Section 2: Documentation Requirements

2. Introduction

Study staff members are responsible for the 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 the study. It also contains information related to establishing adequate and accurate participant research records for MTN-038.

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* specifies 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 the MTN-038 Management Team. The suggested filing structure assumes that participant research records will be stored separately from the other essential documents. SSP Section 2.3 below provides information on the required contents of these records. Study sites are not required to adopt this filing 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 and/or in binders, which may be subdivided, consolidated, and/or re-organized.
- 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.
- Certain documents related to the investigational study products will be stored in site pharmacies. A listing of essential documents to be maintained in the pharmacies is provided in SSP Section 2.4.
- To facilitate routine inspection by study monitors, certain laboratory-related essential documents should be stored in the study essential documents files/binders. Other lab-related essential documents (e.g., lab standard operating procedures [SOPs]) may be filed in site laboratories.

- The MTN-038 PTID-Name Linkage Log and Screening and Enrollment Log must be maintained in hard copy throughout the duration of the trial. 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.

Note: When required documents are modified or updated, the original and all modified or updated versions must be retained.

2.2 Financial Disclosure Forms

Each clinical investigator listed on the Form 1572 must disclose any financial interests that may be affected by the outcome of the research or attest to the absence of relevant significant financial interests. Per 21 CFR 312.53, financial disclosure must be completed prior to study involvement. The IoR and site Regulatory Coordinator must ensure that *prior to* completing (adding or removing investigators) and signing the FDA Form 1572, all investigators listed on the form must complete and sign the study-specific financial disclosure form (FDF). In addition, investigators listed on the current FDA Form 1572 must submit a new FDF at the completion of all study-specific activities (i.e. the date of the last participant follow-up visit at the study site).

A blank FDF is available on the MTN-038 webpage. All items can be entered electronically except for the signature and date. The '*Study start date*' is the date on the cover of the most current version of the protocol. The '*Study end date*' is the date of last follow-up at the site; this section on the FDF may be left blank until the end of follow-up at the site.

At the beginning of the study and throughout study duration, whenever an FDF is completed, sites should upload the form to the DAIDS Protocol Registration System (DPRS), under the "Other" submission category. Training slides on the requirements for FDF completion can be found here: http://www.mtnstopshiv.org/node/7331.

2.3 Participant Research Records

MTN-038 study sites must maintain adequate and accurate participant research records containing all information pertinent to each study participant. See Protocol section 13.6 for further information regarding confidentiality of participant information; participant charts should be stored in locked file cabinets with access limited to authorized study staff.

2.3.1 Concept of Source Data and Source Documentation

The *International Conference on Harmonization 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 and enrollment 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 records and notes; memoranda; participants' diaries and/or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies of transcriptions certified after verification for accuracy and completeness; microfiche; photographic negatives; microfilm or magnetic media; x-rays; participant files; and records kept at the pharmacy, laboratories, and 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. Source documents must be created and maintained using Good Documentation Practices (GDP), as outlined in the MTN MOP.

2.3.2 Required Source Documentation

For MTN-038, participant research records should consist of the following source documents:

- Chart notes
- Documentation that the participant provided written informed consent to screen for and participate in the study prior to the conduct of any screening or study procedures
- Documentation that the participant met the study's eligibility criteria
- Prescription documentation
- A record of the participant's use of the investigational study product
- Pharmacy investigational product accountability, dispensing and chain of custody records (maintained in the study site pharmacy), as well as clinic study product accountability documentation (maintained in the study clinic)
- 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 any other document defined as a source document for a test result
- Case Report Forms (CRFs) and other forms provided by the MTN SDMC (both paper and electronic)
- Study-related information on the participant's condition before, during, and after the study, including:
    - Data obtained directly from the participant (e.g., interview 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, logs)

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 recommended source for specific study procedures has been specified in the Source Documentation SOP. Supplemental information on the use of chart notes, visit checklists, and forms provided by the MTN SDMC is provided below. Detailed information on proper completion, maintenance, and storage of product dispensing documentation is provided in SSP Section 7 Study Product Considerations and in the MTN-038 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.

2.3.2.1 Chart Notes

Study staff must document every contact with a study participant in a signed and dated chart note or contact log specifying the following information when necessary to document adherence to protocol requirements:

- 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 screening and enrollment informed consent process (if an Informed Consent Coversheet is not used)
- Procedures performed that are not recorded on other source documents
- Additional information related to clinical exam findings to ensure appropriate follow-up
- Study-specific counseling sessions and any associated referrals that are not documented on other source documents
- 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
- Explain 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

2.3.2.2 Visit Checklists

Visit checklists are convenient tools which may serve as source documentation if designed and completed appropriately. These checklists alone may not be sufficient for documenting all procedures, but can be used to indicate that the procedure was completed. Chart notes may be required to supplement the information recorded within visit checklists. Sample Visit Checklists are available on the MTN-038 website.

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

- Enter the participant identification (PTID) number and visit date on the top section of each checklist. If checklists are multiple pages, enter the PTID and visit date on each page.
  - For screening visits, write the screening attempt number in the applicable checklist item.
  - For follow-up visits, enter the visit code/number on the top section of each checklist.
- Enter your initials only beside the procedures that you perform. Do not enter your initials beside procedures performed by other staff members. If other staff members are not available to initial checklist items themselves, enter, initial, and date a note on the checklist documenting who completed the procedure, e.g., “done by {name}” or “done by nurse.”
- 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. Bracketing procedures which are consecutive, and all done on the same date by the same staff is also acceptable.
- If a procedure listed on the checklist is not performed, enter “N/D” for “not done” or “N/A” for “not applicable” 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 sample visit checklists is a suggested ordering. In consultation with the MTN LOC (FHI 360), site staff 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.
- On the day of enrollment, randomization must take place after confirmation of eligibility and collection of blood for plasma archive.
  NOTE: It is recommended that sites collect blood for HIV serology and plasma archive together to limit venipuncture to a single blood draw. If a participant is subsequently found to be ineligible and is not enrolled, 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 ring insertion.
- Any laboratory testing that is intended to be performed rapidly in the clinic, such as hCG and HIV testing, should be performed and results provided to the participant prior to study product provision or the participant leaving the clinic, in the case of continued study product use. Additionally, clinicians should review the hCG and/or HIV test results prior to the clinical examinations and further specimen collection (i.e. rectal, pelvic, and subsequent blood collection) to ensure no procedures need to be modified in the case of a positive result.
- Pelvic exam procedures must be performed in the sequence shown on the pelvic exam checklists at visits where a pelvic exam is required. For clinically indicated pelvic exams, procedures may be documented in the chart notes and/or the Pelvic Exam checklist.
- During certain study visits, blood and specimen collection procedures must be completed at specified time-points in relation to ring insertion and removal, and/or to one another. Any timing specification indicated on the sample study visit checklists and in SSP Section 10 and Section 5 should be followed.
- During follow-up, behavioral assessments administered either as a CRF or a CASI questionnaire should be administered prior to the HIV/STI risk reduction and protocol counseling.
- It is recommended that procedures for determining eligibility for continued product use be conducted early in the visit to ensure that these procedures are conducted if the participant needs to abruptly leave the clinic or is short of time.

2.3.2.3 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.

2.3.2.4 Case Report Forms (CRFs)

See SSP Section 12 Data Management for further details regarding the use of CRFs with the Medidata Rave data management system. As shown in the Source Documentation SOP template, CRFs have been designed to be used as source whenever possible. Prior to study activation, each study site will indicate in its SOP for Source Documentation the CRFs used as source as well as which CRFs are not used as source. The specifications of this SOP must be followed consistently for all study participants. In the event that study staff is 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 enter a note on the form stating the alternate source document used
- Write a chart note stating the relevant study visit date and the reason why an alternative source document was used

2.3.3 Protocol Deviations and Critical Events

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

For MTN-038, the Protocol Deviation Log CRF will be used to document each reportable deviation identified. Missed visits are considered protocol deviations per the MTN policy, however these will *not* be captured on the Protocol Deviation Log CRF. The Missed Visit CRF will capture this information instead. For protocol deviations that impact more than one participant, a separate Protocol Deviation Log CRF should be submitted for each PTID.

Corrective and preventive action plans are required components of protocol deviation documentation. It is important to ensure that chart notes or other source documents include any associated counseling that was done to address the protocol deviation (e.g. counseling on the importance of retention for missed visit deviations). Note that the corrective and preventive actions must be documented, but are not required to be completed prior to reporting the deviation to SCHARP.

Protocol deviations should be reported within seven days of site awareness, even if all actions/plans are still in-progress. If there is a question as to whether a deviation has occurred, or how it should be documented, MTN Regulatory and the MTN-038 Study Management Team should be contacted at mtnregulatory@mtnstopshiv.org and mtn038mgmt@mtnstopshiv.org, respectively. Once the potential protocol deviation has been confirmed, the site will be contacted with this confirmation and the seven-day reporting requirement will begin. Once the CRF is submitted, MTN Regulatory may follow up with the site if any clarifications or additional information on the CRF is needed.

It is recommended that all protocol deviations occurring at the site be submitted to the local IRBs/ECs in accordance with their reporting policies. Some protocol deviations may need to be reported in real time (e.g. those with a potential impact on participant safety) while others can be submitted as part of a summary listing later. If a local IRB/EC does not have a specific reporting policy, the MTN recommends that a full listing of study protocol deviations be submitted at the time of IRB renewal submission, annually or semi-annually per local requirements. These listings may be provided by the MTN SDMC to the sites upon request.

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, preventive and corrective action plans, 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. Site staff who choose to use this document should email the completed form to their OCSO Program Officer, 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 Program Officer will work with the site to develop, review and carry out any planned corrective and preventive action(s) associated with the reported critical event.

2.3.4 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 is 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 a file folder/binder 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 also must 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 participants' 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 PTID or the participant name. The PTID should be used whenever possible to maximize participant confidentiality. 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.

Note: Regardless of whether the identifier on a particular document is 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 participants' study notebooks.

All on-site databases 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). 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.

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

Pharmacy staff will document the receipt and dispensing of each vaginal ring (VR) and the return/destruction of each unused (never dispensed) VR on the MTN-038 Pharmacy Vaginal Ring Accountability Record. Separate accountability records must be maintained for each lot of product, per instructions provided in the MTN-038 Pharmacy Study Product Management Procedures Manual available from the MTN LOC Pharmacist.

Study clinic staff will contribute to the documentation of product provision and chain of custody as described in SSP Section 7 Study Product Considerations and in the Clinic Study Product Accountability and Destruction SOP.

The specifications related to document security and participant confidentiality described in SSP Section 2.3.4 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-038 Protocol
- Investigator's Brochure for the tenofovir vaginal ring: current version and any updates
- Current FDA Form 1572
- Current list of authorized prescribers and staff authorized to sign Prescriptions and Vaginal Ring Request Slip (names and signatures)
- Pharmacy Establishment Plan (DAIDS PAB approved or MTN LOC Pharmacist approved)
- MTN-038 Pharmacy Study Product Management Procedures Manual and applicable SOPs for investigational study product management and Chain of Custody
- MTN-038 product shipping and receipt documentation, product storage temperature logs, and investigational product accountability records

- MTN-038 participant-specific records (including prescriptions and request slips)
- MTN-038 VR chain of custody records (including records of receipt of site-specific VRs and records of return of site-specific unused VRs)
- MTN-038 monitoring visit reports
- MTN-038 communications with site clinic staff, communications with the MTN Pharmacist, IPM Clinical Supply Coordinator and/or product distributor
- MTN-038 communications with site clinic staff, the MTN LOC, and/or the MTN SDMC or other communications or locally-required administrative, operational, and/or regulatory documentation

2.5 Record Retention Requirements

All study records must be maintained for at least two years following the date of marketing approval for the study product for the indication in which they were studied. If no marketing application is filed, or if the application is not approved, records must be retained for two years after the US Food and Drug Administration is notified that the Investigational New Drug (IND) application for the product(s) is discontinued.

All records must be retained on-site throughout the study's period of performance, and for at least three years after completion or termination of the study. Study product records must be stored in site pharmacies, with access limited to authorized study pharmacy staff only. DAIDS will provide further instructions for long-term storage of study records after the study is completed. Study records should not be re-located to an off-site location or destroyed without prior approval from DAIDS.