SOP#: PM-6	**Guidelines for the Development and Maintenance of Investigator Site File (ISF)**
Version # 4.4	**Next Review Date: 08/2026**
Approved Date: 08/2024	**Review Interval Period: Biennial**
NCI Clinical Director Signature/ Effective Date:	James Gulley, M.D., Ph.D. Digitally signed by James Gulley, M.D., Ph.D. Date: 2024.08.12 07:45:43 -04'00'

POLICY

It is the responsibility of the Principal Investigator to create and maintain an Investigator Site File (ISF), (i.e., regulatory binder or file) of essential documents for each study (both interventional and observational) and ensure compliance with applicable regulations and guidelines, including the Code of Federal Regulations, Good Clinical Practice, and National Institutes of Health policies. This task may be delegated, and the Delegation of Activities Log must reflect this action.

Essential documents are maintained in electronic form on a secure NCI shared drive with routine back-up. For those essential documents that are on paper, please see CCR SOP ADCR-8: *Certifying Scanned Paper Documents.*

SCOPE

All studies conducted by a Principal Investigator in the Center for Cancer Research are subject to the requirements of this SOP.

Additional information on requirements for multicenter studies for which CCR is a participating site is addressed in a separate SOP.

PURPOSE

The purpose of this standard operating procedure (SOP) is to provide consistent processes/procedures to be followed for essential documents management/maintenance. Essential documents serve to ensure the compliance of the investigator with the standards of good clinical practice (GCP) and with all applicable regulatory requirements. These documents are generated throughout the various stages of a study, including, before the study begins, during the conduct of the study, and after completion or termination of the study.

RESOURCES

- 21 CFR 312.62, Investigator record keeping and record retention
- 21 CFR 812.140, Records
- Frequently asked questions, Statement of Investigator (1572)

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Efficacy Guidelines website
    - E6 Good Clinical Practices (R2), Section 8, Essential Documents for the Conduct of a Clinical Trial
- Center for Cancer Research SOP website
    - ADCR-8: *Certifying Scanned Paper Documents*
    - PM-1: *Principal Investigator (PI) Delegation of Activities for Research*
    - PM-5: *Research Protocol Training Requirements*
    - PM-9: *Research Team Training Requirements for IRB Modifications*
- NIH Records Management Schedule and Storage website

PROCEDURES

STEP 1: Develop Investigator Site File (ISF) for Each Study

Essential documents are maintained in electronic form and the ISF outline and nomenclature established by the Center for Cancer Research (CCR) Protocol Support Office (PSO) will be used. For each study that is activated, an ISF folder is created by the PSO Manager. The ISF is located in the "CCR Regulatory Files folder", in hierarchical subfolders for the PI's branch/program, the PI's name then the study number

The electronic regulatory file will serve as the official ISF and will be retained in accordance with the records schedule outlined in Step 3: Record Retention.

In cases where a Sponsor/collaborator requires that original documents be sent to them, it is acceptable to keep a scanned copy in the ISF. All documents will be kept in electronic format.

STEP 2: Maintain ISF for Each Study

The following documents (all versions) should be collected and filed in the ISF if applicable to the study. Documents should be collected before study initiation/recruitment begins as well as throughout the study.

The following documents will be maintained by PSO Manager:

Note: For documents submitted in PROTECT, please include submission form as applicable with approval/acknowledgement documents

- FDA Form 1572 (IND studies only) or investigator agreement (IDE studies only). Though new labs, testing facilities and sub-investigators **may** be recorded in real time on 1572s, it is not necessary to update and sign the document until a change requiring an FDA submission (e.g., PI change) is made.

  For CCR sponsored studies, individuals listed on the 1572 should also be listed as KSP. PI's name on 1572 needs to match with current CV. Please consult with other sponsors for their guidelines.

- Investigator's Brochure if applicable to the study (IND studies only with approval from the manufacturer)
- Drug package inserts if applicable to study
- Device package insert if applicable to study
- IRB approved initial Protocol and subsequent Protocol Modifications (filed by modification approval date), including the IRB approvals
- IRB approved initial Informed Consent Form(s) and subsequent modifications (filed by modification approval date), including the IRB approvals
    - Translated informed consent forms (if applicable) and corresponding certificate of translation
- Advertisements, participant educational materials, including IRB approval letter
- Continuing review report and approvals OR Progress Report and acknowledgement correspondence from the IRB
- Unanticipated Problem, deviation and non-compliance reports submitted to and reviewed by the OHSRP Office of Compliance, including IRB outcome letter
- IND Safety reports received from Sponsor/manufacturer (even if they are not submitted to the OHSRP Office of Compliance and Education as an Unanticipated Problem)
- Radiation Safety Committee (RSC) submission and approval, as applicable
- IRB membership roster for the reviewing IRB, updated as needed. Keep historical copies of all rosters. If the reviewing IRB does not provide a roster, documentation of the IRB's position should be saved in the file.
- Federal-Wide Assurance (FWA) Number for the reviewing IRB
- Principal Investigator and Associate Investigator CVs, signed and dated and current within 2 years of the time the investigator begins their participation in the study. No additional CVs will be required for CCR-led studies not under IND/IDE; however, Sponsor (e.g., OSRO) may have additional requirements.
- Laboratory certification (e.g., CLIA, CAP, or other applicable certificates) (update when the certificate expires, keep all historical copies). CLIA documentation for non-military labs may be found here.

Note: The Clinical Research Coordinator MUST notify the PSO Manager when a new lab or testing facility is being used for protocol-directed assessments. The PSO Manager will secure the lab certification for non-military, US-based labs.

- Range of normal values for NIH laboratories
- Sponsor and/or manufacturer correspondence

  Note: PI will send all sponsor/manufacturer correspondence to the PSO Manager if PSO staff member not included on the correspondence.
- Additional required authorization/approvals of protocol and modifications (e.g., Institutional Biosafety Committee)
- Additional required periodic committee review approvals/minutes (e.g., Data and Safety Monitoring Board, Safety Monitoring Committee, Independent Monitoring Committee)
- Training certificates: Human Subjects Protections (HSP), Good Clinical Practice (GCP)

- Other documents that may be required by a Sponsor such as financial disclosures and medical licenses. In that case, keep all copies in the file, even those that have expired.

Note: For CCR sponsored studies which are not monitored by OSRO as well as non-IND/IDE studies – medical licenses are not required.

- Documentation of study closure
- Protocol signature page(s) for original protocol and each amendment, if required
- Note(s) to File as applicable

The Clinical Research Coordinator (CRC) will forward the following documents to the PSO Manager for saving in the ISF:

- Protocol and consent specific training records –
    - Initial training for all AIs and other listed on the delegation log – see CCR SOP PM-5: *Research Protocol Training Requirements*
    - Modification training for active staff - see CCR SOP PM-9: *Research Team Training Requirements for IRB Modifications*
- Range of normal values for reference laboratory (for each non-NIH lab used in the study)
    - Make copy of lab result, redact personally identifiable information, add study number and unique ID, scan and save to file entitled "Lab Normals and Certification" using the appropriate nomenclature. Laboratory certification for US military, or non-US labs should also be requested from patient and provided to the PSO.
- Redacted subject screening log and enrollment log
- Redacted subject identification code list
- Delegation of Activities log – see supporting documents under CCR SOP PM-1: *Principal Investigator (PI) Delegation of Activities for Research*
    - Signature Sheets of research team members, if needed
- Monitor Visit Log
- The CCR Protocol Deviation Tracking System (PDTS) is used for recording protocol deviations. A copy of the final spreadsheet may be added at the end of the study unless needed at an interim IMV for external monitors to CCR (e.g., pharmaceutical collaborator).
- Monitoring reports and all relevant correspondence, including site initiation visit, interim monitoring visits and close-out visit reports. Pre- and post-visit letters from the monitor are included in the ISF. The CRC must copy the PSO Manger on all monitoring correspondences.
- Sponsor correspondence if PSO Manager not copied on email/letter
- Serious Adverse Event Reports sent to the Sponsor and/or Manufacturer, and other SAE reports required per protocol
- Relevant communication other than site visits (letters, meeting notes, etc.)
- Record of retained body fluids/tissue samples (if applicable)
- Note(s) to File as applicable

The following documents will be retained in the Clinical Center Investigational Drug Control Unit during the study:

- Drug accountability forms and shipping records

After the study closure is approved by the IRB, these forms and records will be saved in the ISF.

STEP 3: Record Retention

All essential documents will be maintained in the ISF for the duration of the study and for the designated time requirement (e.g.., FDA, ICH, NIH, EU) after study closure. Records must be kept for the longest applicable period for record retention as per the NIH Intramural Research Records Schedule and FDA/EU Regulations.