Complete Regulatory Binder with Instructions

Purpose

The Regulatory Binder is available to help study sites achieve and maintain regulatory compliance and adhere to high standards of practice in the conduct of research involving human subjects.

Each section outlines the regulatory documentation requirements, general guidance for organization and record keeping, and, when applicable, references to federal regulations and Good Clinical Practice guidelines.

General Guidance for using the Regulatory Binder

- Tailor the binder to meet the needs of your specific protocol:
    - The Regulatory Binder is a template. Include only sections pertinent to your protocol. Omit unused sections and add sections as needed. See "Applicable sections" below for more information. If unsure what sections to include/exclude, contact the OCR Office.
    - Organize and order the sections to facilitate easy use and reference, e.g., file the most frequently used or referenced sections in the front of the binder.
    - Add additional tabs and/or documents to each section as needed.

- Keep the Regulatory Binder accessible, current, and up-to-date.
    - Identify an individual(s) responsible for maintaining the binder.
    - Store binder in a safe and secure location, but accessible to study staff at all times.

- Participant-specific documentation and information, e.g., signed consent forms, test results, and completed case report forms, should be maintained separately in participant-specific binder/file.

What sections apply to your Research Protocol

Depending on the nature of the research, some tabs may or may not be required. Use the below list to ensure that the applicable sections are maintained. For questions, contact the Office of Clinical Research.

1. **Human Research**
    a. Protocol
    b. IRB
    c. Consent Forms
    d. Data Collection

e. NIH
f. Sponsor
g. DSMB
h. Training
i. Local Ethical Review
j. Scientific Review
k. Other

2. **Good Clinical Practice.** In addition to #1 above (Human Research), maintain the below tabs:
    a. CVs
    b. Licensure
    c. Investigator's Brochure/Device Manual/Package Insert
    d. Laboratory Documents
    e. FDA

3. **FDA-regulated Human Research (e.g., IND, IDE)**. In addition to above, maintain the below tabs:
    a. Logs
    b. Investigator's Brochure/Device Manual/Package Insert
    c. Drug/Device
    d. FDA

Protocol

Requirements

- ☐ Original Protocol and all amended versions
- ☐ All versions should contain a version date and/or number

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Federal Regulations/Good Clinical Practice

GCP: 8.2.2; 8.3.2

CVs

Requirements

CVs for all key personnel

Guidance

- ✓ CVs should be signed, dated, and updated every 2 years to verify that the information is accurate and current.

- ✓ If CVs are filed collectively for the department, write a signed and dated note-to file indicating the location (include copy of note-to-file here).

- ✓ If CVs are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Federal Regulations/Good Clinical Practice

GCP: 4.1.1; 8.2.10; 8.3.5

Licensure

Requirements

- ☐ Valid licenses/certification for all professional study staff (e.g., medical or nursing license)
- ☐ Current professional certification, as indicated

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).
- ✓ Medical and nursing licenses must be renewed every 2 years. Licensure renewal dates coincide with birth dates. It is important to monitor licensure expiration dates so that those nearing expiration can be promptly replaced.
- ✓ Professional certification information should be included in individual CVs. The frequency with which certification must be renewed varies widely, depending on the requirements of the certifying body.

Federal Regulations/Good Clinical Practice

GCP: 4.1.1

Logs

Examples

- ☐ Pre-Screening Log
- ☐ Enrollment Log
- ☐ Staff Signature Log
- ☐ Delegation of Responsibility Log
- ☐ Monitoring Log*
- ☐ Adverse Event Tracking Log
- ☐ Protocol Deviation/Exception Tracking Log
- ☐ Retained Tissue Log
- ☐ Training Log
- ☐ Other

***Required for FDA-regulated protocols**

Guidance

- ✓ Update logs in a timely manner. To ensure accuracy, logs should be updated as soon as possible after a recordable event occurs, preferably on the same day.

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

IRB

Requirements

- ☐ Copies of signed and dated submissions:
  - Initial Application for Human Research
  - Continuing Review(s)
  - Modifications/Amendments
  - Reportable New Information
  - Adverse Events
  - Protocol Violations
  - Unanticipated Problems
- ☐ Original Approval letters and/or notification of IRB decisions
- ☐ Copy of investigator response to IRB notification (if applicable)
- ☐ Approved/validated recruitment materials
- ☐ Approved/validated additional study information distributed to participants
- ☐ Any foreign language materials (if applicable)
- ☐ IRB Membership Roster*
- ☐ Any additional correspondence related to the study (e.g. e-mails)

***Required for FDA-regulated protocols**

Guidance

- ✓ Submissions should be signed and dated.
- ✓ Approved/validated recruitment materials and additional study information distributed to participants should include version dates and/or numbers.
- ✓ File documents in reverse chronological order.
- ✓ Request a copy of missing documentation from the Organization-specific contact.
- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Consent Forms

Requirements

- ☐ Original copies of all IRB approved versions (evident by the IRB approval/validation stamp) with version dates or numbers
- ☐ Copies of foreign language consent materials, if applicable

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Federal Regulations/Good Clinical Practice

HHS: 45 CFR 46
FDA: 21 CFR 50; 21 CFR 56
GCP: 8.2.3; 8.3.2; 8.3.12

Investigator's Brochure/Device Manual/ Package Insert

Requirements

- ☐ Most recent version of investigator brochure or product information, e.g., package insert or sample label (for investigational drugs)
- ☐ Device Manual or Report of Prior Investigations, ROPI, (for investigational devices)

Guidance

- ✓ Send updated versions to the IRB.
- ✓ If the investigational product is marketed and its pharmacology is widely understood, a basic product information brochure or package insert may be an appropriate alternative.
- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Federal Regulations/Good Clinical Practice

FDA: 21 CFR 312.55
GCP: 8.2.1; 8.3.1

Laboratory Documents

Requirements

- ☐ Lab certification (e.g. CLIA, CAP) and updates
- ☐ Lab Director's CV
- ☐ Handling Instructions (if not specified in Investigator's Brochure, Device Manual, or Package Insert)
- ☐ Normal lab/reference values and updates

Guidance

- ✓ Keep updated documents to exhibit the competency of all lab facilities being utilized, and to support the reliability of test results.
- ✓ If lab documentation is filed separately, write a signed and dated note to file indicating the location (include note to file here).
- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).
- ✓ Research labs typically do not have lab certifications, e.g., CLIA, CAP, and may not have "normal" lab values. If research labs are used, ensure that the lab director's CV and research lab references values are on file.

Federal Regulations/Good Clinical Practice

GCP: 8.2.11; 8.2.12; 8.2.14; 8.3.6; 8.3.7

Drug/Device

Requirements

- ☐ Drug/device shipment and receipt records
- ☐ Drug/device Accountability Log
- ☐ Drug/Device Dispensing Log

Guidance

- ✓ If applicable, write a signed and dated note-to-file indicating where documentation is kept (e.g. Research Pharmacy). Include the note-to-file here.
- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).
- ✓ The PI is responsible for the following with respect to investigational drugs/devices:
  - Maintain records of investigational product delivery to the study site. Include dates, quantities received, batch/serial numbers, and expiration dates.
  - Maintain an inventory of the investigational product at any site. Inventory control records should be updated, signed, and dated by the PI in a timely manner.
  - Record/track use of the investigational product by each participant. Documentation should verify that dosing/device use was in accordance with the approved protocol. Maintain an accountability log that records when the participant(s) received the drugs/device and the specific dosage/device the participant(s) received.
  - Return/dispose of unused investigational product as specified by the sponsor. Maintain documentation of return/disposal.
  - Store the investigational product. The storage area should be locked/secure with access limited to approved study staff only. Drugs/devices should not be stored with standard clinical inventory.

Federal Regulations/Good Clinical Practice

FDA: 21 CFR 312.57; 312.62; 812.140

Data Collection

Requirements

- ☐ Blank set of case report forms (CRFs), data collection sheets, and/or study questionnaire

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).
- ✓ The difference between data collection sheets and case report forms is that data collection sheets typically act as source documentation. That is, during study visits, information is written directly onto the worksheets. An industry sponsor usually provides CRFs; all protocol-required information is transferred to CRFs from data collection sheets. Some studies do not use CRFs. All studies should use some type of data collection sheet.

Federal Regulations/Good Clinical Practice

FDA: 21 CFR 312.53; 312.62
GCP: 8.3.14; 8.3.15; 4.9.3

FDA

Requirements

Sponsor-Investigator:

- ☐ Copy of all Form FDA 1571 submitted to the FDA, Initial IND or Application
- ☐ Amendments to the application
- ☐ Adverse Event Reports
- ☐ Annual Progress Reports

Clinical Investigator:

- ☐ Copy of all versions of the Form FDA 1572 (for investigational drugs)
- ☐ Copy of all versions of Investigator Agreement (for investigational devices)
- ☐ Copy of all Safety Reports submitted to the FDA

Financial Disclosure:

- ☐ Signed and dated copy of all Form FDA 3455 (Disclosure: Financial Interests and arrangements of Clinical Investigators)

Guidance

- ✓ The Form FDA 1571 should be used as the cover sheet for all correspondence sent to the FDA.
- ✓ Instructions for completing The Form FDA 1572 can be found at: http://www.fda.gov/cder/forms/1571-1572-help.html

- ✓ Update the 1572 each time there is a change to any of the information originally provided. Notify the Sponsor of updates.

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Federal Regulations/Good Clinical Practice

FDA: 21 CFR 54; 312.30; 312.32; 312.33; 812.150(b)(1); 812.150(b)(5); 812.35; 812.43(c)
GCP: 4.11; 5.16.2; 5.17.1; 8.3.16; 8.3.17; 8.3.18; 8.3.19

NIH

Requirements

- ☐ Copy of the NIH grant application and progress report

Guidance

- ✓ Submit a copy of the most recent progress report to the IRB at the time of continuing review.
- ✓ Any additional study correspondence (e.g. e-mails) with the NIH and Collaborators.
- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Sponsor

Requirements

- ☐ All correspondence to and from the sponsor (e.g. letters, meeting notes, and notes of telephone calls)
- ☐ Signed Agreements, including Financial Agreements
- ☐ Insurance Statement (when required)

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

DSMB

Requirements

- ☐ Copy of all DSMB reports
- ☐ Copy of all audit reports

Guidance

- ✓ Submit a copy of the most recent DSMB report to the IRB at the time of continuing review
- ✓ Any additional correspondence (e.g. e-mails, letters, meeting minutes) with the DSMB and its members
- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Federal Regulations/Good Clinical Practice

GCP: 8.3.10; 5.19.3

Training

Requirements

- ☐ Copy of human subjects training certification for all study staff
- ☐ Copy of GCP training certification for all staff required to do so (note, NIH and DOD requires GCP training for all staff)
- ☐ Additional training certification of study staff (e.g., phlebotomy, vital signs, etc.)

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Local Ethical Review

Requirements

- ☐ Copy of local ethical approval notices (e.g. IRB)
- ☐ Initial Review approval
- ☐ All Continuing Review approvals
- ☐ All Amendment approvals
- ☐ Closing Report

Guidance

- ✓ It is not sufficient for a U.S.-based institution to approve non-exempt human research conducted abroad. Local ethical review is required.

- ✓ For HHS-funded protocols:
  - The review should be done by the IRB of the collaborating institution or that of another institution in the same geographical area.
  - The local IRB must be registered with OHRP and have an FWA.

- ✓ For non HHS-funded protocols:
  - Review should be done by a Local Ethical Review Board or
  - Community Advisory Board

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Scientific Review

Requirements

- ☐ Copy of materials submitted for scientific review
- ☐ Original, signed notification letters (when applicable)

Guidance

- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Other