.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

The following information is to be used in conjunction with the instructions in OII SOP: *Establishment Inspection Report Classification Process* to determine the OII OBMI division recommended classification and center final classification of inspections of IRBs.

1. Classification

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

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

C. Official Action Indicated (OAI) – Objectionable conditions or practices were found, and the scope, severity, or pattern of violations(s) support a finding that:

1) 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

2) Subjects' rights, welfare, or safety would be or have been seriously compromised; or

3) Data integrity or reliability is or has been compromised.

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

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

2. Administrative Actions for Noncompliance

A. Advisory, administrative, and judicial actions may be pursued based on the inspectional observations and will be in accordance with applicable regulations. FDA can invoke other legal sanctions under the Federal Food, Drug, and Cosmetic Act (FFDCA) and/or Title 18 of the United States Code (U.S.C.), where appropriate. If apparent noncompliance with FDA regulations in the operation of an IRB is observed during an inspection, the FDA may move forward with the following advisory and/or regulatory actions, as appropriate (21 CFR 56.120):

1) Issuing an Untitled Letter may be considered when the violations do not meet the threshold of regulatory significance for a Warning Letter;

2) Issuing a Warning Letter may be considered when the violation meets the threshold of regulatory significance and there is a reasonable expectation that the responsible firm (e.g., IRB) will take prompt corrective action;

3) Reinspecting to confirm the adequacy of corrective actions;

4) Withholding approval of new studies subject to 21 CFR 56 that are conducted at the institution or reviewed by the IRB;

5) Directing that no new subjects may be recruited for ongoing studies;

6) Terminating ongoing studies when doing so would not endanger subjects; and

7) Notifying relevant federal and state agencies, and other parties of the noncompliance.

B. 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), and the Commissioner of the FDA determines the disqualification of the IRB or parent institution is justified, 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 56; and

2) The noncompliance adversely affects the rights, welfare, or safety of the human subjects in a clinical investigation.

FDA will issue an order that explains the basis for the determination and will send a notice of disqualification to the IRB and the parent institution.

FDA will not approve an application for a research permit (e.g., IND) 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 application or permit the data from a clinical investigation that was reviewed by a disqualified IRB.

C. Actions alternative or additional to disqualification (21 CFR 56.124). The FDA may institute appropriate judicial proceedings (civil or criminal) and other regulatory action through the Department of Justice at any time. The FDA may also refer the matter to other federal, state, or local agencies for any action they determine to be appropriate.

3. Follow-Up Inspections

A. OII OBMI division follow-up actions, including re-inspection, will be made at the request of the center. Centers should evaluate whether the violations found indicate systemic problems with the conduct of the study or the reliability of the data and whether additional inspection assignments should be issued (e.g., clinical investigator, sponsor).

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.

PART VI REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

1. References

A. FDA Laws

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

1) Most Relevant 21 CFR Regulations

Part 50 – Protection of Human Subjects

Part 56 – Institutional Review Boards

Part 312 – Investigational New Drug Application

Part 812 – Investigational Device Exemptions

2) Other 21 CFR Regulations

Part 11 - Electronic Records; Electronic Signatures

Part 814 - Premarket Approval of Medical Devices (includes HDE Requirements in 814.100)

Part 320 – Bioavailability and Bioequivalence Requirements

B. FDA Guidelines, Guidance, and Inspection Guides

1) General

Inspection Processes: Investigations Operations Manual (IOM) Chapter 5 (Establishment Inspections).

2) Relevant FDA Guidance

Guidance documents and information sheets pertaining to good clinical practice (GCP) and the conduct of clinical studies are accessible on FDA's website: https://www.fda.gov/regulatory-information/search-fda-guidance-documents. Below is not an all-inclusive list.

a) Key Information and Facilitating Understanding in Informed Consent Guidance for Sponsors, Investigators, and Institutional Review Boards, March 2024

b) Institutional Review Board (IRB) Review of Individual Patient Expanded Access Submissions for Investigational Drugs and Biological Products, Guidance for IRBs and Clinical Investigators, September 2023

c) Informed Consent Guidance for IRBs, Clinical Investigators, and Sponsors, August 2023

d) Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers, March 2023

e) Ethical Considerations for Clinical Investigations of Medical Products Involving Children, Draft Guidance for Industry, Sponsors, and IRBs, September 2022

f) FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency - Guidance for Industry, Investigators, and Institutional Review Boards, August 2021

g) Humanitarian Device Exemption (HDE) Program Guidance for Industry and Food and Drug Administration Staff, September 2019

h) Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations - Guidance for Sponsors, Investigators, and Institutional Review Boards, October 2018

i) Institutional Review Board (IRB) Written Procedures: Guidance for Institutions and IRBs, May 2018

j) Minutes of Institutional Review Board (IRB) Meetings- Guidance for Institutions and IRBs, September 2017

k) Use of Electronic Informed Consent in Clinical Investigations: Questions and Answers - Guidance for Institutional Review Boards, Investigators, and Sponsors, December 2016

l) Guidance for IRBs, Clinical Investigators, and Sponsors Considerations When Transferring Clinical Investigation Oversight to Another IRB, May 2014

m) Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND - Guidance for Clinical Investigators, Sponsors, and IRBs, September 2013

n) IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed - Guidance for IRBs, Clinical Investigators, and Sponsors, August 2013

o) Exception from Informed Consent Requirements for Emergency Research: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors, April 2013

p) Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review after Clinical Investigation Approval, February 2012

q) Guidance on Exculpatory Language in Informed Consent, August 2011

r) Guidance for Institutional Review Boards (IRBs) Frequently Asked Questions – IRB Registration, July 2009

s) Adverse Event Reporting to IRBs — Improving Human Subject Protection - Guidance for Clinical Investigators, Sponsors, and IRBs, January 2009

t) Guidance for Industry: Computerized Systems Used in Clinical Investigations, May 2007

u) 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, December 2006

v) Guidance for Industry: Using a Centralized IRB Review Process in Multi-Center Clinical Trials, March 2006

w) FDA Institutional Review Board Inspections Guidance for IRBs, Clinical Investigators, and Sponsors, January 2006

x) Guidance for Industry: IRB Review of Stand-Alone HIPPA Authorizations Under FDA Regulations, October 2003

y) Guidance for Industry: Part 11: Electronic Records, Electronic Signatures -- Scope and Application, August 2003

z) General Principles of Software Validation; Final Guidance for Industry and FDA Staff, January 2002

3) Relevant FDA Information Sheets

a) Information Sheet, Payment and Reimbursement to Research Subjects, Guidance for IRBs and Clinical Investigators, January 2018

b) Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Waiver of IRB Requirements for Drug and Biological Product Studies, October 2017

c) Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: FDA Institutional Review Board Inspections, January 2006

d) Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Frequently Asked Questions About Medical Devices, January 2006

e) Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies, January 2006

f) Information Sheet, Institutional Review Boards Frequently Asked Questions, Guidance for Institutional Review Boards and Clinical Investigators, January 1998

g) Information Sheet, Recruiting Study Subjects, Guidance for Institutional Review Boards and Clinical Investigators, January 1998

2. Program Contacts

A. 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 POC identified in the assignment.

1) For operational questions, contact:

Office of Inspections and Investigations (OII)
Office of Bioresearch Monitoring Inspectorate (OBMI) - OII OBMI Immediate Office Inspection POC, OIIbimoinspectionpoc@fda.hhs.gov

2) For questions about GCP and CP issues specific to a center product area, contact:

Center for Drug Evaluation and Research (CDER)
Office of Compliance (OC)
Office of Scientific Investigations (OSI)
BIMO-CDEROSI@fda.hhs.gov

Center for Biologics Evaluation and Research (CBER)
Office of Compliance and Biologics Quality (OCBQ)
Division of Inspections and Surveillance (DIS)
CBERBIMONotification@fda.hhs.gov

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

Human Foods Program (HFP)
HFP-BIMO@fda.hhs.gov

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

Center for Veterinary Medicine (CVM)
Office of Surveillance and Compliance
CVMBIMORequests@fda.hhs.gov

3) For crosscutting questions about GCP policy and program issues impacting the agency's BIMO programs, contact:

Office of Clinical Policy (OCLP)
Office of the Chief Medical Officer (OCMO)
gcpquestions@fda.hhs.gov

PART VII – FDA CENTER AND OFFICE RESPONSIBILITIES

1. CENTER

A. Select IRBs for surveillance inspections based on the centers' internal processes and sends OII a list of IRBs selected for surveillance inspections.

B. Identifies and issues IRB for-cause inspection assignments and provides background materials to OII.

C. Communicates specific concerns, if any, to the OII investigator prior to inspection.

D. Addresses inquiries regarding IRB inspection assignments and compliance issues.

E. Participates in inspections as a SME, if needed. Refer to Part II (Implementation) of this CP for additional information regarding responsibilities of center participants when participating on an inspection.

F. Provides guidance and support to the OII investigator during all phases of inspections and investigations.

G. Reviews and evaluates EIRs, attachments/exhibits, and regulatory recommendations from OII OBMI divisions.

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

I. Determines final classifications of inspections, enters the classification into the appropriate information technology system, and notifies OII of the final classification decision.

J. Issues post-inspectional correspondence to the inspected entity.

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

L. Promptly provides copies of all relevant correspondence between the inspected firm and FDA to the OII OBMI division.

2. OFFICE OF INSPECTIONS AND INVESTIGATIONS

A. OFFICE OF BIORESEARCH MONITORING INSPECTORATE

1) Provides inspection quality assurance, training of OII personnel, and operational guidance.

2) Maintains liaison with centers, OII OBMI divisions, and OCLP, and resolves operational questions.

3) Receives and reviews for-cause IRB inspection assignments from the centers via OII OBMI Immediate Office Inspection POC email and forwards to the appropriate division.

4) Tracks inspection assignments and accomplishments.

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

B. DIVISION OF FIELD ENFORCEMENT

1) Works with center personnel on behalf of OII, on all administrative warrants and disqualification actions; also liaises with centers to ensure coordination of cases.

2) For disqualification actions, issues the Notice of Opportunity for a Hearing (NOOH) to the IRB and the parent institution.

3. OFFICE OF CLINICAL POLICY

1) Addresses key clinical policy issues across the FDA's regulated product centers.

2) Serves as the FDA focal point for Good Clinical Practice (GCP) and Human Subject Protection (HSP) issues related to FDA-regulated clinical trials.

3) Sets priorities for the development of GCP and HSP policy.

4) Works to ensure consistency in GCP and HSP policy across the agency.

5) Participates in international GCP and HSP harmonization activities and serves as the liaison to other federal agencies and external stakeholders committed to the protection of human research participants.