Regulatory Binder Instructions

Instructions
A Regulatory Binder refers to the regulatory documentation ("Essential Documents") related to the conduct of your research study. Per ICH GCP, Essential Documents are "those documents that individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced." They "serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and all applicable regulatory requirements."

These Regulatory Binder tabs are 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

- These Regulatory Binder tabs should serve as a template. It is important to note that **one size does NOT fit all when it comes to regulatory documentation**. You must tailor the binder to meet the needs of your specific protocol. Include only sections pertinent to your protocol. Omit unused sections and add sections as needed. Your institution may have additional documentation requirements not outlined in this template.

- Organize and order the sections to facilitate easy use, reference, and retrieval.

- Keep the Regulatory Binder current and up to date.

- Identify an individual(s) responsible for maintaining the binder. Ensure that this person is on file with the IRB as an Additional Person to Contact to ensure that all IRB correspondence and documents are received/filed in a timely manner.

- 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 files.

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.

Regulatory Binder Essentials

- Protocol and Supporting Documents
- Study Personnel (CVs, licenses, training, delegation of responsibility, etc.)
- IRB Documentation
- Consent Forms
- Data Collection
- Screening/Enrollment
- Adverse Event Monitoring and Reporting
- Monitoring/Auditing/Site Initiation

If FDA-regulated Human Research (e.g. IND, IDE) include these tabs in addition (as applicable) to the Essentials listed above:

- Drug/Device Accountability
- FDA Documentation

If the Human Research involves labs, include the tab below:

- Laboratory Documents tab
    - CLIA/CAP certifications
    - Current/past lab normal ranges

If this research is a multi-site trial and utilizing a single IRB, include these tabs (as applicable) to the Essentials listed above:

- Single IRB (Relying Institution site)
- Single IRB (Lead Study Team site)

What documentation should NOT be kept in the Regulatory Binder?
Items that should NOT be kept in regulatory binder:

- internal audit reports
- study budget info
- participant information or protected health information (PHI)
- any other sensitive information

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Protocol and Supporting Documents

Requirements

- ☐ Initial protocol and all amended versions
- ☐ All versions should contain a version date and/or number
- ☐ If applicable, include copy of fully executed protocol signature page for initial protocol with signed principal investigator (PI) signature page
- ☐ Data Safety Monitoring Plan (DSMP)
    - This may be described within the protocol document
    - If your DSMP includes an independent safety monitoring board, such as a Data Safety Monitoring Board (DSMB), reports from the board should be placed in the IRB tab.
- ☐ If applicable, copy of NIH Grant Application
- ☐ Public registration of research study (if applicable)
    - All research studies that are applicable clinical trials must be registered at ClinicalTrials.gov as per ICMJE, FDAAA, and local institutional policy.

Guidance

- ✓ Organize in reverse chronological order.
- ✓ If you have questions about registering your study on ClinicalTrials.gov, discuss with your research compliance or clinical trials office.
- ✓ 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

Study Personnel

Requirements

- ☐ CVs for all study staff
- ☐ Valid licenses/certification for all professional study staff (e.g., medical or nursing license, controlled substances registration, etc.)
- ☐ Current professional certification, as indicated
- ☐ Documentation of training (e.g., human subjects, HIPAA, phlebotomy, etc.)
- ☐ Delegation of Authority/Duties/Responsibilities Log
- ☐ Staff Signature Log (can be combined with Delegation Log)

Guidance

- ✓ A best practice recommendation is to sign and date CVs. CVs can be updated every 2-3 years to ensure they are accurate and current.
- ✓ For NIH funded studies, investigators can use their NIH Bio Sketch.
- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Templates

- ☐ Documentation of training (e.g., human subjects, HIPAA, phlebotomy, etc.)
- ☐ Delegation of Authority/Duties/Responsibilities Log

Federal Regulations/Good Clinical Practice

GCP: 4.1.1; 8.2.10; 8.3.5

IRB Review/Approval Documentation

Requirements

- ☐ Documentation of approvals:
    - Initial Application
    - Continuing Review(s) or Progress Report(s)
    - Modifications/Amendments
    - Close-Out Report
    - For DoD funded research, include documentation of approval by HRPO
- ☐ Approved/validated recruitment materials
- ☐ Approved/validated additional study information distributed to participants
- ☐ Any foreign language materials (if applicable)
- ☐ Print out of Institution's FWA Information from OHRP website
- ☐ IRB Membership Roster
- ☐ Any additional correspondence related to the study
- ☐ Other reviews:
    - Documentation of scientific, ethics and/or Community Advisory Board review, Data Safety Monitoring Board (DSMB), if applicable

Guidance

- ✓ Submissions should be signed and dated as applicable.
- ✓ If your institution uses an electronic system for submitting and storing IRB documents, ensure that the electronic file contains all required documents and write a note-to-file indicating the location (include copy of note-to-file here).
- ✓ File documents in reverse chronological order.
- ✓ Request a copy of missing documentation from your institutional representative.

Federal Regulations/Good Clinical Practice

GCP: 8.2.7, 8.2.9, 8.3.2-8.3.4

Informed Consent

Requirements

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

Guidance

- ✓ Organize documents in reverse chronological order.
- ✓ 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 46.116 and 46 CFR 46.117
FDA: 21 CFR 50; 21 CFR 56
GCP: 8.2.3; 8.2.7; 8.3.2; 8.3.12

Screening/Enrollment

Requirements

- ☐ Screening/Enrollment Log
    - Captures subjects who have been screened to determine initial eligibility for enrollment, and all subjects who signed a consent form.
- ☐ Withdrawal/Termination Log
    - A list of participants who withdrew or were terminated and reasons why.

Guidance

- ✓ Information on individual study participants is typically maintained in a participant specific file or chart (not in the regulatory binder).

- ✓ For participants who were screened but did not enroll in the study, maintain information on reasons why enrollment did not occur.

- ✓ If your study has a participant identification log, do **NOT** include it in the regulatory binder. Confidential list of participants and their information linked to participant IDs should be kept in a secure location with limited access.

- ✓ 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: Guidance for Sponsors, Clinical Investigators, and IRBs – Data Retention when subjects withdraw from FDA-regulatory Clinical Trials, 2008; FDA info sheet guidance for IRBs and Clinical Investigators: Recruiting Study Subjects;
GCP: 8.3.20; 8.3.21

Data Collection

Requirements

- ☐ Blank set of case report forms (CRFs), data collection forms (if applicable), and/or study questionnaires

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).

- ✓ CRFs and data collection forms should include version number/date. Version date should be used in the event that data collection sheets change during course of study.

- ✓ The difference between data collection sheets and case report forms is that data collection sheets typically act as source documentation tools. 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 tool, whether hardcopy or electronic data capture system.

Federal Regulations/Good Clinical Practice

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

Adverse Event Monitoring and Reporting

Requirements

- ☐ Adverse Events/Protocol Violations/Unanticipated Problems
- ☐ Data Safety Monitoring Board (DSMB) reports (or other monitoring committee)

Guidance

- ✓ To ensure accuracy, logs should be updated as soon as possible after a recordable event occurs, preferable on the same day.
- ✓ AE reports and AE source documentation should be filed in participant-specific files.
- ✓ If documents are maintained electronically, write a note-to-file indicating the location and who maintains them (include copy of note-to-file here).

Templates

- ☐ AE Report Tracking Log
- ☐ Safety Report Tracking Log
- ☐ Protocol Deviation Log

Monitoring/Auditing/Site Initiation

Requirements

- ☐ Site visit log (monitoring log)
- ☐ Copies of all monitoring/auditing reports
- ☐ Documentation of site initiation
- ☐ For DoD funded research, include medical monitor communication and documentation (for studies greater than minimal risk)

Guidance

- ✓ To ensure accuracy, logs should be updated as soon as possible after a recordable event occurs, preferable 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).

Templates

- ☐ Study Monitoring/Site Visit Log

Federal Regulations/Good Clinical Practice

GCP: 8.3.20-8.3.25

Drug/Device Information and Accountability

Requirements

- ☐ Drug/Device Shipment and Receipt Records
- ☐ Most recent version of Investigator Brochure (IB) 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 of the investigator brochure (IB), package insert, and device manual, as applicable, 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 to the IB.

- ✓ 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.
- ✓ 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 behind tab).

✓ If drug/device shipment, receipt, and accountability are managed by the research pharmacy, include note-to-file here.

Templates/Logs

☐ Drug/Device Accountability Log

☐ Drug/Device Dispensing Log

Federal Regulations/Good Clinical Practice

FDA: 21 CFR 312.55; 312.57; 312.62; 812.140
GCP: 8.2.1; 8.3.1

Study Correspondence

Instructions

Document and maintain all relevant, significant communication from the sponsor, CRO, etc. in this section. Study related newsletters may be placed in this section.

Requirements

- ☐ Copy of all significant correspondence (could include emails, letters, meeting notes, 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).

FDA Documentation

Requirements

Clinical Investigator:

☐ Copy of all versions of FDA 1572 (for investigational drugs)

☐ Copy of all versions of Investigator Agreement (for investigational devices)

Financial Disclosure:

☐ Signed and dated FDA Financial Disclosures for all clinical investigators listed on the FDA 1572 (drug) or IRB application (device)

Sponsor-Investigator:

☐ Copy of all Form FDA 1571 submitted to the FDA (for investigational drugs only)

☐ All submissions to the FDA:

- Initial IND/IDE
- Amendments/Supplements to the application
- Safety Reports
- Annual Progress Reports
- Form 3674, certification of registration to ClinicalTrials.gov

Guidance

✓ The Form FDA 1571 should be used as the cover sheet for all correspondence sent to the FDA.

✓ Instructions for completing and updating the Form FDA 1572 (for drug studies) can be found at: https://www.fda.gov/media/78830/download

✓ 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; 8.3.16; 8.3.18; 8.3.19

Laboratory

Requirements

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

Guidance

- ✓ Keep updated documents to exhibit the competency of all lab facilities being utilized, and to support the reliability of test results.

- ✓ If documents are filed separately or 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.

Templates

- ☐ Biospecimen Log

Federal Regulations/Good Clinical Practice

GCP: 8.2.11; 8.2.12; 8.2.14; 8.3.6; 8.3.7

EC/CAB Documentation

Instructions

Use this binder tab when conducting international research to maintain local host-country Ethics Committee (EC) and/or Community Advisory Board (CAB) documentation, including applicable local, regional, and/or national reviewing bodies in host country site(s).

Requirements

- ☐ EC or CAB documentation, including complete submissions, notifications, and significant correspondence.

Guidance

- ✓ It is insufficient for a U.S.-based institution to approve non-exempt human research conducted abroad. Local ethics review is required.

- ✓ For HHS-funded protocols:
  - The review is recommended by the EC of an engaged organization or that of another organization in the same geographic area
  - The local EC should be registered with the Office for Human Research Protections and have a federal wide assurance (Check online here)
  - For non-Health and Human Service-funded protocols:
    - Review is recommended by a local EC or CAB
  - When documentation is maintained locally in the host country and/or electronically, use a note-to-file to document their location and who is responsible
  - If helpful, maintain links to applicable local, regional, and/or national regulation/guidance on file

Study-related SOPs

Instructions

Use this tab to file study-specific standard operating procedures (SOPs). These can also be known as manual of procedures (MOPs), study operations manual (SOM) or another similar name. SOPs include procedures for various aspects of the study including screening, consenting, lab processing procedures, etc. and are often supplied by the sponsor. Study site may also develop their own site-specific SOP in addition to sponsor-provided SOPs. SOPs help to operationalize the study protocol and ensure that all study-specific procedures are performed consistently throughout the study.

Requirements

☐ Standard operating procedures of study site

Guidance

✓ Keep all final versions (even if they are updated).

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

Single IRB (Relying Institution Site)

Use this tab if your site is ceding review to an outside IRB. Documentation on the following should be maintained by the Relying Institution Site:

- Copy of **Executed Reliance Agreement** between Relying Institution and the Reviewing IRB: Provides confirmation of agreement between both IRBs, and spells out the responsibilities of the institution providing IRB review as well as the institution relying on the external IRB.
- Departmental approval documents
- Documentation that the following information was provided to the Relying Institution Site Point of Contact (POC); copies of these items should be maintained in the regulatory binder:
    - Changes in Relying Institution investigator or study team.
    - Relying Institution changes in COI disclosures and COI management plans.
- Reviewing IRB Policies and Procedures Documents/Manual: The Relying Institution investigator must adhere to the reviewing IRB's policies and procedures for reporting unanticipated problems, noncompliance, and other important items.
- Copies of communication from the lead site investigator regarding all reviewing IRB determinations.
    - Initial approval letter
    - Continuing review/progress approval letters
    - Amendment approval letters
    - Final close-out acknowledgement letters
- Reviewing IRB Approved Study Documents: Copies of communication from the lead investigator regarding all approved IRB documents.
    - Informed consent forms
    - Authorization forms (if applicable)
    - Recruitment materials
    - Participant handouts, flyers, surveys, etc.
    - Case report forms
    - Amendments (including funding changes)
- Documentation of communication of local considerations ("local context") through the Point of Contact.
- Documentation of communication to the Reviewing IRB of communications to and from the Relying Institution and FDA, OHRP, and/or other regulatory agencies.
- Documentation showing "prompt reporting" to lead study team of any unanticipated problems, suspension of the study or noncompliance at the local site.
- Documentation that the Relying Institution Sponsored Programs Office has Received Relying IRB Approval Documentation.

- Relying Institution IRB Materials/Documents Submitted to Lead Investigator.
    - Initial IRB approval materials
    - Relying institution IRB-approved informed consent form (if applicable)
    - Study staff lists and training documents
    - Continuing review information

NIH Policies

- NIH Single IRB Policy for Multi-site Research: https://grants.nih.gov/policy/humansubjects/single-irb-policy-multi-site-research.htm
- NIH FAQs on Single IRB Policy for Multi-site Research: https://grants.nih.gov/grants/policy/faq_single_IRB_policy_research.htm

Single IRB (Lead Study Team Site)

Use this tab only if your site is the Lead site of a multi-center study utilizing a single IRB. Documentation on the following should be maintained by the Lead Study Team Site about the Relying Sites.

- Copy of Executed Reliance Agreement between Relying Institutions and the Reviewing IRB: The Lead Investigator should maintain executed reliance agreements for each participating Relying Institution. These documents provide confirmation of agreement between the reviewing and Relying IRBs, and spells out the responsibilities of the institution providing IRB review as well as the institution relying on the external IRB.

- COI documents received from Relying Institutions:
    - COI disclosures and, if applicable, COI management plans.
- Documentation that the reviewing IRB Policies and Procedures documents were provided to each Relying Institution investigator.
- Documentation of the reviewing IRB's determinations regarding the research.
- Documentation of notifying relevant Point of Contacts from Relying Institutions of findings and actions with respect to Unanticipated Problems or research related subject complaints or injuries or serious and/or continuing non-compliance.
- Documentation on Relying Sites local context.
- The Lead Investigator should ensure (and document) that each Relying Institution investigator was provided with a copy of IRB approval letters and IRB-approved study documents:
    - Reviewing IRB initial approval letter
    - Reviewing IRB continuing review/progress approval letters
    - Reviewing IRB amendments, approval letters
    - Reviewing IRB final close-out acknowledgment letter
    - Reviewing IRB Informed Consent Form
    - Reviewing IRB authorization forms
    - Reviewing IRB recruitment materials
    - Reviewing IRB participant handouts, flyers, surveys, etc.
- Documentation of communications with Relying Sites including responses to questions or requests from site investigators/staff at Relying Institutions.
- The Lead Investigator should maintain all copies of all Relying Institution IRB documents provided by the Relying Institution investigator:
    - Initial IRB approval materials
    - Relying Institution approved IRB Informed Consent Form (if applicable)
    - Study staff Lists and Training Documents
    - AE/UP information
    - Other Items

Miscellaneous

Instructions

Use this tab to maintain other agreements, certificate of confidentiality (CoC), equipment calibration, or other important documents.

Requirements

- ☐ _____
- ☐ _____

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).