# Standard Operating Procedure:

# SOURCE DOCUMENTATION

## Purpose

The purpose of this standard operating procedure (SOP) is to provide guidance to research personnel when a system of records is established. Documentation of source data is necessary for the reconstruction, evaluation, and validation of clinical findings, observations, and other activities during a clinical trial. Source documentation serves to substantiate the integrity of trial data, confirm observations that are recorded, and confirm the existence of subjects. This SOP also serves to ensure data quality by creating audit trails and enabling verification that data are present, complete, and accurate. In multi-site clinical trials it is important for documentation of source data to be standardized across all sites to ensure consistency of the trial 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 good clinical practice (GCP). It 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 requirements for source documentation that are listed in this document, suggestions and/or comments are also included regarding implementation and references to the pertinent Federal regulations and/or guidances.
- 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 data must be verifiable and all documentation needs an audit trail.
- Always refer to local, state, institution, institutional review board (IRB)/independent ethics committee (IEC) policies and procedures and follow them if they are more stringent than the DAIDS SOPs.
- Apply ALCOA* to achieve data quality.
  1. **A**ttributable: is it obvious who wrote it?
  2. **L**egible: can it be read?
  3. **C**ontemporaneous: is the information current and in the correct time frame?
  4. **O**riginal: is it a copy; has it been altered?
  5. **A**ccurate: are conflicting data recorded elsewhere?

  *Source: "The Facts About Source Documents" by Stan W. Woollen, Presented at the 1999 DIA Annual Meeting

# Source Documentation SOP

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| **Addenda** | |
| Requirement | • If source documentation is incorrect, incomplete, or otherwise deficient, it may be corrected/completed by making an additional entry or addendum to the source documentation. The later entry must be signed/initialed and dated.<br>• All addenda must be signed and dated in present time by the person making the entry.<br>• Sites must NOT modify past-dated source documentation in research records in an attempt to resolve deficiencies. Altering past-dated records is potentially fraudulent.<br>• If it is noted in the research record that data are missing and those data are then obtained/found at a later date, its incorporation in the research record must be noted in the research record. The notation must be signed/initialed and dated. |
| Suggestions | • Identification of incomplete/deficient source documentation may occur by site staff during internal QA or by a monitor during a site visit.<br>• Addenda that are not appropriately signed and dated are prohibited because such entries are not verifiable.<br>• It is recommended that when including addenda to source documentation, the deficiency and the circumstances (if known) surrounding the situation be documented in a note.<br><br>Also refer to the following sections:<br>• Documentation Standards<br>• Error Corrections |
| Reference | • FDA Guidance: E6 Good Clinical Practice (GCP), Sections 4.9 and 5.18.4<br>• Thompson Publishing Group, *Guide to Good Clinical Practice*, Sections 2l0, 300, 410 |
| **Assent** | |
| Requirement | • Assent of children and permission of parents or legal guardians as determined by the IRB/IEC is required as per the provisions of 45CFR46.<br>• State/local law where the research is taking place defines the age of a minor and requirements for emancipation.<br>• Local IRB/IEC determine the age for obtaining assent.<br>• 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 (45CFR46.408c) are met.<br>• Keep on file all versions submitted and approved by site's IRB/IEC. |
| Reference | • 45CFR46, Subpart D<br>• 21CFR50<br>• 21CFR56<br>• FDA Guidance: FDA Information Sheets, Guidance for IRBs and Investigators 1998 Update, Q&A Nos. 47 and 48; and Page 5.<br>• FDA Interim Rule: Federal Register, Vol. 66, No. 79, 24April2001, pp. 20589-20600. |
| **Case Report Forms used as Source Documentation** | |
| Requirement | • Case report forms (CRFs) may be used as source documents if they represent data collected |

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| | for the study and are where data were initially recorded.<br>1. If data are obtained at a later date (i.e., after the study visit) and are recorded on the CRF as source documentation, it must be signed/initialed and dated.<br>2. If data are transcribed from another source onto the CRF, the CRF is not considered to be the original source document and it cannot be used as source documentation. Examples of data that are routinely transcribed from other sources include: laboratory results, radiology reports, histories documented in referral letters, etc.<br>• As a source document, the original CRF must be signed/ initialed and dated by the individual recording the data on the CRF so that there is a clear audit trail of who completed the documentation.<br>• Maintain a list of the CRFs being used as source documentation at the site.<br>1. To ensure consistency at the site.<br>2. The site needs to clearly indicate at the start of a monitoring visit or audit, which CRFs are being used as source documentation.<br>• CRFs used as source documents are not meant to replace ALL source documentation—there will still be a need for progress notes, lab results, X-rays, etc.<br>• CRFs used as source documentation need to be maintained and made available for review in the same manner as other source documents.<br>• Also refer to the section on questionnaires for the procedures specific to those types of CRFs. |
| Suggestions | • If a site chooses to use a CRF as source documentation, it should be used consistently as source documentation during the trial for all subjects at the site.<br>• CRFs are an adjunct to other source documents and may be filed with the source documents.<br>• The SAE reporting form or CRF may be used to record SOME data pertinent to the SAE and also be considered source documentation BUT it is not considered all-inclusive. There should be additional source documentation to reflect other possible etiology for the event, treatments/interventions, resolution, etc.<br>1. Often with a SAE, there are medical or research record notations, lab values, etc. to support the reporting and evaluation of the SAE.<br>2. The SAE form itself prompts you to attach progress reports, labs, diagnostic reports, etc., to the form. So when that data is recorded on the SAE form, the original source documentation for that data needs to be included in the research record for verification.<br>3. HOWEVER, some information on the SAE report could be used as source documentation (e.g., assessment of relationship to drug, severity of the event) IF that is where it is initially recorded.<br>➢ The data that is source documentation must be signed/initialed and dated like other documentation.<br>4. By itself, the SAE form will be considered incomplete source documentation because it clearly requires information that is extracted from other records (e.g., research record or medical record).<br><br>Also refer to the following sections:<br>• Addenda<br>• Copies<br>• Documentation Standards<br>• Error Corrections<br>• Inadequate Source Documentation<br>• Initials<br>• Medical Records<br>• Questionnaires<br>• Storage of Source Documents |
| Reference | • 21 CFR 312.62<br>• FDA Guidance: E6 GCP, Sections 1.11, 1.51, 1.52, 4.9, 5.23, 5.5, and 6.4.9 |
| **Chart Note** | |
| Requirement | • Refers to all notes related to study visits that are entered in the research or medical record by site staff. (e.g., progress note, nursing note, clinic note, etc.)<br>1. This does NOT apply to source documents that originate outside the site since the individuals making the notations may not be involved with the study.<br>2. Follow the institution's record-keeping procedures if they are more stringent.<br>• All data entries must be signed/initialed and dated:<br>1. Each time a new entry is made.<br>2. By the person making the entry. |

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| | 3. Entries by different people must be signed/initialed and dated by the individual making the entry.<br>➢ Exceptions:<br>✓ Multiple entries to a source document made by the same person on the same day require only one signature/initials and date on the page IF there have been no interim entries made by other individuals. It is incumbent upon the individual signing the source document to ensure that there have been no entries other than his/her own.<br>✓ A single date on a document with multiple entries is permitted if all entries were made on that same date. |
| Suggestions | • All chart notes and other source documentation should be filed in order by date to support the chronology of subject events.<br>• Entries that continue across more than one page should be signed/initialed and dated on each page. Refer to local institution policy.<br>• Refer to the Research Record section for requirements pertaining to hospital records subsequently used as source documentation.<br>• Includes any note used to support:<br>1. Data entered onto CRFs<br>2. Eligibility criteria<br><br>Also refer to the following sections:<br>• Addenda<br>• Copies of Outside Records<br>• Documentation Standards<br>• Entry Criteria<br>• Error Corrections<br>• Inadequate Source Documentation<br>• Initials<br>• Research Record |
| Reference | • 21CFR11<br>• Thompson Publishing Group's *Guide to Good Clinical Practice*, Sections 2l0, 300, 410<br>• FDA Guidance: E6 GCP, Section, 4 |
| **Communications: verbal** | |
| Requirement | • Verbal communications pertinent to research data collection must be documented in the research record in enough detail to support the data collected.<br>• Document in one of the following:<br>1. Chart note<br>2. Contact report (i.e., any written documentation of conversation that is signed and dated) |
| Suggestions | • A third party communication may be used to document vital status and other situations.<br>• Includes actual or attempted contacts with:<br>1. Subject<br>2. Parent/legal guardian<br>3. Family members/significant other<br>4. Friends<br>5. Healthcare providers<br>6. Other healthcare facilities |
| Reference | • FDA Guidance:E6 GCP, Section 4.9.1 |
| **Communications: written** | |
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| | • Written communications pertinent to research data collection must be documented in the research record.<br>• Documents must have appropriate identifiers to verify that they correspond to the specified subject.<br>• Includes documents such as the following examples:<br>1. Letter<br>2. Memo<br>3. E-mail<br>4. Reply correspondence<br>5. Admission/discharge summaries |
| Suggestions | • If no other documentation exists regarding written communications sent to the subject via special carrier (e.g., Fed Ex, Airborne, certified mail, etc.), it is recommended to retain copies of tracking forms/receipts.<br>• Includes actual or attempted contacts with:<br>1. Subject<br>2. Parent/legal guardian<br>3. Family members/significant other<br>4. Healthcare providers<br>5. Other healthcare facilities<br>6. Other contacts identified by the subject<br><br>Also refer to the following sections:<br>• Confidentiality<br>• Identifiers |
| Reference | • FDA Guidance: E6 GCP, Section 4.9.1 |
| **Compliance: study drug / agent** | |
| Requirement | • Compliance data is to be captured as specified by the protocol.<br>• Document in one of the following:<br>1. Chart note<br>2. CRF used as source document<br>3. Pharmacy records |
| Suggestions | To meet GCP Guidelines for documentation of compliance data, it is important to remember that compliance data has two components, quantitative data and qualitative data.<br>• Quantitative data that should be captured includes:<br>1. Quantity of study drug/agent dispensed<br>2. Quantity returned, if any*<br>3. Reported number of missed doses<br>*If the study does not provide the drugs/agents through the site or site pharmacy, but rather the subject secures drugs/agents through prescriptions filled at their own pharmacy, the information on quantity returned is not applicable.<br>• Qualitative data that should be documented in a chart note include:<br>1. The directions for taking all study drugs/agents have been reviewed with the participant.<br>➢ When study drugs/agents are initially provided.<br>➢ At intervals determined by the protocol.<br>2. Deviations from the instructions or problems in following the instructions.<br><br>Also refer to the following sections:<br>• Prescriber<br>• Prescriptions<br>• Study Drug/Agent |
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| | • 21CFR312<br>• FDA Guidance: E6 GCP, Sections 4.5.3, 4.6.5, 4.6.6 |
| **Computer Records (Computerized Systems / Electronic Records)** | |
| Requirement | • When data are entered directly into a computer system, the electronic data in the computer system is the original source document.<br>• A paper record (printout/hard copy/"print screen") of the electronic data is considered to be a copy.<br>• Requirements for documentation, record keeping and record retention apply to computer records as they do for paper systems.<br>• Computer records may be signed with an electronic signature.<br>• One type of an electronic signature is when a user signs-on to a computer system using two (2) distinct identification components, such as an identification code (user name) AND a password.<br>1. Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.<br>2. Signed electronic records must contain information associated with the signing that clearly indicates all of the following:<br>➢ Printed name of the signer.<br>➢ Date and time when the signature was executed.<br>• If original source documents are signed with electronic signatures then it is necessary to certify to the FDA that the electronic signatures in the computer system are intended to be the legally binding equivalent of traditional handwritten signatures.<br>1. The institution may submit certification for the employees as a whole to the FDA rather than on an individual basis.<br>2. A principal investigator may submit certification for the research staff to the FDA in place of the institution. |
| Suggestions | • If a paper record of electronic data used as a source document, the copy should be certified ONLY if the original, electronic file is not maintained.<br>• Computer records may include information such as:<br>1. Subject data, reports and/or results.<br>2. E-mail communications pertaining to a subject or protocol management (e.g., directives from protocol chairs, site investigators to research nurses, etc.).<br>3. IRB/IEC correspondence pertaining to a subject or study.<br>• If an institution's computer system does not meet the requirements of 21CFR11:<br>1. Systems should be moving toward compliance—upgrade their system if they plan to use electronic records.<br>2. FDA currently accepts existing hospital systems. |
| Reference | • 21CFR11<br>• FDA Guidance: Computerized Systems Used in Clinical Trials |
| **Concomitant Medication: non-study** | |
| Requirement | • Document subject/caregiver reported use of concomitant medication, non-study drugs, and prohibited medication according to protocol requirements. |
| Suggestions | In addition to prescription medication, this includes non-prescription drugs such as aspirin, cocaine, heroin, vitamins, etc. |

| **Confidentiality** | |
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| Requirement | Inform Subject<br>• Subjects must be informed of the extent to which confidentiality of records identifying them will be maintained:<br>1. Extent permitted by law.<br>2. Personal information is not released without subjects' written permission.<br>3. Subjects are not personally identified in any publication about the study.<br>4. Data is to be identified by code (e.g., PID) outside of the site.<br>5. Research records may be reviewed by representatives[1, 2] of:<br>➢ Food & Drug Administration (FDA) for studies under an IND<br>➢ Office for Human Research Protections (OHRP)<br>➢ National Institutes of Health (NIH)<br>➢ Study monitors<br>➢ Pharmaceutical companies involved in the study<br>➢ Responsible IRB/IEC<br><br>[1]A potential subject, in the informed consent process, must be made aware of the appropriate representatives (listed in item #5) that may review all of his/her medical records (research specific or otherwise) that are held by the institution conducting the research.<br><br>[2]While the research-specific record is the document being monitored for compliance with regulations and guidelines, access to the full medical record held by the institution that is conducting the research must be available to monitors at the time of review for purposes of identifying supporting documentation of research record data.<br><br>Storage<br>• All research records must be securely stored:<br>1. Double-lock when not in use.<br>2. Restricted access during work hours and/or when unattended.<br>3. Also refer to local institutional policies & procedures.<br><br>Labeling<br>All source documents must be labeled with subject identifiers to enable verification that the documents correspond to particular subjects.<br><br>Information Leaving the Site<br>If research records leave the site, follow local institution policy to ensure that confidentiality is maintained. |
| Suggestions | • Subjects' written permission in DAIDS studies is obtained via the signed informed consent and/or signed release.<br>• Non-site staff usually do not require information that would connect a subject to his/her study records. For this reason, PID/SID numbers should not be routinely used in hospital charts or medical records used by non-research personnel and/or charts/records outside of the site.<br>• Examples of storing records under double-lock include:<br>1. Lock on the office and lock on the file cabinet.<br>2. Locked office inside a clinic that is locked when not in use.<br><br>Also refer to the following sections:<br>• Identifiers<br>• Informed Consent<br>• Storage<br>• Research Record |
| Reference | • 21CFR11<br>• 21CFR50.25 |

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| | • Federal Privacy Act<br>• FDA Guidance: E6 GCP, Sections 4.6.5, 4.6.6<br>• DAIDS Policy<br>• Thompson Publishing Group's *Guide to Good Clinical Practice*, Sections 2l0, 300, 410 |
| **Consult Notes** | |
| Requirement | Chart note or other summary inserted into a subject's research record must contain:<br>• Subject identifier<br>• Signature and date by responsible clinician (may be electronic if computer generated) |
| Suggestions | Also refer to the following sections:<br>• Chart Notes<br>• Copies<br>• Electronic signatures<br>• Identifiers<br>• Computer Records |
| **Contraception: protocol-required** | |
| Requirement | Vaccine and Prevention clinical trial sites:<br>• Protocol required subject counseling on use of appropriate contraception must be documented prior to randomization/enrollment by one of the following:<br>1. Chart note with documentation to support the protocol defined entry criteria for contraception.<br>2. Completed Eligibility Checklist used as source documentation to support the protocol defined entry criteria for contraception. The Eligibility Checklist must correspond with the protocol text.<br>• If the protocol specifies that the subject must agree to practice 1 (one) or more forms of contraception, document one of the following:<br>1. The methods the subject chooses to use.<br>2. Subject counseling which included all of the following information:<br>➢ The number of forms of contraception that are necessary;<br>➢ A list of acceptable forms of contraception was given to the subject;<br>➢ The subject agreed to use contraception when necessary.<br>3. Subject-reported history of menopause or sterilization (hysterectomy, oophorectomy, tubal ligation, or vasectomy).<br><br>Therapeutic clinical trial sites:<br>• Protocol required subject counseling on use of appropriate contraception must be documented prior to randomization/enrollment by one of the following:<br>1. Chart note with documentation to support the protocol defined entry criteria for contraception.<br>2. Completed Eligibility Checklist used as source documentation to support the protocol defined entry criteria for contraception. The Eligibility Checklist must correspond with the protocol text.<br>• If the protocol specifies that the subject must agree to practice 1 (one) or more forms of contraception, document either of the following:<br>1. The methods the subject chooses to use.<br>2. Subject counseling which included all of the following information:<br>➢ The number of forms of contraception that are necessary;<br>➢ A list of acceptable forms of contraception was given to the subject;<br>➢ The subject agreed to use contraception when necessary.<br>3. Acceptable documentation of menopause or sterilization (hysterectomy, oophorectomy, tubal ligation, or vasectomy) as specified in the protocol; or that a child does not have reproductive potential: |

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| | ➢ Refer to the DAIDS TRP policy: "Guidance for Selecting and Modifying the Appropriate Protocol Eligibility Criteria Template for Pregnancy Prevention" for detailed information if not specified in the protocol. |
| Suggestions | • The research clinician is responsible for providing the subject with information about the importance of using contraception as per the protocol; and then documenting that counseling occurred.<br>1. It doesn't matter if the subject is heterosexual, homosexual, or abstinent. It may be helpful to stress:<br>➢ The importance of the requirement is due to the risk to the unborn.<br>➢ That the research staff cannot make assumptions about the subject's sexual activities or interest in parenting a child.<br>2. The important factor is whether or not the subject is physically capable of fathering a child or becoming pregnant—regardless of age. This also applies to the pediatric/adolescent population.<br>➢ If the subject is, then the research clinician needs to document:<br>✓ The subject has been counseled regarding birth control/prevention of pregnancy as per protocol<br>✓ The subject agrees to follow those requirements when necessary.<br>➢ If the subject is NOT physically capable, then the research clinician needs to document why.<br>• This source documentation is in addition to the signed informed consent that acknowledges any such requirements.<br>• It is important for site staff to be attentive to the following with pediatric and adolescent patients:<br>1. Subjects that have entered puberty are physically able to become pregnant/father a child.<br>2. Preteens/teens may be sexually active without the knowledge of their parents/guardian.<br>3. Site staff need to document their assessment of puberty onset.<br>4. Monitors cannot assume contraceptive counseling and pregnancy tests aren't applicable if there is no documentation in the research record to indicate whether or not the onset of puberty has occurred.<br>5. Such documentation is not expected for very young children; however, site staff are expected to assess pre-pubescent subjects and not just base their judgment of reproductive potential solely on the subject's age. |
| Reference | • 21 CFR 50.25<br>• 45 CFR 46<br>• DAIDS, TRP policy: "Guidance for Selecting and Modifying the Appropriate Protocol Eligibility Criteria Template for Pregnancy Prevention", Revised August 2002. |
| **Copies: certified** | |
| Requirement | • If the original document is retained elsewhere, the copy does NOT need to be certified (e.g., original lab results are filed in the laboratory).<br>• Monitors and FDA auditors may request to see the original documents or certified copies to verify validity of data for trial related monitoring.<br>• Certification of a copy may be indicated by any of the following methods:<br>1. A signed/initialed and dated statement on the copy that indicates it is an *exact copy of the original information*.<br>➢ This is to be done by the person making the copy, or, the person verifying that the copy is the same as the original.<br>➢ The statement may be in the form of a stamp as long as it is accompanied by an original signature/initials and date.<br>2. Signature/initials and date without a statement.<br>➢ The dated signature/initials means that the signer has verified that the copy is an exact copy of the original as per this SOP.<br>3. Certification for copies received from an outside institution indicates it is an *unaltered copy as received*.<br>• Documentation received via fax ARE copies, and NOT originals.<br>• Printouts retrieved from a computer system ARE copies and NOT originals.<br>• Documents consisting of more than one page may be verified in a package as being one (1) copy if the package of copies is to remain intact in the file.<br>1. For verification, the first page of the copy must have on it a signed and dated statement that indicates *the package consisting of X (specify) number of pages is an exact copy of the* |

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| | *original information*.<br>2. Each page must then be initialed and dated to verify that it is part of the package. |
| Suggestions | • A copy-used as a source document should be certified that it was verified to be an exact copy of the original, having all of the same attributes and information as the original.<br>1. This provides an audit trail in the event that the copy appears to have been altered.<br>2. This is strongly recommended to comply with FDA Guidance; however, it is not required by regulation.<br>• Monitors may occasionally request to see the original documents during routine monitoring to verify their existence—it does not mean that alterations or fraud is suspected.<br><br>Also refer to the following sections:<br>• Computer Records<br>• Initials<br>• Research Record |
| Reference | • 21 CFR 11<br>• FDA Guidance: E6 GCP, Section 1.51<br>• FDA Guidance: Computerized Systems used in Clinical Trials (CSCT) |
| **Death** | |
| Requirement | • Document by one of the following:<br>1. Obituary<br>2. Autopsy report<br>3. Death certificate<br>4. Contact report documenting verbal communication with subject's healthcare provider, family member, significant other, friend, etc.<br>• If the death is reported via verbal communication, the following must be recorded in the source document to substantiate the date reported cause of death:<br>1. Name of person reporting death and his/her relationship to subject<br>2. Date death reported to site<br>3. Date of death<br>4. Reported cause of death<br>5. Dates and methods site attempted to obtain official documentation to verify the verbal report of the date and cause of death<br>• SAE reporting according to DAIDS requirements. |
| Suggestions | Official documentation is preferred and includes an autopsy report or death certificate. A copy of the document is to be included in the subject's file for verification of the date and cause of death. |
| Reference | • 21CFR312.62(b)<br>• **45CRF46.103(b)**<br>• FDA Guidance: E6 GCP, Sections 1.52, 8.3.11, 8.3.16<br>• DAIDS SAE Reporting Manual<br>• DAIDS Policy for SAE Reporting on Non-IND Studies |
| **Departures / Deviations / Violations** | |
| Requirement | • All protocol departures/deviations/violations must be recorded in the subject's research record.<br>• If pertinent, reasons for the departures and/or attempts to prevent or correct the departures are to be included in the documentation.<br>• Refer to local IRB/IEC/institution policies for reporting protocol departures to the IRB/IEC. |

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| | • Examples of departures and appropriate documentation:<br>1. A missed visit needs a note stating it is a missed visit and the site's attempts to locate the subject to request that he/she come in to make up that visit.<br>2. Changes in procedures or medication based on clinical judgment need a note explaining the problem, what was done, communications with the protocol team and IRB/IEC if necessary, actions, and resolution. An AER may need to be filed. |
| Suggestions | • Departures from protocol also include incomplete laboratory evaluations, physical assessments, questionnaires, etc.<br>• If the vital status of a subject is known during the time period that a visit was missed, that information and the means by which it was obtained (e.g., telephone contact, conversation with relative, or other medical records, etc.) should be reflected in the subject's research record. |
| Reference | • 21CFR312.53(c)<br>• 21CFR312.60<br>• FDA Guidance: E6 GCP, Section 4.5.2 and 5.18.4<br>• FDA Guideline for the Monitoring of Clinical Investigations: Part D and Part E |
| **Documentation Standards** | |
| Requirement | • All research personnel must comply with applicable standards for medical documentation as determined by their institutional policy, professional Code of Ethics, and licensing authority.<br>• At a minimum, the following general standards must be followed:<br>1. Keep handwritten notes and signatures legible (if necessary, print name underneath the signature).<br>2. Sign and date all entries. Include credentials if required by the institution.<br>3. Make error corrections in the following manner: draw a single line through the incorrect information, initial, date, and state reason for change (if necessary).<br>4. Never obliterate entries that require correction.<br>5. Never destroy original documents if they require error correction.<br>6. Keep subject records secure yet accessible.<br>7. Do not alter past-dated notes, chart notes/progress notes (e.g., by writing alongside or adding to prior entries).<br>8. Only use dark ink.<br>9. Never use whiteout.<br>10. Never use pencils. |
| Suggestions | • Hospital records used to substantiate data must meet institutional policy and are not held to GCP standards as are research records.<br>• Records should be maintained chronologically.<br><br>Also refer to the following sections:<br>• Addenda<br>• Error Corrections<br>• Identifiers |
| Reference | • 21 CFR 312.57<br>• 21 CFR 312.58<br>• 21 CFR 312.62<br>• 21 CFR 312.68<br>• FDA Guidance: E6 GCP, Sections 2.1, 4.5.2, 4.5.3, 4.9.1, 4.9.2, 4.9.3, 8.3.13, 8.3.14, and 8.3.15<br>• FDA Guideline for the Monitoring of Clinical Investigations: Part E<br>• Thompson Publishing Group's *Guide to Good Clinical Practice*, Sections 2l0, 300, 410 |

| **Endpoints** | |
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| Requirement | • For study defined clinical or laboratory-based endpoints, the subject's research record must document the specifics of the event or test result as required by the protocol.<br>• Results of all diagnostic evaluations needed to substantiate the diagnosis must be included in the subject's research records.<br>• Document endpoints by any of the following examples, as applicable to the type of endpoint (e.g., clinical or laboratory):<br>1. Chart note<br>2. Consult note<br>3. CRF used as a source document<br>4. Documentation of death<br>5. Radiology diagnostic interpretation<br>6. Laboratory report<br>7. Paper copy of electronic report<br>8. Hard/fax copy lab report from research/ commercial lab<br>9. Hard/fax copy of correspondence from protocol team member (e.g., email from Data Manager) that subject has reached a study-defined lab based endpoint |
| Suggestions | Also refer to the following sections:<br>• Copies<br>• Documentation Standards<br>• Electronic Data<br>• Identifiers<br>• Lab Tests |
| Reference | • FDA Guidance: E6 GCP, Sections 6.4 and 6.7 |
| **Entry Criteria (Inclusion / Exclusion Criteria)** | |
| Requirement | • Documentation to address each of the protocol's inclusion and exclusion criteria must be present in the research record.<br>1. Chart notes to address the entry criteria.<br>2. Eligibility checklists used as source documentation as long as the criteria included corresponds with the protocol and each inclusion/exclusion criterion is addressed.<br>3. Original documents or certified copies of protocol required diagnostic results and/or history (e.g., laboratory results, radiology report, medication history, etc.).<br>• Documentation to address pertinent negatives must also be present in the research record. For example, exclusion criteria may require that the subject not be using any concomitant medications, or has not been diagnosed with another disease. Appropriate documentation includes but is not limited to, the following:<br>1. Chart notes to address each negative criterion. For example, "None of the concomitant medications excluded by the protocol are being used by the subject" is an acceptable way to document that the criterion has been met.<br>2. Eligibility checklists used as source documentation as long as the criteria included corresponds with the protocol and each inclusion/exclusion criterion is addressed.<br>NOTE: A blanket statement regarding all such exclusion criteria, such as "The subject does not meet any of the exclusion criteria outlined in the protocol" is NOT considered adequate. |
| Suggestions | Also refer to the following sections:<br>• Chart Note<br>• Contraception<br>• Copies<br>• Exemptions |

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| | • Karnofsky Score<br>• Medical History<br>• Medication History |
| Reference | • FDA Guidance: E6 GCP, Sections 4, 5.18.4, 6.5 |
| **Error Corrections** | |
| Requirement | • Error corrections must be done as follows:<br>1. Draw a single line through the incorrect information.<br>2. Initial, date, and state reason for change (if necessary).<br>3. Insert the correction.<br>• Never use pencil to write entries.<br>• Never use "white-out".<br>• Never obliterate entries that require correction.<br>• Never destroy original documents, even if they require error correction.<br>• Do not alter past-dated notes, chart notes/progress notes (e.g., by writing alongside or adding to prior entries).<br>• Error corrections that are not done according to procedure will result in inadequate source documentation. |
| Suggestions | • Guidance for when to state a reason for changes to documentation is as follows:<br>1. If it is something a reviewer can "see" or is obvious, such as a transcription error, then it needs no explanation.<br>*For example, if the site corrected a lab value that was transcribed incorrectly, then an explanation for the correction is not necessary as long as it can be verified with the original lab report.<br>2. If it is not clear, like a diagnosis or symptom that was deleted after initial entry, then there should be a rationale for the change.<br><br>Also refer to the following sections:<br>• Addenda<br>• Chart Note<br>• Documentation Standards<br>• Initials |
| Reference | • FDA Guidance: E6 GCP, Sections 4.9 and 5.18.4<br>• Thompson Publishing Group's *Guide to Good Clinical Practice*, Sections 2l0, 300, 410 |
| **Flow Sheets** | |
| Requirement | • Flow sheets to be used as source documentation must be:<br>1. Signed/initialed and dated by the clinician responsible for the entry.<br>2. Labeled with an appropriate subject identifier.<br>• If more than one person makes entries on a flow sheet, each entry must be signed/initialed and dated.<br>➢ Exceptions:<br>✓ Multiple entries to a source document made by the same person on the same day require only one signature/initials and date on the page IF there have been no interim entries made by other individuals. It is incumbent upon the individual signing the source document to ensure that there have been no entries other than his/her own.<br>✓ A single date on a document with multiple entries is permitted if all entries were made on that same date.<br>• Entries for timed serial evaluations (e.g., vital signs, pharmacokinetic studies, etc.) must also note times if required by the protocol. |

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| Suggestions | Examples of flow sheets:<br>• Pharmacokinetic flow sheets<br>• Vital signs flow sheets<br>• Weight/anthropometric data<br>• Medication logs<br><br>Also refer to the following sections:<br>• Chart Note<br>• Documentation Standards<br>• Identifiers<br>• Initials<br>• Source Documentation |
| Reference | • FDA Guidance: E6 GCP, Sections 4.9 and 5.18.4<br>• Thompson Publishing Group's *Guide to Good Clinical Practice*, Sections 2l0, 300, 410 |
| **Identifiers** | |
| Requirement | • All source documents must be consistently labeled with at least 1 (one) unique identifier so monitors can verify that documents correspond to particular subjects.<br>• Examples of unique identifiers:<br>1. Hospital identification number<br>2. Medical record number<br>3. Social Security Number<br>4. Patient identification (PID) number<br>5. Full name if there are no other subjects with that name at the site<br>6. Two non-unique identifiers in combination<br>• Identifiers that are NOT unique:<br>1. Date of birth<br>2. Subject initials<br>3. Full name if there are other subjects with that name at the site<br>• Identifiers on original documents must NEVER be obliterated, even if a new identifier is added to the document (e.g., placing a PID label over a subject's name). |
| Suggestions | • COPIES of original records may have PID/SID numbers obliterated and replaced with an acceptable identifier if records containing such numbers are to be viewed by non-research staff.<br>1. The change must be dated and initialed.<br>2. ORIGINAL source documents must NEVER be modified in this way.<br>3. Monitors must have access to the original documents for review.<br><br>Also refer to the following sections:<br>• Confidentiality<br>• Documentation Standards |
| Reference | • FDA Guidance: E6 GCP, Section 5.5.5 |
| **Informed Consent** | |
| Requirement | • Informed consent must be documented by the use of a written consent form:<br>1. Except if the IRB has waived the requirement for a signed written consent form in accordance |

with the requirements of 45CFR46.117(c) and 21CFR56.109(c).
  - Documentation of the IRB's decision to waive the requirement for written consent must be present in the regulatory files at the site.
2. All consent forms must be approved by the local IRB/IEC.
3. All consent forms must be submitted to DAIDS for review.
4. All consent forms for new protocols and amendments must be approved by DAIDS.
5. Protocol-specific consent must be obtained prior to randomizing/enrolling a subject.

- Signatures on the consent form:
  1. Must be legal name and may not include fabricated/falsified names.
  2. Must not use an initial for the last name.
  3. Strongly recommend not using an initial for the first name; however, if the person commonly signs his/her name using an initial for the first name, it will be accepted as long as it is also acceptable as per the policy of the institution.
  4. Must be in ink.
  5. Must be dated by each person signing the form. It is NOT acceptable for research staff to complete the date for another signer.
- Sites are not expected to routinely verify a person's legal name; however, if the site becomes or is aware that a person has not used his/her legal name to consent, then the following must be done:
  1. Obtain a new, signed consent with the legal name.
  2. Notify the local IRB/IEC. Retain IRB/IEC correspondence on this issue in their files.
  3. Document the events in the research record and the actions taken by the site.
  4. Ensure that there is documentation linking the two names.
     - For monitoring and audits, the site must be able to show that the names refer to the same person, (i.e., John Doe is really John Smith).
  5. Follow local institutional/IRB policy regarding continued use of the alias.
- If a subject is not able to write or sign his/her name in the form of a traditional "signature" as indicated above:
  1. If permitted under state/local law or institutional/IRB policy, document in the research record that the person cannot sign his/her name and that it is their "mark".
  2. Also refer to the bullet on illiterate persons in this section.
- Information given to the subject or the representative must be in a language they can understand.
  1. When the study subject population includes non-English speaking people so that the clinical investigator or the IRB/IEC anticipates that the consent interviews are likely to be conducted in a language other than English.
  2. IRB/IEC approved translated consent form.
  3. A consultant may be utilized to assure that the translation is correct.
  4. A copy of the translated consent document must be given to each appropriate subject.
  5. While a translator may be used to facilitate conversation with the subject, routine ad hoc translation of the consent document may NOT be substituted for a written translation.
  6. If a non-English speaking subject is unexpectedly encountered, investigators will not have a written translation of the consent document and must rely on oral translation.
     - Investigators should carefully consider the ethical/legal ramifications of enrolling subjects when a language barrier exists.
     - If the subject does not clearly understand the information presented, the subject's consent will not truly be informed and may not be legally effective.
     - If investigators enroll subjects without an IRB/IEC approved written translation, a "short form" written consent document, in a language the subject understands, should be used to document the elements of informed consent.
     - Requirements for signature of a witness to the consent process and signature of the person conducting consent interview must be followed if a short form is used. Refer to the provisions of 45 CFR 46.116, 46.117 and 21 CFR 50.25, 50.27(b)(2).
     - Financial burden to the institute/IRB/IEC is NOT an acceptable reason for lack of translated consent forms and non-compliance with the Federal regulations.
- Illiterate persons may have the consent read to them in a language they can understand and "make their mark" if appropriate under applicable state/local law.
  1. Investigators should be cautious when enrolling subjects who may not truly understand what they have agreed to do.
  2. The IRB/IEC should consider illiterate persons as likely to be vulnerable to coercion and

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| | undue influence and should determine that appropriate additional safeguards are in place when enrollment of such persons is anticipated.<br>3. Requirements for signature of a witness to the consent process and signature of the person conducting consent interview must be followed, if a short form is used. Refer to the provisions of 45CFR46.116, 46.117 and 21 CFR 50.25, 50.27(b)(2).<br>➢ The witness will need to be literate if a short form is used.<br>• Refer to 45CFR46 for special requirements of obtaining the informed consent of special populations in research.<br>1. Prisoners<br>2. Pregnant women, fetuses (perinatal studies)<br>3. Children<br>➢ Sites must obtain proof of guardianship before screening the subject for protocol enrollment if it is not clear who the subject's the legal guardian is. For example, chart notes from previous medical care indicates parent provided consent for treatment in the past, but now a different relative is caring for the subject.<br>4. Wards of the state and/or foster children<br>5. IRB/IEC may waive the requirement for parental consent of adolescents as per the requirements of 45CFR46.408(c) if within state law.<br>➢ Documentation of the IRB's decision to waive the requirement for parental consent must be present in the regulatory files at the site.<br>• If a revised informed consent form is required, it must be obtained as soon as possible.<br>• Additional documentation of the informed consent process and obtaining informed consent may be necessary as per local IRB/IEC or institution policy. |
| Suggestions | • Signatures on the consent form may include the person who conducted the consent process, a witness to the consent process, translator, or others according to the requirements of the local IRB/IEC.<br>• It is acceptable for sites to maintain consents in a file separate from a subject's research record, provided the site does this consistently for all subjects enrolled in the study and maintains any updated versions of the signed consents in the same manner.<br>• The process of obtaining informed consent should be documented in the research record in addition to obtaining a signed informed consent form.<br>• The following should be documented:<br>1. The date and time. A notation of the time is especially important when consent is obtained the same day that randomization/enrollment occurs.<br>2. A description of the consent process to substantiate that it was not coercive.<br>3. Information about the study, including all available options, was provided in a language understood by the subject.<br>4. The subject was given adequate opportunity to consider all available options.<br>5. The subject's questions were answered.<br>6. The subject's comprehension of the information.<br>• It is strongly recommended that this additional documentation be performed.<br>• Options for documentation in the research record:<br>1. Use forms, templates, quizzes, etc. to facilitate documentation.<br>2. Create a detailed informed consent checklist incorporating the items above and use this to document the process.<br>➢ This would need to be signed and dated by the person obtaining the informed consent.<br>3. The person obtaining the informed consent could write a comprehensive progress note that covers the items listed above.<br>4. Have the process documented, in detail, in a Standard Operating Procedure.<br>➢ The person obtaining the informed consent could document in the patient's chart that the informed consent was obtained per SOP.<br>➢ A copy of the SOP should be kept in a central regulatory file.<br><br>Also refer to the following sections:<br>• Assent<br>• Confidentiality<br>• Screening |
| Reference | • 45CFR46 |

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| | • 45CFR46.117(c)<br>• 45CFR46.408(c)<br>• 21CFR50<br>• 21CFR56<br>• 21CFR56.109(c)<br>• 21CFR312.62<br>• FDA Guidance: E6 GCP, Sections 4.8, 8.3.12, 8.2.3, 8.3.2<br>• FDA Information Sheets, Guidance for IRBs and Investigators 1998 Update, Q&A Nos. 40, 41, 51, and Page 5.<br>• OHRP Guidance: Informed Consent, Non-English Speakers, November 1995<br>• DAIDS Protocol Registration Policy and Procedure Manual<br>• DAIDS SOP: Essential Documents |
| **Initials** | |
| Requirement | Initials may be used in place of signatures provided that a signature key inclusive of the following is maintained at the site or on the document itself:<br>• Initials<br>• Signature<br>• Credentials (if applicable) |
| Reference | • FDA Guidance: E6 GCP, Section 8.3.24<br>• Thompson Publishing Group's *Guide to Good Clinical Practice*, Sections 2l0, 300, 410<br>• DAIDS Essential Documents SOP |
| **Karnofsky Score** | |
| Requirement | • Record in the research record the actual score assigned to a subject at a given point in time (as specified in the protocol).<br>• Provide documentation as per protocol requirements. |
| Suggestions | Data to support the assigned score is usually obvious upon reviewing the subject's medical record; if it is not, then rationale for the score should be noted. |
| Reference | • FDA Guidance: E6 GCP, Section 4 |
| **Lab Tests: Specimen Collection (Research and Routine)** | |
| Requirement | • Document that specimens were obtained as required by the protocol.<br>• If required by the protocol, specimen collection time must be noted.<br>• If fasting is required by the protocol, confirmation by subject of fasting more than 8 (eight) hours, or as specified by the protocol, must be noted. Some protocols may require that the specific date and time of the last food and fluids be recorded. |
| Suggestions | It is acceptable to write a note that broadly indicates that specimens were obtained for the protocol required tests.<br><br>Also refer to the following sections:<br>• Case Report Forms<br>• Computer Records |

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| | • Copies |
| Reference | • 21CFR11 subpart C<br>• FDA Guidance: E6 GCP, Section 4, 8.3.25<br>• FDA Guidance: Computerized Systems Used in Clinical Trials, Parts III and IV |
| **Lab tests: Results (Research and Routine)** | |
| Requirement | • All reports must have appropriate subject identifiers and date of specimen collection.<br>• Lab reports must identify where the test was performed.<br>• When reporting lymphocyte counts/percentages, a notation of the corresponding CBC with differential to verify total lymphocyte count may be required, depending on the lab's reporting format.<br>• For batched and/or blinded research lab analyses, no documentation of results is required in the subject's research record unless the unblinded results were disclosed to the site for the purposes of subject management, study termination, or re-randomization/step assignment. |
| Suggestions | Also refer to the following sections:<br>• Case Report Forms<br>• Computer Records<br>• Copies<br>• Endpoints<br>• Identifiers |
| Reference | • 21CFR11, Subpart C<br>• FDA Guidance: E6 GCP, Sections 4, 8.2.11<br>• FDA Guidance: Computerized Systems Used in Clinical Trials, Part IV |
| **Medical History: General and HIV-specific** | |
| Requirement | • Written documentation of medical history as defined by protocol. Including, *but not limited to*, diagnoses, signs/symptoms, medications, tests.<br>• Verbal history, recorded in research record, is acceptable. Note the source (person providing history).<br>• Chart note or referring healthcare provider's letter is acceptable.<br>• Obtain reports of laboratory tests, diagnostic procedures, and examinations as necessary to substantiate history. |
| Reference | • 21CFR312.62<br>• FDA Guidance: E6 GCP, Sections 2.11, 4 |
| **Medical Records** | |
| Requirement | • Review of medical records is necessary to extract all information that may be relevant to the protocol.<br>1. Monitors and FDA auditors may request to see original documents or certified copies to verify validity of data for trial related monitoring.<br>2. The following are examples of data: physical exams, concomitant medications, signs and symptoms/adverse events, diagnoses, laboratory results, diagnostic reports, etc. |

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| | • Medical records at institutions with primary care facilities:<br>1. All records including the subject's primary care chart must be accessible to the monitor for review/audits.<br>2. Note if records are missing and efforts to locate them.<br>• Copies of medical records from outside institutions and primary care providers are required if they support endpoints or SAEs, or if a DAIDS Medical Monitor in the process of investigating AEs requests them.<br>1. Records sent from other treating facilities that are incorporated into the subject's research record.<br>2. Monitors and FDA auditors may request to see original documents or certified copies to verify validity of data for trial related monitoring.<br>3. Subject must sign a release form if needed.<br>4. Unique identifier.<br>5. Record in the research record efforts to obtain outside medical records as needed for protocol participation.<br>6. Notations of follow-up efforts for records requested but not received.<br>• Monitors must have access to the source documents located in these records during audits. |
| Suggestions | • Sites should document all attempts to secure records pertaining to the subject while on-study that are required for, or are considered relevant to, the subject's study participation.<br>• Sites should acknowledge (record in research record) when medical records are missing despite efforts to obtain them.<br>• Retrieval of medical records from outside sources is driven by the need to gather sufficient information for adequate clinical assessment of the subject's medical condition.<br>• Sometimes it is impossible for a site to obtain copies of medical records while a subject is on-study.<br>1. This may occur, for example, when a research subject is seen in an out-of-town clinic or hospital, and the site is unable to persuade the outside facility to send copies of pertinent treatment records despite signed release of study subject.<br>2. In this case, site personnel are to include in the research record an acknowledgment that certain medical records are missing and the site's efforts to obtain them.<br><br>Also refer to the following sections:<br>• Computer Records<br>• Confidentiality<br>• Copies<br>• Identifiers<br>• Research Record<br>• Source Documentation |
| Reference | • 21 CFR 312.62<br>• FDA Guidance: E6 GCP, Sections 1.21, 1.22, 1.23, 1.24, 1.51, 1.52, 1.58, 2.10, 2.11, 4, 5.5.5 |
| **Prescriber** | |
| Requirement | Investigational agents are dispensed only upon the written order of the Investigator of Record (IOR) or upon the order of a licensed practitioner directly responsible to the IOR as stated on the Form FDA 1572 (IND studies) or the authorized prescribers list (non-IND studies).<br><br>• Prescriptions shall be written with ink, indelible pencil, typewriter, or computer generated and shall be signed by the practitioner:<br>1. Manually/hand written or with an electronic signature.<br>2. Signature stamps are NOT permitted.<br>3. Signing blank prescription forms is NOT permitted.<br>4. It is NOT permitted for an individual who is not an authorized prescriber to sign a prescription with an authorized prescriber's name and then add her/his own name to it in an effort to make it legal. For example, a nurse may not sign a doctor's name to a prescription and then add |

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| | her/his name to it if she/he is not an authorized prescriber.<br>• By signing the Form FDA 1572, the IOR has certified that the investigational agent will be administered only to subjects under his/her personal supervision or under the supervision of subinvestigators responsible to him/her.<br>• Only subinvestigators listed on the Form 1572 or authorized prescribers list may write orders for study products.<br>• An agent for the IOR or subinvestigator may prepare prescriptions in advance for the SIGNATURE of a practitioner.<br>• The prescribing practitioner is responsible in case the prescription does not conform in all essential aspects of the protocol, to the law and regulations. |
| Suggestions | • The following is a test question to determine if an individual is authorized in that jurisdiction to write prescription for study drugs/agents: Can the prescriber sign a prescription for non-study medication that could legally be filled?<br><br>Also refer to sections:<br>• Electronic Signatures<br>• Prescriptions<br>• Study Drug/Agent |
| Reference | • 21 CFR 312.61<br>• FDA Form 1572<br>• DAIDS Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Groups |
| **Prescriptions** | |
| Requirement | Documentation of Prescriptions for Study Drugs/Agents:<br>• Chart note or flow sheet indicating prescription was written; OR, copies of the prescriptions that were sent to the pharmacy (investigational or commercial).<br>1. Specify the study drug/agent, dose, schedule, and route of administration.<br>• All study prescriptions must be signed by a clinician authorized to prescribe in the site's jurisdiction who is listed on the current FDA Form 1572 (IND studies) or authorized prescribers list (non-IND studies) for a given protocol at the participating site.<br>• Prescriptions must include:<br>1. PID/SID numbers (subject's name instead if it is for a commercial pharmacy)<br>2. Name of study agent<br>3. Dose<br>4. Schedule<br>5. Route of administration, (or protocol number if that provides equivalent information)<br>6. Number of dosing units to be dispensed, OR, instructions (e.g., sufficient supply until next visit) in place of an exact quantity.<br>• Prescriptions may be written with refills.<br><br>Documentation of Changes in Study Treatment:<br>• Any change in study drug/agent status must be documented with sufficient detail to support and provide an explanation for the change as recorded on the CRF.<br>• Entries regarding dose modifications must include the reason for the change and the actual dosage change.<br>• Notes regarding the holding of study drug/agent must include the reason for the hold.<br>• Notes regarding the reinstitution of study drug/agent must include the reason for reinstitution of drug/agent and the dosage. |
| Suggestions | • Quantity or other dispensing instructions need to be specified on the prescription to prevent an open-ended supply of drug/agent from being dispensed.<br>• DAIDS, as sponsor of a study, requires the pharmacists to keep records of the disposition of all study |

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| | drugs/agents that are distributed from the NIAID CRPMC.<br><br>Also refer to sections:<br>• Prescriber<br>• Study Drug/Agent |
| Reference | • FDA Form 1572<br>• 21 CRF 312.50, .57, .59, .61, .62<br>• FDA Guidance: E6 GCP, Section 5.14<br>• DAIDS Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Groups |
| **Procedures: Diagnostic, Therapeutic, Surgical, etc.** | |
| Requirement | As appropriate, results, interpretations and/or diagnostic procedures required by the protocol must be documented. For example:<br>• Chart note<br>• CRF used as a source document<br>• Report<br>• Flow sheet<br>• Monitors and FDA auditors may request to see the original document or certified copy to verify validity of data for trial related monitoring. |
| Suggestions | Also refer to the following sections:<br>• Chart Note<br>• Computer Records<br>• Documentation Standards<br>• Error Correction<br>• Identifiers<br>• Medical Records |
| Reference | • 21CFR11<br>• 21CFR312<br>• FDA Guidance: E6 GCP, Section 4 |
| **Questionnaires: Subject/guardian and/or study personnel completed** | |
| Requirement | • The actual data on a subject/guardian completed questionnaire or CRF does not need supporting source documentation.<br>• Documentation is required is to show that the protocol required questionnaire was given to the subject/guardian in accordance with protocol requirements.<br>1. If the questionnaire IS completed by the subject:<br>➢ Enter a note into the subject's chart indicating the questionnaire/form was given to the subject/guardian to complete on a specified date.<br>➢ Indicate on a checklist that the subject/guardian completed the specified form on a specified date.<br>➢ Retain the completed questionnaire, test, or form as part of the research record.<br>✓ Except if site staff are blinded to the completed questionnaire per the protocol, then the site will not have it in the research record.<br>2. If the questionnaire is NOT completed by the subject, indicate who completed it and why.<br>3. If questions are completed by study personnel:<br>➢ Those questions/sections must be signed/initialed and dated.<br>➢ Supporting documentation for data must be in the research record (when applicable).<br>➢ Note if the form was completed via study personnel interviewing the subject/guardian.<br>➢ This pertains ONLY to questions that are an actual part of the questionnaire/data, not |

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| | information related to form keying or headers.<br>➢ Retain the completed questionnaire, test, or form as part of the research record. |
| Suggestions | Examples of questionnaires:<br>• Adherence<br>• Health Status<br>• Neuropsychology tests<br>• Nutrition surveys<br>• Quality of Life<br>• Patient logs<br>• Subject diaries<br><br>Also refer to the following sections:<br>• CRFs used as Source Documentation<br>• Communications<br>• Confidentiality<br>• Documentation Standards<br>• Initials |
| Reference | • FDA Guidance: E6 GCP, Section 4 |
| **Research Record** | |
| Requirement | • All documents that substantiate data collected and/or are relevant to a subject's participation in a clinical investigation constitute a research record. They include the following:<br>1. Subject-signed informed consent<br>2. Source documents<br>3. Case history<br>4. Investigational pharmacy records<br>5. CRFs<br>• Individuals authorized to review the records may request to inspect any or all of the above types of documents.<br>• Investigators are responsible for maintaining accurate and complete research records.<br>• Each subject must consent in writing to direct access to his/her research record, including original medical records held by the institution conducting the research, for trial-related monitoring, audit, IRB review, and regulatory inspection by authorized individuals.<br>• Sites must be able to produce a research record in its entirety for monitoring and/or audit.<br>1. Sites must provide direct access to each subject's research records, including the entire medical record held by the institution conducting the research.<br>2. Direct access to all records held at the institution is necessary for purposes of identifying and monitoring trial-related and/or pertinent data (e.g., medical history, contraindications for enrollment, adverse experiences, etc.) in the source documents.<br>3. The source of study data must be verifiable in original source documents or certified copies.<br>• Shadow files are an adjunct to the subject's medical record or clinic chart.<br>1. These files, consisting of copied source documents, are intended to reflect a subject's complete, study specific record.<br>2. Copied documents in these files are NOT the original source documents.<br>3. Monitors and FDA auditors may request to see the original documents or certified copies to verify validity of data for trial related monitoring.<br>➢ If the site is not able to produce original source documents or certified copies during a monitoring review, the data will be considered as having inadequate source documentation.<br>4. May include protocol required documentation such as the following examples:<br>➢ Informed consent<br>➢ Screening results<br>➢ Baseline events<br>➢ Vital status<br>➢ Clinical and laboratory findings |

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| | ➢ Management of study drugs/agents and toxicities |
| Suggestions | • Original records are ideal but shadow files are acceptable. Monitors may occasionally request to see the original documents during routine monitoring to verify their existence—it does not mean that alterations or fraud is suspected.<br>• Hospital records used to substantiate data must meet institutional policy and will not be monitored for adherence to the GCP standards that research-specific records are required to follow.<br>Also refer to the following sections:<br>• Confidentiality<br>• Copies<br>• Documentation Standards<br>• Identifiers<br>• Source Document<br>• Storage |
| Reference | • 21 CFR 312<br>• 45 CFR 46<br>• FDA Guidance: E6 GCP, Sections 4.9, 5.15, 6.10, 7, and 8 |
| **Screening** | |
| Requirement | • Federal regulations and institutional policy must be followed when screening subjects to determine potential eligibility.<br>1. Screening is defined as any procedure done solely for the purpose of determining a potential study subject's eligibility or to enter a subject into a research study.<br>2. Consent must be obtained before invasive procedures are performed.<br>3. It is required unless the IRB has waived the requirement for a signed written consent form as per the requirements of 21CFR56.109(c).<br>➢ Documentation of the IRB's decision to waive the requirement for written consent must be present in the regulatory files at the site.<br>4. Either an IRB/IEC approved generic screening consent form or the IRB/IEC approved protocol consent form is acceptable.<br>5. If a site customarily uses IRB/IEC approved screening consents for all study subjects, or for all subjects screened for certain protocols:<br>➢ The screening consent must be signed & dated before screening for protocol eligibility begins.<br>➢ The protocol-specific consent must be signed & dated before randomization/enrollment into the protocol.<br>6. Access, and consent for access, to medical records and/or databases for use in identifying potentially eligible study subjects is dependant upon the policies of the local institution/IRB/IEC.<br>➢ Review of medical records and/or databases outside of your institution is NOT permitted without the prior consent of the potential study subjects.<br>7. Maintain a list/log of subjects screened for a protocol.<br>➢ It is not required to include broad medical records/database reviews; however, it would be good practice to include those subjects for verification that there was no bias in the selection of potential subjects. |
| Suggestions | Also refer to the following sections:<br>• Assent<br>• Confidentiality<br>• Informed Consent |
| Reference | |

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| | • 45CFR46<br>• 45CFR46.117(c)<br>• 45CFR46.408(c)<br>• 21CFR50<br>• 21CFR56<br>• 21CFR56.109(c)<br>• 21CFR312.62<br>• FDA Guidance: E6 GCP, Sections 4.8, 8.3.12, 8.2.3, 8.3.2<br>• FDA Information Sheets, Guidance for IRBs and Investigators 1998 Update, Q&A Nos. 40, 41, 51, and Page 5.<br>• OHRP Guidance: Informed Consent, Non-English Speakers, November 1995<br>• DAIDS Protocol Registration Policy and Procedure Manual<br>• DAIDS SOP: Essential Documents |
| **Source Document** | |
| Requirement | • Any original documents or certified copies that include documentation pertaining to the subject's condition while on a research study. This includes *but is not limited to* the following:<br>1. Medical record<br>2. Clinic chart<br>3. CRFs used as source documents<br>4. Primary care provider's office chart<br>5. Laboratory reports and radiology reports<br>6. Flow sheets, medication records, prescriptions, EKG tracings, etc.<br>• Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution must make available for direct access all requested documentation that may be relevant to the subject's trial participation. This includes CRFs and medical records.<br>• If there is no supporting evidence to verify protocol-required data and procedures, source documentation will be considered inadequate. |
| Suggestions | • Source documents should contain at least the following:<br>1. Medical History, including relevant history for the disease being treated.<br>2. Current physical condition.<br>3. Current illness and injuries.<br>4. Current medications.<br>5. Medications discontinued within the last month (or longer if required by protocol).<br>6. Descriptions of the informed consent process.<br>7. Dates of actual subject visits.<br>8. Completion of study procedures (laboratory samples, X-rays, EKGs), including dates and results.<br>9. Adverse experiences, illness, or problems reported by the subject during the course of the study.<br>10. Deviations from the protocol and the reason.<br>11. Unexpected occurrences/problems.<br>12. Existing record of all study treatments.<br>13. Any additional information required by the protocol.<br>• It is not the monitor's responsibility to search for source documents or to travel to another site to obtain access to research records.<br>• When a source document is not in the research record, the monitor may ask the site staff if they can obtain the document during the course of the site visit. (e.g., a missing lab slip or a document that is temporarily in another department of the hospital.)<br>1. The record will not be cited for inadequate source documentation if the missing document is provided to the monitor for review before completion of the site visit and it is found to be adequate.<br>2. It is unacceptable for study personnel to submit missing documentation to a monitor between site visits.<br><br>Also refer to the following sections:<br>• Chart Notes<br>• Copies |

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| | • Informed Consent<br>• Medical Record<br>• Research Record |
| Reference | • 21CFR 312.62 (b), 312.68<br>• FDA Guidance: E6 GCP, Sections 1.51, 1.52, 4.8.10 (n) 4.9.7, 4.9.5, 4.11.1, 5.18.1, 5.18.4, and 8.3.13<br>• FDA Compliance Program Guidance Manual 7248.811<br>• Thompson Publishing Group, *Guide To Good Clinical Practice*, Section 410 |
| **Storage of Source Documents** | |
| Requirement | • Sites must retain research records according to Federal regulation, institutional policy, DAIDS SOP, the protocol, and/or Group SOPs. Includes:<br>1. Source documents<br>2. CRFs<br>3. Pharmacy records<br>4. Regulatory files<br>• For electronic data storage, the FDA expects to be able to reconstruct the study.<br>1. This applies not only to the data, but also how the data were obtained and managed.<br>2. All versions of application software, operating systems, and software development tools involved in processing of data or records need to be available as long as data or records associated with these versions are required to be retained.<br>3. Records should be backed up regularly in a way that would prevent a catastrophic loss and ensure the quality and integrity of the data.<br>➢ Backup records should be stored in a secure location specified in the SOPs.<br>➢ Storage needs to be separate from the original records, such as in a separate building or an off site facility.<br>➢ Backup and recovery logs need to be maintained to facilitate an assessment of the nature and scope of data loss resulting from a system failure.<br>• Refer to the separate DAIDS SOP, Storage of CRFs and Pharmacy Records, for the procedure on shipping CRFs to DAIDS for permanent storage.<br>1. If CRFs are used as source documentation, submit copies of those CRFs to DAIDS for permanent storage.<br>2. The site should then retain the original CRFs used as source documentation with the other source documents. |
| Suggestions | • This SOP pertains to record storage within the institution.<br>• CRFs are an adjunct to other source documents and may be filed with the source documents; however, it is recommended that source documents be stored separately from CRFs.<br>1. Provides a safeguard against the simultaneous loss of both the source documents and the CRFs.<br>2. Assists in maintaining subject confidentiality.<br>3. If CRFs are used as source documentation:<br>➢ The original CRFs used as source documents should be filed with the other source documents.<br>➢ Copies of those CRFs should then be filed with the other CRFs if in accordance with Group SOPs.<br>• Sites may store copies of source documentation as computer records, microfiche or microfilm.<br>1. Site personnel should verify the quality of the copies and certify them.<br>2. If applicable, the monitor must be given access to a computer system, microfiche/microfilm reader during his/her site visit to reviewed documents stored in this manner.<br><br>Also refer to the following sections:<br>• Case Report Forms<br>• Computer Records<br>• Copies<br>• Electronic Signatures<br>• Source Document |

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| Reference | • 21CFR11<br>• 21CFR312.62<br>• FDA Guidance: Computerized Systems Used In Clinical Trials, Sections VI, D and IX, C<br>• DAIDS SOP: Storage of CRFs and Pharmacy Records<br>• DAIDS SOP: CRF Destruction List |
| **Study Drug / Agent** | |
| Requirement | • Supplied study drugs/agents are dispensed only upon the written order of the Investigator of Record (IoR) or upon the order of a licensed practitioner directly responsible to the IoR as stated on the Form FDA 1572 (IND studies) or authorized prescribers list (non-IND studies).<br>• Study drug/agent use by the subject must be recorded in the research record.<br>• Medications that meet one or more of the following criteria for protocol-specified drugs/agents or non-specified drugs/agents are considered to be "study drugs/agents" UNLESS otherwise directed by the protocol:<br>1. Protocol-Specified Drugs/Agents<br>➢ Drugs/agents specified by name for use in the study. The following criteria apply:<br>✓ All drugs/agents distributed through NIAID's distribution center (CRPMC). (In rare instances this may not apply, and in that event, site staff will be notified.)<br>✓ All drugs/agents that are specifically required by the protocol, including those that are individually specified or any that are chosen from a list of specified drugs/agents. **EXCEPT** if the study is designed to evaluate subjects already receiving specified drugs as part of their routine medical care before study entry.<br>➢ Risks for each of these drugs/agents must be included in the informed consent form.<br>➢ The protocol will specify whether SAE reporting is required and, if so, the intensity or level of AE reporting.<br>2. Non-Specified Drugs/Agents:<br>➢ In addition to any drugs/agents specifically named for use in a study, other drugs/agents that are being used to address the study's primary therapeutic objective(s) and any other study objective designated for this purpose by the protocol will be considered to be study drugs/agents.<br>✓ Includes drugs/agents that are not individually specified by name in the protocol nor distributed by the CRPMC. For example: GART/PART studies, treatment strategy studies, and long-term follow-up studies.<br>✓ Protocols may designate distinct types or classes of drugs/agents that will or will not be "study drugs/agents".<br>➢ Risks of individual non-specified drugs/agents do not need to be included in the informed consent document; however, general statements regarding study treatment risk may need to be made. For example, including common risks for relevant drug classes or referral to package inserts/approved patient education material need to be considered.<br>➢ The protocol will specify whether SAE reporting is required and, if so, the intensity or level of AE reporting. Unless the protocol gives further instructions, all drugs/agents meeting this definition must be taken into account in deciding the intensity of AE reporting and included in assessments concerning relationship of SAEs to "study drug/agent".<br>3. Some protocols may have BOTH "specified" and "non-specified" study drugs/agents. |
| Suggestions | Also refer to the following sections:<br>• Prescriber<br>• Prescriptions<br>• Pharmacy Accountability Records |
| Reference | • 21CFR312.32(c)<br>• 21CFR312.64(b)<br>• DAIDS Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Groups |

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| | • DAIDS Serious Adverse Experience (SAE) Reporting Manual |
| **Study Drug / Agent Accountability** | |
| Requirement | • The Pharmacist of Record must keep records to account for the disposition of study drugs/agents by documenting the following:<br>1. Shipment records<br>2. Lot numbers<br>• Allows tracking of:<br>1. Product lot numbers<br>2. Accountability<br>• Documents that the study drugs/agents have been used according to the protocol.<br>• Document the final accounting of study drugs/agents:<br>1. Received at the site<br>2. Dispensed to subjects<br>3. Returned by subjects<br>4. Returned to sponsor |
| Suggestions | A sample accountability record is provided in the DAIDS Pharmacy Guidelines and Instructions. Site pharmacists are not required to use this exact form as long as the monitor can adequately determine the disposition of the agent. |
| Reference | • 21 CFR 312.62<br>• FDA Guidance: E6 GCP, Sections 8.2.15, 8.3.8, 8.3.23, and 8.4.1<br>• DAIDS SOP: Essential Documents |
| **Toxicities**: **grading (adverse events, signs and symptoms, lab results)** | |
| Requirement | • All toxicities and/or signs/symptoms, including those reported by the subject, must be recorded in the subject's research record and assessed for clinical significance by one of the following methods:<br>1. A numerical grade that corresponds to the applicable toxicity table.<br>2. A written description that corresponds to the definitions in the applicable toxicity table.<br>3. Exceptions:<br>➢ For abnormal laboratory results: It is <u>not</u> necessary to record a grade in the research record or on the laboratory report if the protocol's toxicity table lists what grade it is based on the value. However, it <u>is necessary</u> to indicate that the event has been assessed.<br>➢ For non-reportable AEs that are not clinically significant: It is <u>not</u> necessary to record a grade in the research record. However, it <u>is necessary</u> to indicate that the event has been assessed.<br>➢ The following are examples of how it may be documented to indicate that the event has been assessed:<br>✓ Note in the research record.<br>✓ Sign/initial & date the lab report.<br>4. If toxicities or signs/symptoms are not listed in the toxicity tables, then a grade or written descriptor must be recorded in the research record.<br>➢ "Not clinically significant" (NCS) is an acceptable descriptor to use when appropriate.<br>5. If non-study staff documents toxicities or signs/symptoms:<br>➢ Study staff must document in the research record their assessment of the event, including grade or written description. Relationship to study drug/agent is required |

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| | only if the event is reportable as an SAE.<br>➢ For example, if a subject is seen in an emergency room for a stroke, the research clinician must document in the research record the grade and since it is a reportable SAE, the relationship of the event to the study drug/agent.<br>• Reportable AEs/SAEs must have documentation to support the determination of relationship to study drug/agent when it is found to be "Not Related".<br>• The protocol will specify whether SAE reporting is required and, if so, the intensity or level of AE reporting. |
| Suggestions | The following are examples of where data may be recorded:<br>• Chart Note<br>• Flow sheet<br>• Adverse Event (AE)/Symptom Checklist<br>• Annotated lab slip, signed and dated by responsible clinician<br>• Serious Adverse Event (SAE) form signed by clinician completing the form. |
| Reference | • 21CFR312.62(b)<br>• 21CFR312.64(b)<br>• FDA Guidance: E6 GCP, Sections 2.3, 4.5.1, 4.11, 5.18.1, and 8.3.13 |
| **Transferring Subjects** | |
| Requirement | • At a minimum, the transferring site will provide a written evaluation regarding the subject's condition along with a synopsis of the subject's involvement in the study.<br>1. Any supporting documentation deemed necessary is forwarded to the receiving site.<br>2. If the receiving site requests additional subject records from the transferring site, document in the research record what is sent.<br>3. Refer to your Group's own SOP regarding the transfer of subjects for additional requirements. |
| Suggestions | • A transferring site, prior to the subject being evaluated by the receiving site, should send the relevant subject information/documentation.<br>• It is the transferring site's responsibility to provide this information, and the receiving site's responsibility to review and request any additional information prior to the actual transfer. |
| Reference | DAIDS Policy<br>Group Policy |
| **Vital Signs and Other Assessments** | |
| Requirement | • The protocol must specify the required vital signs (e.g., temperature, pulse, respirations, etc.) and other assessments (e.g., height, weight, body surface area, head circumference, etc.) and at which study visits they are required.<br>• Record on one of the following:<br>1. Chart Note<br>2. Flow sheet<br>3. CRF used as source documentation |
| Suggestions | Also refer to the following sections:<br>• Chart Note<br>• Case Report Forms<br>• Documentation Standards |

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| | • Flow sheets<br>• Initials<br>• Source Document<br>- |
| Reference | • 21CFR312<br>• FDA Guidance: E6 GCP, Sections 4.5 and 6 |