Section 2: Documentation Requirements

2. Introduction

Study staff are responsible for proper collection, management, storage, quality control and quality assurance of all study-related documentation. This section contains information on the essential documents that each study site must maintain throughout MTN-035. It also contains information related to establishing adequate and accurate participant research records for the study.

2.1 Essential Documents

The DAIDS policy on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and E6 Good Clinical Practice: Consolidated Guidance specify the essential documents that study sites must maintain. Although all required documentation must be available for inspection at any time, all documents need not be stored together in one location.

A suggested essential document filing structure is available upon request from FHI 360. Study sites are not required to adopt the suggested structure but are encouraged to consider it when developing their filing approach for the study. Further clarifications of the suggested filing structure are as follows:

- Essential documents may be stored in files, binders, and/or electronically. The files/binders listed in essential documents filing structure may be further subdivided, consolidated, and/or re-organized.

   NOTE: Sites that chose to file documents electronically must ensure computer systems are 21 CFR Part 11 compliant and are required to have documentation on file certifying that their systems meet such requirements. Refer to the MTN Manual of Operational Procedures, Section 9, for further details on the requirements that must be met when using electronic systems/software.

- It is recommended that a contents sheet be maintained and inserted as the first page(s) of each file/binder. Within each file/binder, it is recommended that documents be filed in ascending date order (most recent documents in front).

- Certain documents related to the study product(s) will be stored in site pharmacies. A listing of essential documents to be maintained in the pharmacies is provided in Section 2.3.6 below.

- Certain laboratory-related essential documents should be stored in the main study essential documents files/binders. Other lab-related essential documents (e.g., lab SOPs) may be filed in site laboratories.

- The suggested filing structure assumes that MTN-035 participant research records will be stored separately from the other essential documents listed in the essential documents filing structure. Section 2.2 below provides information on the required contents of these records.

- The MTN-035 PTID-Name Linkage Log and Screening and Enrollment Log must be maintained in hard-copy. The suggested filing structure assumes that these logs will be stored in the study clinic or data management area throughout the screening and accrual process and not necessarily with the other essential documents listed.

- All significant communications between the study sponsor and/or management team and study sites should be printed and filed with other essential documents.
    - All site responses to priority emails (thereby indicating they were read and responded to)
    - All study management team and/or sponsor communications that document agreements or significant decisions involving trial administration or conduct, protocol deviations, eligibility and informed consent, safety and/or study endpoints, or study product
    - All notifications of critical events (CE) that are submitted to DAIDS
    - Protocol Team call slides and/or supplemental materials
    - Final training reports, including sign-in sheets
    - Final study activation notification memo and activation checklist
    - Final reports from assessment visits conducted by FHI 360, or others on the study management team, as well as the completed list of action items stemming from the report, if applicable
    - Emails and/or other key communications from the study management team that specify to print and file

Note: When required documents are modified or updated, the original and all modified or updated versions must be retained in the files. Communications that are PTID-specific should be printed and filed in the participant binder. Communications that are overarching (i.e. are not PTID-specific) can be printed and filed with regulatory documentation. All clinical site monitoring reports and correspondence can be accessed through the DAIDS Enterprise System (DAIDS-ES) within the NIAID Clinical Research Management System (NCRMS) and do not need to be printed and filed.

2.2   Participant Research Records

Study sites must maintain adequate and accurate participant research records containing all information pertinent to MTN-035 for each study participant. See protocol sections 11.2 and 13.6 for further information regarding all participant information that should be stored in locked file cabinets with access limited to authorized study staff. Please note that all records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by PTID.

The International Conference on Harmonisation Consolidated Guidance for Good Clinical Practice defines the terms *source data* and *source documentation* as follows:

The term **source data** refers to all information in original records and certified copies of original records related to clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the trial (including all screening, enrollment and randomization activities). Source data are contained in source documents (e.g., original records or certified copies).

The term **source document** refers to original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory reports, logs and certain other documents, memoranda, participants' diaries and/or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the study).

Source documents are commonly referred to as the documents – paper-based or electronic – upon which source data are first recorded. All study sites must comply with the standards of source documentation specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. The DAIDS policy specifies both requirements and recommendations. Study sites must comply with all requirements and are encouraged, but not required, to comply with all recommendations.

2.3   Required Source Documentation

For MTN-035, it is expected that participant research records will consist of the following source documents:

- Narrative or chart notes
- Documentation that the participant provided written informed consent to screen for and participate in the study prior to the conduct of any study procedures
- Documentation that the participant met the study's eligibility criteria
- A record of the participant's use of the study products
- Pharmacy study product accountability, dispensing and chain of custody records (maintained in the study site pharmacy)
- A record of all contacts, and attempted contacts, with the participant
- A record of all procedures performed by study staff during the study (e.g. on visit checklists and/or other site-specific procedural flow sheets or chart notes)
- Local laboratory testing logs and result reports, or other defined source document, for a test result
- Case report forms (CRFs) and other forms provided by the MTN Statistical and Data Management Center (SDMC) or MTN LOC
- Study-related information on the participant's condition before, during, and after the study, including:
  - Data obtained directly from the participant (e.g., interview/audio recordings, SMS data, and/or other self-reported information)
  - Data obtained by study staff (e.g., exam and lab findings)
  - Data obtained from non-study sources (e.g., non-study medical records)
  - Other source documents (e.g., site-specific worksheets)

As a condition for study activation, each study site must establish an SOP for Source Documentation that specifies the source documents for all study procedures. To establish consistency in source documentation across sites, the source for specific study procedures is noted in the Source Documentation SOP template. Supplemental information on the use of chart notes, visit checklists, and forms provided by the MTN SDMC or MTN LOC is provided below. Detailed information on proper completion, maintenance, and storage of product dispensing documentation is provided in Section 6 of this manual and in the MTN-035 Pharmacy Study Product Management Procedures Manual. Detailed information on proper completion of CRFs is provided in the CRF Completion Guidelines provided by the MTN SDMC.

2.3.1 Chart Notes

Study staff <u>must</u> document every contact with a study participant in a signed and dated chart note or contact log specifying the following information:
- Visit date at which a contact takes place or at which a particular procedure takes place
- Visit type (scheduled, interim, etc.)
- Purpose of the visit and location of the contact if other than the research clinic
- General status of the participant at the time of the visit

Chart notes should also be used to document the following:
- The informed consent process (if an Informed Consent Coversheet is not used)
- Procedures performed that are not recorded on other source documents (e.g. visit reminder phone calls, emails etc.)
- Additional information related to clinical exam findings to ensure appropriate follow-up
- Study-specific counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements, if not documented on other worksheets)
- Other pertinent data about the participant that are not recorded on other source documents and/or any clarifications or information needed to supplement data recorded on a CRF
- Reason(s) why protocol-specified procedures were not performed
- Explanation of why procedures in addition to those listed on a checklist were performed
- Contact attempts to follow up on participants who missed a scheduled study visit

2.3.2 Visit Checklists

Visit checklists are convenient tools that may serve as source documentation if designed and completed appropriately. These checklists alone may not suffice for documenting all procedures but can be used to indicate that the procedure was completed. Chart notes may be required to supplement this for any of the reasons mentioned above. Visit checklist templates are available on the MTN-035 website under Study Implementation Materials.

Instructions for completing visit checklists in accordance with these requirements are as follows:

- Enter, as applicable, the participant identification number (PTID), visit date, visit type and visit code on the top section of each checklist page.

- Enter your initials only beside the procedures that you perform. Do not enter your initials beside procedures performed by other staff members.

- Ideally, only one person should initial each line of the checklist. If the line includes multiple procedures and they are performed by different staff, indicate who performed which procedure in the comments. Checklists should be designed to avoid this practice. If all procedures listed on a checklist are performed on the date entered in the top section of the form, the date need not be entered beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item.

- For items on the checklist that contain checkboxes, one set of initials is still sufficient, even if multiple boxes are checked.

- If a procedure listed on the checklist is not performed, enter "N/D" for "not done" beside the item and record the reason why on the checklist (if not self-explanatory); initial and date this entry. The sequence of procedures presented on the visit checklist templates is a suggested ordering. In consultation with the MTN LOC (FHI 360), sites should modify the checklists to maximize the efficiency of site-specific study operations. Visit checklists, and visit flow, should be monitored and updated as needed to ensure that study visits are completed as quickly as possible, with minimal delays for participants and study staff. Sites may alter the sequence of procedures to suit local staffing and logistical requirements, with the following exceptions:

- Written informed consent must be obtained before any study procedures are performed. Study visit procedures are listed in protocol section 7.

- On the day of enrollment, randomization assignment must take place after final confirmation and verification of eligibility and collection of blood for plasma archive. It is recommended that for sites not doing finger stick HIV testing, blood for HIV serology and plasma archive be collected together, to limit venipuncture to a single blood draw. If a participant is subsequently found to be ineligible and is not randomized, the plasma archive sample should be destroyed.

- The Baseline Behavioral CASI Questionnaire may be done before or after randomization but must be completed prior to provision of study product and first dose or insertion.

- Pelvic, genital, and rectal exam procedures must be performed in the sequence shown on the applicable exam checklist. The "Required at Visit(s)" column indicates when the item is required per protocol.

- During follow-up visits, CASI questionnaires should be administered prior to the delivery of HIV pre-and post-test counseling, HIV/STI risk reduction counseling and protocol adherence and product use counseling.

- It is recommended that procedures for determining eligibility for continued product use be conducted early in the visit to ensure that these procedures be conducted in case the participant needs to abruptly leave the clinic or is short of time.

Note that the time of each study procedure does not need to be documented to demonstrate the order of visit procedures if this can be accomplished through other approaches. Acceptable alternatives include using a statement in the chart note or on visit checklists which verifies that the correct order was executed, or by documenting that procedures were conducted 'per site SOPs' which specify order. Deviations from SOPs should be explained in chart notes. This applies to the procedures listed above, whose order is required. The order of procedures listed above as 'ideal' or 'recommended' does not need to be demonstrated in source documentation.

2.3.3   Laboratory

Each lab test must have a defined source document which is the first place the result is recorded or generated. Site laboratories will have a plan for the storage of these documents so that they are easily retrievable.

2.3.4   Case Report Forms (CRFs)

See SSP Section 12 (Data Collection) for further details regarding the use of case report forms (CRFs) with the Medidata Rave data management system. CRFs have been designed to be used as source whenever possible. Prior to study activation, each study site will document the CRFs used as source as well as which CRFs are not used as source in its SOP for Source Documentation. The specifications of this SOP must be followed consistently for all study participants. In the event that study staff are not able to record data directly onto forms designated as source documents, the following procedures should be undertaken:

- Record the data onto an alternative source document.
- File the alternative source document in the participant's study chart.
- Transcribe the data from the alternative source document onto the appropriate form and, if possible, enter a note on the form stating the alternative source document used.
- Write a chart note stating the relevant study visit date and the reason why an alternative source document was used.
- Perform QC procedures as specified in the site-specific Data Management SOP to ensure accurate and correct data transcription.

2.3.5   Document Organization and Participant Confidentiality

Study staff must make every effort to store all study records securely and confidentially. Case history records must be stored in the same manner for all participants, in areas with access limited to authorized study staff only. Study staff are responsible for purchasing file folders, binders, storage cabinets, and any other equipment or supplies needed to properly store all records.

Study-related documentation collected during the screening process should be stored in file folders/binders for each potential participant. All screening documentation – for potential participants who eventually enroll in the study as well as for those who do not enroll or "screen out" – must be maintained and available for monitoring throughout the study. This documentation must also be available for reference should participants present to the site for re-screening. For participants who enroll in the study, screening documentation should be transferred to a separate file folder/binder that will serve as the participant's study notebook for the duration of their participation in the study.

All documents contained in participant case history records must bear a participant identifier, which generally will consist of either the participant identification number (PTID) or the participant name. The PTID should be used whenever possible to maximize participant confidentiality. As a best practice, it is recommended that records bearing names or other personal identifiers, such as locator forms and informed consent forms, be stored separately from records identified by PTID. Any documents transferred or transmitted to a non-study site location must be identified by PTID only. Care should also be taken to only refer to participants by PTID in email communication when people outside of the site are included.

Regardless whether the identifier on a particular document consists of the participant name or PTID, the original identifier may not be obliterated or altered in any way, even if another identifier is added. When necessary to maintain confidentiality, identifiers may be obliterated on copies of original source documents. For example, if medical records obtained from a non-study health care provider bear the participant's name, the original documents bearing the name must be stored unaltered with other study documents bearing the name. However, a copy of the original documents could be made, the PTID could be entered onto the copies, and then the participant name could be obliterated from the copies. Copies handled in this way could then be stored in participant study notebooks and/or transferred or transmitted to non-study site locations.

All on-site databases and CASI questionnaire data must be secured with password-protected access systems. Any lists, appointment books, or other documents that link PTIDs to other participant identifiers should be stored securely (locked cabinet/drawer if hard copy; password protected if electronic) and in a location separate from records identified by participant name only and separate from records identified by PTID only. When in use, documents that link PTIDs to other participant identifiers should not be left unattended or otherwise accessible to study participants, other study clinic patients, or any other unauthorized persons.

2.3.6 Study Product Accountability, Chain of Custody, and Dispensing Documentation in the Pharmacy

Pharmacy staff will document the receipt and dispensing of each study product, and return/destruction of each unused study product. Separate accountability records must be maintained for each sub-lot/lot of product, per instructions provided in the MTN-035 Pharmacy Study Product Management Procedures Manual available from the MTN Pharmacist.

Pharmacy staff will also maintain in the study pharmacies a Pharmacy Dispensing Record for each product, per instructions in the MTN-035 Pharmacist Study Product Management Procedures Manual. Study clinic staff will contribute to the documentation of product provision and chain of custody as described in Section 6 of this SSP Manual.

The specifications related to document security and participant confidentiality described in section 2.3.5 above also apply to records maintained in the study pharmacies. All records must be stored securely in the pharmacies with access limited to authorized study pharmacy staff only.

The following essential documents should be maintained in study site pharmacies:
- Current MTN-035 protocol
- Current DAIDS IoR Form
- Current list of authorized prescribers and staff authorized to sign Prescriptions and Study Product Request Slips (names and signatures)
- Pharmacy Establishment Plan (MTN Director of Pharmacy Affairs Approved)
- MTN-035 Pharmacy Study Product Management Procedures Manual and applicable SOPs for study product management, QA/QC and product Chain of Custody
- MTN-035 product shipping and receipt documentation, product storage temperature logs, and product accountability records
- MTN-035 participant-specific records (including study prescriptions and request slips, participant-specific dispensing records, records of receipt of participant study product and documentation of unused product returns)
- MTN-035 monitoring visit reports
- Communications with site clinic staff, the MTN Pharmacist, MTN LOC and/or the MTN SDMC or other MTN-035 communications or locally-required administrative, operational, and/or regulatory documentation

2.4   Record Retention Requirements

Study records must be maintained onsite for the entire period of study implementation. Thereafter, guidance for record storage will be provided by FHI 360 in consultation with DAIDS and the MTN Executive Committee. No study records may be moved to an off-site location, discarded or destroyed without prior written authorization from the MTN. Refer to the MTN Manual of Operational Procedures (MOP; Section 18) for further requirements pertaining to record storage.

The IoR/designee will maintain all study documentation for a minimum of three years after submission of the site's final Financial Status Report to DAIDS, unless otherwise specified by DAIDS or the MTN LOC. However, documents may be stored for a longer period if required by applicable regulatory requirements or by an agreement with the sponsor.

2.5   Translation Procedures

Per MTN MOP Section 11, all study materials that are read verbatim or provided to the participant must be translated into local language, back-translated, and reviewed by members of the study management and/or behavioral team as appropriate. Participant materials may include the informed consent forms and comprehension assessments, CASI questionnaires and other study materials developed for participant use. Site teams are responsible for establishing a Translation SOP that should, at minimum, contain the following elements:

- Description of the translation and back-translation process and the quality control of it
- Who is responsible for conducting each step of this process (and whether it is done by on-site staff or through a contracted group)

All staff involved in the translation and back-translation process should ensure that language fluency is documented on their CV on file at the research site and that this responsibility is assigned per the site Delegation of Duties Log. A standard *Certificate of Translation* should be issued for translations completed, indicating the specific documents that were translated (with version number/date as appropriate) as well as the individual conducting the translation. It is recommended that, as part of translation procedures, staff members who will be responsible for utilizing the translated study materials review and/or pilot use of the tool to confirm translations are understandable in the context they will be used.

2.6   Protocol Deviations

DAIDS requires that all protocol deviations be documented in participant records, along with efforts made to correct the deviations, and efforts made to prevent similar deviations in the future. The MTN MOP should be referenced for complete guidance on protocol deviations.

For MTN-035 the Protocol Deviation (PD) Log CRF will be used to document each protocol deviation identified. Missed visits are considered protocol deviations per MTN policy, however these will *not* be captured on the PD Log CRF for MTN-035 (the Missed Visit CRF will capture this information instead).

Corrective and preventive action (CAPA) plans are required components of protocol deviation documentation. Note that the corrective and preventive action plans documented on the PD Log CRF are not required to be completed in order to report the deviation. The PD Log CRF should be completed even if the action plans are pending or in progress. It is important to ensure that documentation includes any counseling that was done to address the protocol deviation (e.g., on the importance of retention for missed visit deviations, or the list of prohibited concomitant medications or other products, etc.).

If there is any question as to whether a deviation has occurred, or how it should be documented, the MTN Regulatory Department (mtnregulatory@mtnstopshiv.org) and MTN-035 Management Team (mtn035mgmt@mtnstopshiv.org) should be contacted. Once the potential protocol deviation has been confirmed, the site will be contacted with this confirmation and the 7-day reporting requirement will begin. Once the CRF is submitted, the MTN SDMC will follow up with the site if any clarifications or additional information on the CRF are needed. The study management team will follow up with the site regarding any next steps, as needed.

Note that some protocol deviations may also be considered critical events. Refer to the DAIDS Critical Event Policy and Critical Event Manual for detailed guidance on the definition of critical events and reporting process. The site OCSO Program Officer (PO) should be contacted with any questions related to critical events, including reporting requirements and procedures, CAPAs, and critical events tracking questions. Site consultation with OCSO may be facilitated using the MTN Critical Event Reporting Form, available in the 'Resources' section of the MTN web page; however, use of this form is not mandatory. Sites that choose to use this document should email the completed form to their OCSO PO, who will work with other DAIDS staff to review available details about the event and determine if a critical event has occurred. If a critical event is confirmed, the OCSO PO will work with the site to develop, review and carry out any CAPAs associated with the reported critical event.

Sites are recommended to report to their IRBs/ECs any PDs that pose a potential safety risk to a participant(s) and those that could affect the integrity of the study according to the local IRBs'/ECs' standard operating procedures and guidelines. It is also recommended that a complete list of all PDs occurring at the site, including PDs not meeting immediate reporting standards noted above, be submitted to the local IRBs/ECs in accordance with their reporting policies. If a local IRB/EC does not have a specific reporting policy, MTN recommends that this be done at the time of IRB renewal submission, annually or semi-annually, per local requirements. These listings will be provided to the sites on request. If needed, sites should request these PD listings from SCHARP at least two weeks prior to the planned date of submission to their local IRBs/ECs.