Section 2. Documentation Requirements

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2. Introduction

Study staff members 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 the study. It also contains information related to establishing adequate and accurate participant research records for MTN-042.

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.

Examples of essential documents specific to MTN-042 include (but may not be limited to):

- MTN-042 Protocol, v1.0 (and LoAs/CMs, as applicable)
- MTN-042 SSP Manual, Data Communiques, Operational Guidance Documents
- CTU/CRS Policies & Procedures (SOPs), including Study Specific SOPs for MTN-042
- Personnel Qualification, Training Records, and Delegation
    - CVs, HSP/GCP, clinical licenses as applicable)
    - Financial Disclosures
    - MTN IoR Training
    - Delegation of Duties (DoD) Log
    - Study Specific Training Documentation (i.e. agenda, materials, sign in sheets)
    - SOP Training Logs
- Investigator Signature Page(s) and DAIDS 1572 Form
- All Regulatory Communication (IRB/IEC/ DRAs) including:
    - Submissions packets
    - Regulatory Approvals
    - IRB Rosters
- Contracts (all)
- Notices of IB Receipt
- Network/Site/Sponsor Communications
    - 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 the DAIDS
    - Protocol Team call slides and/or supplemental materials
    - Final study activation notification memo and activation checklist
    - DAIDS Protocol Registration Approval
    - 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
    - Emails and other key communications (e.g., Operational Guidance) from the study management team that specify to print and file
- Study Source Data
    - ICFs, data collection materials [i.e. Case Report Forms (CRFs)], interview transcripts, worksheets, checklists, chart notes, etc.
    - Logs: screening and enrollment, PTID-name link
    - Protocol Deviations and Deviation Reporting
    - Protocol Safety Physician decisions, e.g. PSRT query responses
- All specimen and assay data, including repeat or reanalysis performed for a test sample
- Investigational product accountability
- Monitoring/assessment/audit visit logs
- All documents required by ICH E6(R2)

When developing an 'essential documents' filing structure for MTN-042, study sites are encouraged to consider their experiences implementing previous DAIDS network protocols. While taking into account these experiences, the structure should be tailored to meet the specific needs of MTN-042 and ensure that all required documents are properly filed. Tips for the suggested filing structure are provided below:

- Essential documents may be stored in files and/or in binders. 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 investigational study products will be stored in site pharmacies. A listing of essential documents to be maintained in the pharmacies is provided in Section 2.3.

To facilitate routine inspection by study monitors, 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.

- It is assumed that MTN-042 participant research records will be stored separately from the other essential documents. Section 2.2 below provides information on the required contents of these records.
- The MTN-042 Screening and Enrollment Logs and PTID-Name Linkage Log must be maintained in hard-copy. The suggested filing 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.

Note: When required documents are modified or updated, the original and all modified or updated versions must be retained. Communications that are Participant Identification (PTID)-specific should be printed and filed in the participant binder. Communications that are not PTID-specific can be printed and filed in regulatory documentation. All clinical site monitoring reports and correspondence can be accessed through the DAIDS-ES system 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-042 for each study participant. See Protocol section 13.6 for further information regarding all participant information which should be stored in locked file cabinets with access limited to authorized study staff.

The International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP) 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 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. The DAIDS Source Doc SOP can be accessed at https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations.

2.3 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-042 webpage. All items can be entered electronically except for the signature and date. The 'Study start date' is 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 form 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/1639

2.4 Required Source Documentation

For MTN-042, participant research records should consist of the following source documents:

- Chart notes
- Documentation that the participant provided written informed consent and/or parent/guardian permission 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 investigational study products
- Pharmacy investigational product 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 other as defined as a source document for a test result.
- \CRFs and other forms provided by the MTN SDMC, RTI 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 and/or other self-reported information)
- Infant photographs, if applicable
- 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 recommended source for specific study procedures will be provided within 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 participant product dispensing documentation is provided in SSP Section 6, and the MTN-042 Pharmacist Study Product Management Procedures Manual. Detailed information on proper completion of CRFs is provided in the MTN-042 CRF Completion Guidelines provided by the MTN SDMC.

2.5 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:

- Visit date at which a contact or procedures 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 also should 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
- 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
- Reason(s) why protocol-specified procedures were not performed
- Contact attempts to follow up on participants who missed a scheduled study visit

2.6 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. Visit Checklist templates are available on the MTN-042 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, indicate the screening attempt 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.
- 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 template 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.
- It is recommended that for sites not doing finger stick HIV testing, blood for HIV serology and plasma archive are collected 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.
- Any laboratory testing that is intended to be performed rapidly in the clinic, such as HIV testing, should be performed and results provided to the participant prior to study product provision or the participant leaving the clinic. Additionally, clinicians should review the HIV test results prior to the clinical examinations and further specimen collection (i.e. pelvic samples) 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.
- 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.

2.7 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.

2.8 Case Report Forms (CRFs)

The CRFs for this study are designed for use with the Medidata Rave clinical data management system. As specified in the Source Documentation SOP template, CRFs are designed to be used as source, whenever possible. Prior to study activation, **each study site will document the CRFs to be used as source documents, CRFs that will not be used as source, and specify non-CRF source documents in its SOP for Source Documentation.** The specifications of this SOP must be followed consistently for all study participants. If 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 into 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
- Perform QC procedures as specified in the site-specific Data Management SOP to ensure accurate and correct data transcription

2.9 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 Manual of Operational Procedures (MOP) should be referenced for complete guidance on protocol deviations.

For MTN-042, the Protocol Deviation Log CRF will be used to document each protocol deviation. The Protocol Deviation Log CRF is completed and submitted to the MTN SDMC for each reportable deviation identified. 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. Note that the corrective and preventive actions must be documented, but are not required to be completed, prior to reporting the deviation to SCHARP. The Protocol Deviation Log CRF should be submitted upon identification of the deviation, even if all the actions/plans are still in-progress.

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. Also, study product non-use is not considered a reportable protocol deviation in DELIVER. Refer to the CRF Completion Guidelines for a detailed description of each applicable PD for DELIVER.

Protocol deviations should be reported within 7 days of site awareness. If there is a question as to whether a deviation has occurred, or how it should be documented, the MTN Regulatory Department and the study Management Team should be contacted at mtnregulatory@mtnstopshiv.org and mtn042mgmt@mtnstopshiv.org. 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, SCHARP will follow up with the site if any clarifications or additional information on the CRF is needed.

It is recommended that all PDs occurring at the site be submitted to the local IRBs/ECs in accordance with their reporting policies. Some PDs 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/EC renewal submission, annually per local requirements. These listings may be provided by the MTN SDMC to the sites upon request.

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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.

2.10 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 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 number 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, are 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 CRS are included.

Regardless of whether the identifier on a 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 participants' study notebooks and/or transferred or transmitted to non-study site locations.

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 (such as the PTID-Name Linkage Log) should be stored securely (locked cabinet/drawer if hard copy; password protected if electronic) and it is recommended in a location separate from individual participant records (that identify participant by either PTID or name). 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.

2.11 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 destruction of each unused study product. Separate accountability records must be maintained for each product, per

instructions provided in the MTN-042 Pharmacist Study Product Management Procedures Manual available from the MTN Pharmacist.

Pharmacy staff also will maintain in the study pharmacies a Participant-Specific Pharmacy Dispensing Record for all enrolled study participants, per instructions in the MTN-042 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 manual.

The specifications related to document security and participant confidentiality described in Protocol section 13.6 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-042 Protocol
- Investigator's Brochure for Dapivirine Vaginal Ring: current version and any subsequent updates
- Package Insert for Emtricitabine/Tenofovir Disoproxil Fumarate (Truvada): current version and any subsequent
- Current FDA Form 1572
- Current list of authorized prescribers and staff authorized to sign Study Product Request Slips (names and signatures)
- Pharmacy Establishment Plan (PAB or MTN LOC Pharmacist approved)
- MTN-042 Pharmacist Study Product Management Procedures Manual and applicable SOPs for investigational study product management, dispensation and accountability
- MTN-042 SOP for product Chain of Custody
- MTN-042 product shipping and receipt documentation, product storage temperature logs, and investigational product accountability records
- MTN-042 participant-specific records (including prescriptions and request slips, participant-specific dispensing record, record of receipt of participant study product and documentation of unused product returns)
- MTN-042 monitoring visit reports
- MTN-042 communications with site clinic staff, communications with the MTN Pharmacist, IPM Clinical Supply Coordinator and/or TCG (product distributor)
- MTN-042 communications with the MTN LOC and/or the MTN SDMC or other MTN-042 communications or locally-required administrative, operational, and/or regulatory documentation

2.12 Translation Procedures

Per the 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 include the informed consent and forms and comprehension assessments, interviewer-administered CRFs, qualitative interview guides, and other study materials developed for participant use.

- Site teams are responsible for establishing a site-specific translation SOP that should minimally contain the following elements:
- Description of the translation and back-translation process, and quality control procedures
- Who is responsible for conducting each step of this process (and whether is occurring on-site staff or through a contracted group)

All staff members 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 this responsibility is assigned per the site Delegation of Duties Log. A standard *Certificate of Translation* should be issued for translations conducted, 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.

2.13 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 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 seven years after final reporting or publication of the study's primary results per MTN policies. The strictest record retention requirements that apply must be followed (see MOP section 18.3 for further details). No MTN-042 study records may be moved to an off-site location or destroyed prior to receiving approval from DAIDS (see MOP section 18.2). Investigators and others retaining records covered under this policy will seek guidance from their institution on whether records are subject to any limitations on their disposal. Study product records must be stored in site pharmacies, with access limited to authorized study pharmacy staff only.

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