Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual: Essential Documents

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Essential Documents

Essential documents, individually and collectively, serve to demonstrate Principal Investigator (PI)/Investigator of Record (IoR), DAIDS, and monitoring contractor compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) requirements ("ICH E6") and any applicable local laws and regulations. DAIDS staff and/or designees and regulatory authorities frequently review these documents as part of the process to confirm study conduct validity and data integrity.

Recordkeeping and Retention Requirements for Essential Documents

Essential documents include a variety of documents as described in Section 8 and section 4 of the ICH E6 guidelines and additional documents required by DAIDS, including: DAIDS protocol registration approvals, monitoring reports, financial disclosures, Form FDA 1572s/DAIDS IoR forms, informed consent forms (ICFs), investigator brochures, institutional review board (IRB)/ethics committee (EC) and other regulatory entity/regulatory authority (RE/RA) approvals and correspondence, training records, screening and enrollment/randomization logs, delegation of duties logs, package inserts and source documents.

PIs/IoRs must ensure that Clinical Research Sites (CRSs) store and retain essential documents according to applicable regulatory requirements, and that CRS staff are adequately trained in recordkeeping and retention requirements for all DAIDS clinical trials. Please refer to Essential Documents Recordkeeping appendix of this section for additional guidance.

Note: CRSs may refer to the Electronic Information Systems policy regarding the use of electronic systems, such as electronic files.

For guidance on destruction of any clinical trial documents CRS staff must refer to their local laws and regulations as well as institutional policies. CRS staff should also contact DAIDS Program Officer before destroying any records for DAIDS clinical trials.

Filing Essential Documents

A CRS may organize essential documents in a single file or multiple files. The list below suggests how to organize CRS files:

- **Central File:** Location of non-study specific documents such as staff curricula vitae, professional licenses, credentials, ICH E6 and Human Subject Protection (HSP) training records, and equipment maintenance/calibration records. The clinical trials unit (CTU) may maintain these files for their affiliated CRSs.

- **Investigator Site File (ISF):** Also known as the regulatory file, CRS staff store study-specific documents such as protocols, IRB/EC/RE/RA approvals, letters of amendments, ICFs, and Form FDA 1572s/DAIDS Investigator of Records (IoR) Form, Delegation of Duties Log, Protocol-specific training logs in this location.
- **Participant Research Records:** These are located at the CRS and/or its parent institution, and they contain all source documents used to complete case report forms and all other relevant study documents (e.g., participant diaries or quality of life questionnaires). There is one file (collection of research records) per participant.
- **Pharmacy File:** Located in the pharmacy and maintained by pharmacy staff, this file is used to keep and organize study-specific, pharmacy-related documents such as study product shipment records and accountability logs. The pharmacy may also keep a central file that contains non-study-specific documents such as pharmacy establishment plan (PEP), temperature monitoring records, and pharmacy equipment maintenance/calibration records.
- **Laboratory File:** Located in the laboratory and maintained by laboratory staff, this file is used to keep and organize laboratory related documents like assay validations, routine quality control, chain of custody of biospecimens, equipment maintenance and/or calibration documents etc.

Although CRSs are allowed some flexibility in their filing systems, all required essential documents must be well organized in a secure location where they can be easily retrieved for review by the monitoring contractor and other authorized individuals (e.g., auditors and regulatory inspectors). CRSs should organize and file required documentation as soon as the final study protocol is received, and from that time forward, sites must maintain complete, accurate files according to all applicable record retention requirements. Please refer to the Record Retention Flow Chart appendix of this section for additional guidance.

Tips on Filing Essential Documents

CRS files typically consist of several binders, which may be stored centrally or in different locations. CRS staff should know where all documents are located so they can retrieve them quickly, when needed. Sites may use these recommendations to adequately maintain essential documents:

- Use a table of contents to facilitate navigation and provide an overview of document contents and organization.
- Use tabs for each binder section to ensure documents are filed appropriately.
- Label the binder's cover and spine with the protocol number, PI/IoR name, and CRS number.

- File essential documents in reverse chronological order, placing the most recent documentation on the top of each section.
- Ensure that each binder's documentation corresponds with the protocol identified on the binder's cover/spine.
- Maintain all IRB/EC/RE/RA-approved versions (e.g., protocols, ICFs) in CRS regulatory files. Mark obsolete versions clearly to ensure staff use current, applicable documents.
- Place a note to file (NTF) in each binder that indicates where centralized files/documents are located, as applicable.

Notes to File

When current documentation is unavailable or inadequate, CRS staff may provide additional details or information—known as NTFs—to provide clarity. For example, an NTF may be used to explain:

- A study document's location when it is not filed appropriately (e.g., location when the document is temporarily located elsewhere.)
- A discrepancy between different versions of the same document, actions taken to address the discrepancy, and methods adopted to prevent similar future discrepancies.

Because excessive NTFs may cause auditors/regulatory inspectors to question whether CRSs have strong study procedures and/or study documentation practices, staff should only create NTFs when research records or essential study documents (within CRS files) fail to fully address an action, clarification, or discrepancy. CRSs should never substitute NTFs for prospective and complete source documents.

Before creating an NTF, always ask the following:

- Is this NTF needed to clarify what happened?
- Does this NTF clarify what happened?
- Could this information be documented better via a late entry or clarification in the source documentation?
- Who is the best individual to document necessary details related to this discrepancy?

When NTFs cannot be avoided, be sure to include all pertinent details and sign/initial/date the document before filing it in the appropriate section of the CRS files.

The appendix section includes an NTF File Template that instructs CRSs on how best to create an NTF.

Essential Documents Recordkeeping Appendix

The “Essential Documents Recordkeeping” appendix of this section provides the following:

- Purpose and/or description of each essential document.
- Recommendation for where each essential document should be filed or maintained (i.e., ISF, central file, participant research record, and/or pharmacy file).

Clinical Research Records

DAIDS defines clinical research records (CRRs) as documents that capture or describe clinical research methods, conduct, and/or results, including clinical trial records. Example documents include all essential documents as listed in this section´s appendix “Essential Documents Recordkeeping” appendix. CRRs may be written, electronic, magnetic, and/or optical records, including scans, x-rays, electrocardiograms, case histories, source documents, etc. Site investigators are responsible for keeping copies of completed, signed, and dated CRFs in paper or electronic format according to all applicable policies, guidelines, and regulations.

Requirements for Storing Clinical Research Records

CRS staff must store CRRs in a manner that keeps files private, confidential, secure, and accessible (to appropriate parties) throughout the clinical trial and after it concludes. CRRs may be kept in hard copy, electronic, or other media format.

CRS staff must prevent unauthorized access to files by storing CRRs in a restricted location that uses double locks and/or electronic entry systems. Examples of storing records under double lock include:

- A locked office with a lock on the filing cabinet.
- A locked office inside a clinic that is locked when not in use.

CRRs must be accessible in a timely manner to DAIDS staff and/or their representatives and regulatory agencies, even if records are in a long-term storage facility. These entities must be able to examine CRRs to perform quality assurance reviews and evaluate participant safety and study progress.

Additional information on storage facility requirements, is supplied in the CRS Facility Requirements (Clinic, Laboratory, and Additional Locations) section of the SCORE manual.

Requirements for Retaining Clinical Research Records

This section defines the minimum retention requirements for CRRs generated during DAIDS clinical trials to ensure CRSs comply with DAIDS requirements and applicable regulations.

Under the terms of the Grant Award, CRRs are the property of the awardee institution. U.S. Department of Health and Human Services 45 Code of Federal Regulations (CFR) Part 46.115(b) requires research records to be retained for at least three [3] years after completion of the research, as well as, be retained in compliance with ICH E6. Electronic data must be stored in a format that will be accessible and readable for years to come.

The institution/IRB/EC may delegate responsibility to the PI/IoR to retain certain records (e.g., signed informed consent documents, study data) on behalf of the institution, according to the institution's policies and procedures for retaining records. The institution/IRB/EC must document this transfer of responsibility in writing and maintain it in the CRRs. If the PI/IoR designated to retain records on behalf of the institution leaves that institution, the PI/IoR and the institution must identify a successor responsible for maintaining those institutional records, either at the original institution or wherever the records will be relocated.

For clinical trials involving non-U.S. sites, CRSs must meet any applicable regulatory authority's record retention requirements. These additional requirements include local laws as well as institutional policies that may extend record retention requirements beyond what U.S. regulations require. In these circumstances, CRSs must follow the most stringent applicable retention requirement.

If the clinical trial will be submitted to a regulatory authority to support marketing a pharmaceutical product, DAIDS will work with the marketing authorization holder to store and retain CRRs per applicable requirements.

If a participant withdraws from a DAIDS clinical trial, CRSs must maintain the data accrued to date in the CRRs. For further information, refer to the *Office for Human Research Protections (OHRP) Guidance on Withdrawal of Subjects from Research: Data Retention and Other Related Issues*. In addition, for Food and Drug Administration (FDA)-regulated studies, refer to the *FDA Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials.*

Refer to the "Record Retention Flow Chart" appendix of this section for record retention process guidance.

Note: No records can be destroyed without first obtaining approval from DAIDS and applicable DAIDS Clinical Trials Network.

Recordkeeping Requirements for Studies Subject to U.S. FDA Investigational New Drug Regulations

The PI/IoR must retain records for research conducted under a U.S. FDA investigational new drug (21 CFR Part 312.62[c]) as follows:

- Two years after the date a marketing application is approved for the drug for the indication for which it is being investigated; or
- If no application is to be filed or if the application is not approved for such indication, for two years after the investigation is discontinued and the FDA is notified.

The PI/IoR must retain CRRs (including participant´s research records) under 21 CFR Part 312.62(c). Any electronic CRRs must also comply with 21 CFR Part 11 requirements.

Recordkeeping Requirements for Studies Subject to European Medicine Agency Regulations

The PI/IoR must retain records for clinical trials used to support a marketing authorization under European Medicine Agency regulations (Directive 2003/63/European Commission (EC) amending Directive 2001/83/EC and including Pediatric Use Marketing Authorizations under Regulation 1901/2006), as follows:

- For at least 15 years after completion or discontinuation of the clinical trial
- Or, two years after the last approval of a marketing application in the EC, until there are no pending or contemplated marketing applications
- Or, at least two years have elapsed since the formal discontinuation of the investigational product's clinical development

Note: Storage of personal data is subject to applicable elements of Directive 95/46/EC and of the General 451 Data Protection Regulation (GDPR), Regulation (EU) 2016/679, once applicable.

The sponsor should inform the investigator(s) and the institution(s) in writing when trial-related records are no longer needed.

Appendices

1. Essential Documents Recordkeeping
2. Note to File Template
3. Record Retention Flow Chart

References

1. U.S. Code of Federal Regulations, Title 21, Parts 11, 50, 54, 56, 312 and 812
2. U.S. Code of Federal Regulations, Title 45, Part 46 and Subparts
3. International Council for Harmonisation Good Clinical Practice (ICH E6) Sections 1.11, 4.9, 5.5, 5.23, 8.3.14, 8.3.15.
4. FDA Guidance: Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects [Oct 2009]
5. FDA Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials
6. EMA Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)
7. EMA Guideline on GCP compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials
8. OHRP Guidance on Withdrawal of Subjects from Research: Data Retention and Other Related Issues.
9. FDA Guidance: E6 Good Clinical Practice (GCP), Sections 1.11, 4.9, 5.5, 5.23, 8.1, 8.3.14, 8.3.15

Version History

V1.0	1/19/2021	Original Version

V2.0	5/3/2022	Pg 5,9 - Added information about the IoR's responsibility to have a copy of the eCRFs under CRF section.