Title: Investigator Site File (ISF-Regulatory File)	Version Number: #1	Effective Date: 14 MAY 2025	Page 1 of 3

Revision History		
Version No.	**Effective Date**	**Description**

1. Purpose:

The regulatory binder (or regulatory file) serves as a centralized repository for all study-specific and regulatory documentation. It organizes essential records, facilitates easy access for audits and reviews, and supports study team members in referencing key information. Comprehensive, well-organized documentation should reflect the full lifecycle of a study, from receipt of protocol or development as applicable through to study closeout.

Maintaining a regulatory binder ensures that study-related information is readily available to research staff, trial monitors, auditors, institutional review boards (IRBs), and regulatory authorities, such as the FDA. It also supports compliance with institutional policies, sponsor requirements and applicable regulations.

This document provides guidance on the standard contents and organization of a regulatory binder. It is intended for use in studies where the sponsor provides a regulatory binder or index of required documentation. The Principal Investigator (PI) remains ultimately responsible for ensuring compliance with IRB requirements, institutional standards and best practices.

Note: This guidance is designated to be flexible, sections that do not apply to your study may be omitted, and additional sections may be included as needed based on the study design and sponsor requirements. Additionally, this guide outlines the standard requirements for a regulatory master file for those investigators who also serve the role of sponsor.

2. Personnel Responsible:

The regulatory binder may be maintained by the investigator or their designee.

3. Procedures:

Regulatory documents must be stored securely, with access restricted to authorized study personnel. These records may be maintained in physical binders or in 21 CFR Part 11 compliant electronic file storage system (e.g. Florence Healthcare), as allowed by institutional policy. Sponsors may also require additional documentation beyond institutional expectations.

The regulatory binder may be maintained in either hard copy or electronic form if certain documents are stored elsewhere, include a signed and dated Note-To-File specifying:

- The location of the external document(s),
- The individual responsible for its maintenance, and

- The required retention period, if applicable.

All study documents must be retained for the duration of the study and in accordance with applicable archival period. Updates, such as IRB-approved protocols, consents, and recruitment materials, should be filed promptly. Superseded, expired or obsolete documents must be retained and clearly labeled but not discard. Valid certifications should be on file for as long as the study remains active.

The section headers listed below (in bold) may be used as tab dividers within the binder. Use only the sections relevant to your study protocol. Feel free to adapt or expand the binder content to meet the specific needs of your study. These guidance mostly applied to pharmaceutical trials, but can be used for observation studies as needed.

When a UCSD investigator is also the sponsor, there may be a combined trial Master Regulatory File and an Investigator Site file.

Tips for maintaining a regulatory binder/file:

- Keep the binder/file and its contents current and up to date.
- Store in reverse chronological order, with the newest items within a section placed at the front of the section.
- **I**f multiple binders, label each one (e.g. Binder 1 of 3)
- Ensure all IRB correspondence and documents are received and filed in a timely manner.
- Identify an individual who is responsible for maintaining the binder/file and its contents.
- Store the binder/file in a safe and secure location that is 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.

Note: Participant information should be stored separately in a hard copy binder in a locked cabinet/office or in a secure electronic file.

4. Investigator Site File Tool Template:

The regulatory tool may be filed in the ISF binder.

- Include any relevant study information on the spine of the binder, including but not limited to:
  - Sponsor name
  - Study identifier (protocol number/IRB)
  - Site #
  - Investigator Name:
- Modify the contents of the binder to fit the study's needs
- For studies involving investigational drugs, drug-related documentation may be maintained separately in a dedicated pharmacy binder. The pharmacy should retain a copy of the most current version of the study manual.
- All communication related to investigational product (IP) management, such as scheduling monitoring visits (IMVs), addressing questions related to the IP, or other drug-related matters, should be conducted directly between the sponsor and the pharmacy.

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5. Resources

- 21 CFR Part 11 Electronic Records and Signatures
- 21 CFR 54 Financial Disclosure by Clinical Investigators 21 CFR 56.109 IRB Review of research
- 21 CFR 312.60 General responsibilities of investigators
- 21 CFR 312.62 Investigator recordkeeping and record retention
- 21 CFR 312.64 Investigator reports
- 21 CFR 312 IRB Approval letters, rosters, and communications
- ICH Guidelines for Good Clinical Practice (E6) document – Section 4 Investigator responsibilities
- HIPAA Health Insurance Portability and Accountability Act-US

6. Document Approval

- Name and Title of Approver
- Date in the format (MM/DD/YYYY)
- Insert Name and Title below Signature

Approved By: Date:

_____ _____

Insert Name and Title

Investigator Site File (ISF) - Regulatory Binder Tool

Principal Investigator: _____ **Study #/IRB:** _____

Study Title: _____

Document Name	Check if completed ✓	Investigator Site	Investigator as Sponsor of Trial
AGREEMENTS			
Transfer of obligations *(if using a Clinical Research Organization (CRO))*		N/A	N/A
Signed and dated Investigator Agreement		Agreements relevant to the site	Signed agreement for all sites
PROTOCOL			
All IRB-approved versions of the protocol; including amendments and signature pages		X	X
INFORMED CONSENT AND ASSENT FORMS			
All IRB-approved versions of the consent/assent forms (blank copies)		X	X
IRB/SCIENTIFIC REVIEW DOCUMENTATION			
All IRB submissions (LIRB & CIRB), approvals, responses and related correspondence		All approved IRB submissions and notifications relevant to the site	All approved IRB documents, submission and notifications for all participating sites
Approvals, notices and correspondence related to Activation of study			
Certificate(s) of Confidentiality (if applicable)			
IRB Roster and contacts			
Approvals of advertisement/recruitment materials, handouts, questionnaires, handouts, etc.			
DEVIATIONS, VIOLATIONS, AND EXCEPTIONS			
Ongoing documentation of all deviations, violations and exceptions		Deviations, violations and exceptions occurring at the site and resolutions, include CAPA reports	Deviations, of events for all participating sites

Document Name	Check if completed ✓	Investigator Site	Investigator as Sponsor of Trial
SAE REPORTS/UNANTICIPATED PROBLEMS			
Ongoing documentation of all SAEs and unanticipated problems		Documentation of events occurring at site	Documentation of events for all participating sites
SAE or unanticipated problems reports (SUSARS)			
Correspondence, submissions, and notifications to/from the sponsor, IRB and PI			
DATA AND SAFETY MONITORING			
Data and Safety Monitoring Committee (DSMC) or Data and Safety Monitoring Board (DSMB)		Any relevant communication from the sponsor-investigators pertaining to the site	All reports, summaries and communication for the protocol
MONITORING			
Logs of all monitoring visits including dates and signatures of monitors		Logs of visits occurring at the site, including IMV confirmation and reports related to the monitoring visit	Logs and reports related to visits occurring at all sites (collected at site closure)
Monitoring conformation email			
Monitoring follow up report			
DELEGATION OF AUTHORIZATION (DOA)			
A list of the appropriately qualified persons to whom trial-related duties have been delegated by the PI.		List of persons at the site, approved by the PI. Log must be signed/initial and dated by all personnel. All line items singed/dated by PI	Copies of all logs for all participating sites (collected at site closure)
STUDY PERSONNEL/FORM FDA 1572			
Form FDA 1572 (listing all applicable personnel)		Initial and all revised versions. Do not include CRCs in 1572	Initial and revised all versions for all participating sites
CVs and documentation of medical licenses for all clinicians and CVs for all staff		CVs signed and dated every two years. Include address where research is being conducted (e.g.	Copies of all CVs and Licenses for all participating sites.
Records of site initiation visit (SIV) attendance and report, this includes protocol specific training for all study staff		File SIV follow up report and attendance and training records for site personnel.	Cumulative for all personnel at participating sites
Financial disclosure information (FDF forms) as applicable		FDF form required for all clinicians listed on FDA 1572. CRCs are not typically required to complete a FDF	Cumulative for all personnel listed on each site's 1572, if an IND/IDE is held by a UCSD
CITI Training, including GCP, HIPAA, BMR and UCSD IATA training via UClearning		File all training record for all study staff. UCSD Requires BMR and HIPAA trainings	May file centrally for all participating sites

Document Name	Check if completed ✓	Investigator – Site File	Trial Master File (when investigator is also the sponsor of the trial)
LABORATORY AND SAMPLE COLLECTION			
Current and updated normal values/ranges for all medical, laboratory, technical procedures and/or tests included in the protocol		Copy of laboratory manual share with research clinic (ACTRI). CV of lab director of all applicable locations (e.g. ACTRI, CALM Lab for local labs if applicable, and for Central Lab)	Cumulative for all personnel and facilities at all participating sites.
Current and updated laboratory accreditation certificates (e.g., CLIA and/or CAP) all labs performing procedures and/or tests included in the protocol			
Lab Director's current CV (signed & dated on first page) for DF/HCC and DF/PCC facilities			
SCREENING, ENROLLMENT, AEs , DEVIATION LOGS			
List of all potential subjects consented and screened, regardless of screening outcome		All subjects screen at site as well as any subjects transferred to site from another location. AE and Protocol Deviation Logs are maintained in the subjects' charts	Relevant to site. Collect from all participating sites at close out.
List of all subjects enrolled in the study, regardless of enrollment status (withdrawn, completed, etc.)			
INVESTIGATIONAL PRODUCT (IP)			
Shipment and receipt records		All documents are kept in the Research Pharmacy, unless the study team is managing their own PI. If PI managing IP, ensure all logs are available and up to date.	Relevant to the site. Collect from all participating sites at study close out.
Accountability Logs			
Randomization forms			
Records of IP disposition, return, or destruction			
Temperature Logs			
Pharmacy Manual		IP manual kept with pharmacy	N/A
INVESTIGATOR BROCHURE (IB) OR DEVICE MANUAL PACKAGE INSERT			
Original/initial IB and each revised version of the IB or Device Manual/Package Insert.		All copies	Site only
Investigator Brochure signature page		Not required by regulatory guidelines, but it may be required by the sponsor. It is a GCP to track receipt of IBs	When required by sponsor

Document Name	Check if completed ✓	Investigator Site	Investigator as Sponsor of Trial
IND SAFETY REPORTS			
Sponsor IND Safety Reports		When required by sponsors. PIs use SUSAR worksheet to determine reporting criteria to CIRB or LIRB (may need to be reported to LIRB if serious, unexpected, and related or possibly related to IP). Attach worksheet to SUSAR and file in ISF binder. Review CIRB reporting criteria as submit if applicable	All reports received from the manufacturer(s) and documentation of distribution to participating sites when applicable. IND submission application, reports, acknowledgment and "may proceed" letter, all supplemental submissions to IND, etc.
Documentation of PI's determination as to whether IND Safety Reports require reporting to IRB			
Documentation of IND Safety Reports submitted to the IRB and the IRB response notices, if applicable			
GENERAL CORRESPONDENCE			
Records of all relevant and signification communication that occurs during the conduct of the trial.		Relevant to site, such as: Sponsor approvals of protocol deviations, study meeting minutes, requests for information (from sites/sponsors), newsletters, note to files (NTFs), DMC/DSMB reports, etc.	Communication to/from all participating sites, regulatory authorities, manufacturers, etc.
Include correspondence related to decisions made regarding the conduct of the trial or regulatory obligations			
CELL & GENE THERAPY TRIALS – INSTITUTIONAL BIOSAFETY COMMITTEE CORRESPONDENCE			
For cell or gene-transfer studies under an IND, correspondence will include the following: • IBC approval for site • All Safety Reports and correspondence to NIH/IBC and IRBs		All documents relevant to the communication and approval of IBC	Relevant to the site. Collect from all participating sites at study close out.
For any study agent manufactured and/or shipped by UCSD: • Sample of label(s) attached to the container(s) • Certificate of Analysis for all batches		Only if relevant to the site	NA
FDA DOCUMENTATION			
Signed and dated original application and all subsequent submissions (e.g. amendments, AEs, annual progress and final report) to the FDA and the resulting notifications		N/A	File all documentation
Form FDA 3674 (certification of registration to ClinicalTrials.gov)		N/A	File all documentation