Standard Operating Procedure:

ESSENTIAL DOCUMENTS

Purpose

The purpose of this standard operating procedure (SOP) is to provide guidance to research personnel when a system of records is established. Essential documents are those documents that individually and collectively permit evaluation of both the conduct of a clinical trial and the quality of the data that are produced. These documents are generated throughout the various stages of a clinical trial, including, before the trial begins, during the conduct of the trial, and after completion or termination of the trial.

Essential documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of good clinical practice (GCP) and with all applicable regulatory requirements. These documents are also the ones that are usually audited by the sponsor and regulatory authorities as part of the process to confirm the validity of the trial conduct and integrity of the data.

Scope

This SOP is based upon: 1) the Code of Federal Regulations (CFR), 2) guidances that apply to the involvement of human subjects in clinical research, and 3) standards for GCP. This SOP is applicable to all Division of AIDS (DAIDS) funded clinical trial sites conducting therapeutic, vaccine, or prevention studies on human subjects, both domestic and internationally.

Instructions

- In addition to the list of essential documents in this SOP are, 1) a description of the purpose and/or requirements of each document, 2) a recommendation whether the document should be filed in a central file, protocol files, or subject records, and 3) a reference to the pertinent Federal regulation/guidance.

- It is acceptable to combine some of the documents, as long as the individual elements are readily identifiable. All documents do not have to be combined in one regulatory file.

- Regulatory files must be maintained for all trial sites. It is acceptable for a main site/center/unit to maintain regulatory files for their affiliated sites/subunits if necessary.

- A trial site is the location where the research is conducted and the term site is generally used in this document in place of the terms: unit, main unit, subunit, affiliated site, or center.

- All of the documents addressed in this SOP must be available for audit/inspection by the sponsor and regulatory authorities.

- Documents may be saved in an electronic format when appropriate.

- Always refer to local, state, institution, and/or institutional review board (IRB)/independent ethics committee (IEC) policies/regulations and follow any procedures that are more stringent than DAIDS SOPs.

- Informed consents and regulatory documents are not covered under the DAIDS policy for destroying case report forms (CRFs). Destruction or retention of these documents should be in accordance with Federal regulations and local institution/IRB/IEC policies and procedures.

- Resource tools (e.g., Lab Processing Charts) are not included as essential documents.

Essential Documents SOP

Document	Requirement / Purpose	File	Reference
Assent Form	Assent of children and permission of parents or legal guardians as determined by the IRB/IEC is required as per the provisions of 45CFR46. • State law where the research is taking place defines the age of a minor and requirements for emancipation. • Local IRB/IEC determine the age for obtaining assent. • The requirement for assent of children and/or permission of their parents or legal guardians may be waived by the IRB/IEC as long as the criteria for waiving consent in the regulations (45CFR46) are met. • Keep on file all versions submitted and approved by site's IRB/IEC.	• Central file • Protocol file • Subject's research record	• 45CFR46, Subpart D • 21CFR50 • 21CFR56 • FDA Information Sheets, Guidance for IRBs and Investigators 1998 Update, FAQ Nos. 47 and 48; and Page 5
Assurance Number	The Institution is responsible for obtaining and maintaining a current Health & Human Services (HHS) Assurance through the Office for Human Research Protections (OHRP). • The principal investigator (PI) is responsible for ensuring that a current Assurance is in effect while conducting research on human subjects in HHS funded studies. • All performance sites: ➢ Main site ➢ All affiliated sites that meet the OHRP requirements for having an Assurance. • Must be renewed prior to expiration. • Keep on file the Assurance number and expiration date.	• Central file Note: A copy of the actual Assurance document must be on file with the Institution and/or IRB/IEC.	• 45CFR46 • OHRP Procedures for Registering IRBs and Filing Federalwide Assurances of Protection for Human Subjects (FWA)
Case Report Forms	1. Dated, completed case report forms (CRFs): • To document that the investigator or authorized member of the investigator's staff confirms the observations recorded. • To document all changes/ additions or corrections made to CRFs after initial data were recorded. • Signed if required by Group SOPs or if used as source documentation. 2. Originals retained by sponsor after study completion and/or site closure. 3. Site retains copy. Refer to the DAIDS Source Documentation SOP for CRFs used as source documentation.	• Protocol file • Subject's research record • Data file	• 21CFR312 • FDA Guidance: E6 Good Clinical Practice (GCP), Sections 1.11, 4.9, 5.5, 5.23, 8.3.14, 8.3.15 • DAIDS SOP: Storage of CRFs and Pharmacy Records • DAIDS CRF Destruction List • DAIDS SOP: Source Documentation
Communications	1. All relevant communications, other than site visits, to document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting, etc. For example: • Letters • Meeting notes • Notes of telephone calls	• Protocol file	• FDA Guidance: E6 GCP, Sections 4.4, 4.9, 8.3.11

Document	Requirement / Purpose	File	Reference
	• Email messages 2. Includes communications to and from the Sponsor and/or the protocol team. 3. Communications about a specific subject must be filed with source documents in the subject's research record. 4. Save electronic media, originals, and/or certified copies.		
Curriculum Vitae (CV)	1. The site must have on file CVs and/or other relevant documents evidencing qualifications and eligibility to conduct the trial and/or provide medical supervision of subjects. Includes the following key personnel: • Principal investigator (i.e., individual responsible for the grant/contract at the site). • Investigator responsible for day-to-day activities of the site. • For IND studies: ➢Investigator of Record (IOR) ➢All other investigators/subinvestigators and any other clinicians listed on a Form FDA 1572, Box # 6. • For non-IND studies, all other investigators/ subinvestigators and any other clinicians listed on an authorized prescribers list. • Study coordinator • Pharmacist of record 2. Update to reflect significant changes: • Affiliation • Education • Responsibilities 3. Refer to the DAIDS Protocol Registration Policy and Procedure Manual for additional requirements (e.g., CV content).	• Central file • Protocol file	• 21CFR312 • FDA Guidance: E6 GCP, Sections 4.1, 4.3, 5.6, 8.2.10, 8.3.5 • DAIDS Protocol Registration Policy and Procedure Manual
Final / Close-Out Monitoring Report	1. A close-out report by the monitor to document that all activities required for site close-out are completed and essential documents are in the appropriate files. Includes the following: • Disposition of subjects • Location of research records • Disposition of specimens • Disposition of study drug • IRB/IEC notification 2. Applies only to sites being closed (i.e., no longer enrolling new subjects or following any subjects on-study).	• Central file	• 21CFR312 • FDA Guidance: E6 GCP, Sections 4.13, 8.4.5
Final Study Report	Final report by the investigator to the IRB/IEC, and where applicable, to the regulatory authorities to document completion of the trial. Include the following information: • Disposition of subjects • Location of research records • Disposition of specimens • Disposition of study drug • Other information as required by the institution or local IRB/IEC (e.g., number of patients screened, number enrolled, serious adverse experiences, etc.).	• Central file • Protocol file	• 21CFR312 • FDA Guidance: E6 GCP, Sections 4.13, 8.4.7

Document	Requirement / Purpose	File	Reference
Financial Disclosure	1. To document financial aspects of the trial and the financial agreement between the investigator / institution and the sponsor for the trial. 2. Certification or Disclosure • Certify that there is no financial interest, or • Disclose specific financial interests. • Must complete Forms FDA 3454 or 3455, or equivalent forms. 3. Applies to investigators and subinvestigators 4. Applies to individuals who fit any of the following criteria: • Sign the Form FDA 1572 (Investigator of Record) • Identified as an investigator in initial submissions or protocol amendments under an IND. • Identified as an investigator in the NDA. • For studies not conducted under an IND, the individuals whom the sponsor considers to be investigators and subinvestigators. • Individuals who actually conduct and take responsibility for an investigation. • Individuals who have the ability and opportunity to significantly impact the data *as determined by the site*. • Spouses and dependent children of individuals indicated above. 5. Local institution, IRB/IEC and/or Group SOPs may have additional requirements.	• Central file • Protocol file	• 21CFR54 • 42CFR50, Subpart F • 21CFR312 • FDA Guidance: E6 GCP, Section 8.2.4 • FDA Guidance: Financial Disclosure by Clinical Investigators • NIH Notice OD-00-040
Form FDA 1572	1. Required for each initial protocol registration submission of a new protocol with an IND. 2. The Investigator listed in box 1 of the 1572 is the individual who must sign and date the form. This individual is referred to as the Investigator of Record (IOR). 3. Only laboratories not specified in the protocol need to be listed in Section 4. 4. Section 6 must list any individual: • Responsible for the medical management of subjects. • Authorized to prescribe study medication. • This may include, but is not limited to, the following: ➢MDs ➢Pharmacists ➢Nurse Practitioner ➢Physician's Assistant ➢Study Coordinator • If there are no individuals that need to be listed, then record "NONE". 5. Update as study personnel and/or other data on the form changes. Updated forms must be signed and dated by the IOR. 6. The original version and any updated forms must be submitted to ROC for submission to the FDA. 7. A copy of the forms must be kept on file at the site.	• Central file • Protocol file	• 21CFR312 • FDA Guidance: E6 GCP, Sections 4.1, 4.3 • DAIDS Protocol Registration Policy and Procedure Manual
Information Given to Trial Subject	1. To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent.	• Central file • Protocol file	• 45CFR46 • 21CFR50

Document	Requirement / Purpose	File	Reference
	give fully informed consent. 2. To document that recruitment measures are appropriate and not coercive. 3. Include the following: • Informed consent form • All applicable translations • Advertisement for subject recruitment (if used) • Education materials (protocol specific) • Any other written information		• 21CFR56 • FDA Guidance: E6 GCP, Sections 4.8, 8.2.3
Informed Consent Form	1. Written informed consent form to document that consent is: • Obtained in accordance with regulations, GCP, and protocol. • Dated prior to participation of each subject in trial. • Provided for direct access to records. 2. Non-English speaking subjects must be consented in a language they can understand. • Save all written translations. 3. Consents obtained for screening purposes must be retained even if the subject was not enrolled in the protocol. 4. To document revisions of these trial-related documents that take effect during trial, save all versions submitted and approved by site's IRB/IEC: • Informed consent form. • Any other written information provided to subjects. 5. Continual reviews are at the directive of the site's IRB/IEC. 6. Changes in consent forms due to protocol amendments and important safety information are at the directive of the site's IRB/IEC and/or DAIDS.	• Central file • Protocol file • Subject's research record	• 45CFR46 • 21CFR50 • 21CFR56 • 21CFR312 • FDA Guidance: E6 GCP, Sections 1.28, 4.8, 8.3.12, 8.2.3, 8.3.2 • OHRP Informed Consent Guidance Information
Investigator's Brochures (IBs)	1. To document that relevant and current scientific information about the investigational drug/agent has been provided to the investigator. 2. Include updates to document that investigator is informed in a timely manner of relevant information as it becomes available. 3. Keep on file a copy for EACH of the study drugs/agents used within the protocol. 4. Include the following: • Only the most recent version. ➢ All obsolete versions must be removed. ➢ Obsolete IBs must be shredded since they may contain proprietary information. ➢ Shred upon removal from file, or, upon trial completion. • Addendum to IBs (e.g., all IND safety reports related to the drug/agent).	• Central file • Protocol file	• 21CFR312 • FDA Guidance: E6 GCP, Sections 1.36, 5.12, 7, 8.2.1, 8.3.1

Document	Requirement / Purpose	File	Reference
IRB/IEC Approvals	1. Copies of all materials submitted to the IRB/IEC, including any local committees as required by the IRB/IEC, for example but not limited to: • Clinical Research Center Committee • Radiation Safety Committee • Maternal Fetal Committee • Other Hospital Committees per local site IRB/IEC requirements 2. Dated proof of submission and IRB/IEC approval of the following for both initial submissions and revisions (if any). Revised documents must be labeled (e.g., date and/or version number) to differentiate them from previous versions. • Advertisements – to document that recruitment measures are appropriate and not coercive. • Continuing/interim review of trial in accordance with regulations and local institution/IRB/IEC policy. • Informed consent form • Protocol • Protocol Amendments and/or Letters of Amendment • Protocol-specific education materials • Subject compensation • Any other documents receiving IRB/IEC approval or their favorable opinion. • Any other written information to be provided to subjects, to document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent. • Any other pertinent communications with IRB/IEC or documentation required by the IRB/IEC. • Clarification memos *if required by local IRB/IEC.* 3. Dated proof of IRB/IEC submission of the following for both initial submissions and revisions (if any). Revised documents must be labeled (e.g., date and/or version number) to differentiate them from previous versions. • IND Safety Reports, Safety Memos, and Safety Alerts • Investigator's Brochures 4. Proof of IRB/IEC receipt is necessary only if required by the local IRB/IEC.	• Central file • Protocol file	• 45CFR46 • 21CFR50 • 21CFR56 • 21CFR312 • FDA Guidance: E6 GCP, Sections 3, 4.4, 4.5, 4.10, 5.11, 5.17.3, 8.2.3, 8.2.7, 8.3.2, 8.3.3, 8.3.19 • OHRP IRB Guidebook
Laboratory	1. To document competence of local, central, or Group laboratories to perform protocol required tests and support reliability of results of medical/laboratory/standardized procedures/tests, one of the following must be on file: **<u>Laboratories located in the United States</u>** • CLIA Certification of Compliance • CLIA Certification of Accreditation AND the agency certificate (e.g., CAP Certification of Accreditation) **<u>Laboratories located outside the United States</u>** • Results of established quality control and/or external quality assessment (e.g., DAIDS VQA program) • Other validation 2. To document current competency, updated files when: • Existing certification/accreditation/validation expires. • A new laboratory is added or replaces an existing laboratory.	• Central file • Group-supported central laboratories documents may be filed on Group web sites. • Normal values/reference ranges may be filed in subject records (e.g., on lab	• 21CFR58 • 21CFR312 • 42CFR493.3 • FDA Guidance: E6 GCP, Sections 4.2, 8.2.11, 8.2.12 8.3.6, 8.3.7

Document	Requirement / Purpose	File	Reference
	laboratory. 3. Document normal values/ranges for medical/laboratory/ standardized procedures/tests included in the protocol. • Update when they are revised during the trial. • Does not apply to tests that do not have established normal values/ranges. 4. The preceding (1-3) do NOT apply to laboratories that test protocol specimens but do NOT report any subject-specific results for the diagnosis, treatment or assessment of the health of subjects.	report)	
Monitoring Log	Dated signature of monitor for each study visit.	• Central file	• 21CFR312 • FDA Guidance: Monitoring • FDA Guidance: E6 GCP, Section 5.18
Monitoring Reports	Copies of all site visit reports (hard copy or electronic) to document both the site visits and findings of the monitor.	• Central file	• 21CFR312 • FDA Guidance: E6 GCP, Sections 1.39, 5.18, 8.3.10
Pharmacy Accountability Records	Accountability records must be kept for all study drugs/agents provided as part of the protocol.	• Pharmacy file	• 21CFR312 • FDA Guidance: E6 GCP, Sections 4.6, 5.13, 5.14, 8.2.15, 8.3.8, 8.3.23, 8.4.1
Protocol	To document investigator and sponsor agreement to the protocol, amendments and CRFs; and, to document revisions of trial-related documents that take effect during trial: • Initial version that the site was registered to by ROC • Amendments and Letters of Amendment • Subsequent versions • Clarification memos • Case report forms	• Protocol file	• 21CFR312 • FDA Guidance: E6 GCP, Sections 1.44, 1.45, 4.5, 5.23, 6, 8.2.2, 8.3.2
Protocol Training	Documentation that trial procedures were reviewed with the investigator and investigator's trial staff: • Summary of start-up calls • Training meetings	• Protocol file	• 21CFR312 • FDA Guidance: E6 GCP, Sections 4.5, 5.23, 8.2.20
Record of Retained Body Fluids and/or Tissue Samples	If any blood specimens, other body fluids and/or tissue samples are retained for long-term storage at the site/institution, document location and identification of the retained samples. (e.g., A laboratory data management or tracking system.)	• Central file • Protocol file • Laboratory file	• FDA Guidance: E6 GCP, Section 8.3.25 OHRP Guidance: Issues to Consider in the Research Use

Document	Requirement / Purpose	File	Reference
			of Stored Data or Tissues
Screening and Enrollment / Randomization Logs	1. To document identification of subjects who entered pretrial screening. 2. To document chronological enrollment of subjects by trial number 3. Screening and enrollment/randomization logs may be separate or combined. 4. Include the following information: • Initials of all patients screened for each study • PID if patient receives one • Date screened • Date randomized ➢ If not randomized, indicate reason	• Central file • Protocol file	• 21CFR312 • FDA Guidance: E6 GCP, Sections 8.3.20, 8.3.22
Subject Identification Code List	1. To document that the investigator keeps a confidential list of names of all subjects allocated to trial numbers upon enrolling in the trial. 2. Allows investigator/institution to permit identification of all subjects enrolled in the trial in case follow-up is required. 3. List needs to be kept in a confidential manner.	• Central file • Protocol file	• FDA Guidance: E6 GCP, Sections 1.58, 8.3.21, 8.4.3
Serious Adverse Events (SAE) and Safety Reports	1. Notification by originating investigator to sponsor of serious adverse events, related reports, and other safety information. 2. Notification by sponsor to investigators of safety information. 3. Where applicable, notification by sponsor or investigator to regulatory authorities and IRB/IEC: • Unexpected serious adverse drug reactions • Other safety information	• Central file • Protocol file	• 45CFR46 • 21CFR50 • 21CFR56 • 21CFR312 • FDA Guidance: E6 GCP, Sections 1.1, 1.2, 1.50, 1.60, 4.11, 5.16, 5.17, 8.3.16, 8.3.17, 8.3.18 • DAIDS SAE Reporting Manual • DAIDS Policy for SAE Reporting on Non-IND Studies
Signature Key/Log	1. To document the signatures of individuals using initials in place of a full signature to sign CRFs and source documents. 2. To document the signatures and initials of all persons authorized to make entries and/or corrections on CRFs. Include all site staff working on a study, such as: • Clinicians • Physicians • Pharmacists • Data personnel • Any other individuals authorized to make entries and/or corrections on CRFs.	• Central file • Protocol file	• FDA Guidance: E6 GCP, Section 8.3.24

Document	Requirement / Purpose	File	Reference
	3. Key/log must include: • Initials • Printed Signature • Legal Signature, including first and last name • Credentials (if appropriate)		
Signed Agreements	To document agreements between involved parties, if any. For example: • Investigator/institution and sponsor (e.g., grant) • Investigator/institution and affiliated sites (e.g., contracts) • Investigator/institution and authorities (where required)	• Central file • Business office file	• 21CFR312 • FDA Guidance: E6 GCP, Sections 4.9.6, 5.6, 8.2.6
Source Documents	1. To document the existence of the subject and substantiate integrity of trial data collected. 2. To include original documents related to the trial, medical treatment, history of subject, and subject's condition while on-study or in follow-up. 3. Electronic media, original documents or certified copies. 4. Refer to the DAIDS Source Documentation SOP for additional requirements.	• As per requirements of local institution.	• 21CFR11 • 21CFR312 • FDA Guidance: E6 GCP, Sections 1.51, 1.52, 5.20, 8.3.13
Unblinding	A copy of the Group's SOP for unblinding must be on file at the site.	• Central file • Protocol file	• 21CFR312 • FDA Guidance: E6 GCP, Sections 1.10, 4.7, 8.2.17, 8.4.6