Section 2. Documentation Requirements

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-028.

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 documents 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 and/or in binders. The files/binders listed in essential documents filing structure may be further 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 (most recent documents in front).
- Certain documents related to the investigational 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.
- 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.
- The suggested filing structure assumes that MTN-028 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-028 PTID-Name Linkage Log and Screening and Enrollment Log must be maintained in hard-copy unless an electronic system is 21 CFR Part 11 compliant. 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.

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

2.2 Participant Research Records

Study sites must maintain adequate and accurate participant research records containing all information pertinent to MTN-028 for each study participant. See protocol section 11.2 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 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 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. This document can be accessed on the MTN website under *Resources* (http://www.mtnstopshiv.org/resources).

2.3 Required Source Documentation

For MTN-028, 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
- FSTRF randomization confirmation email documenting participants' random assignments
- Prescription documentation
- 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 other as defined as a source document for a test result.
- DataFax and Non-DataFax 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 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 has been specified in Appendix 2-1. 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 Sections 7 of this manual and in the MTN-028 Pharmacy Study Product Management Procedures Manual. Detailed information on proper completion of CRFs is provided in Section 12 of this manual.

2.3.1 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:

- Visit date at which a contact takes place or at which a particular 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 (e.g. visit reminder phone calls, emails etc.)
- 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
- 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 Visit Checklists

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 this for any of the reasons mentioned above. Visit Checklist templates are available on the MTN-028 website under MTN-028 Study Implementation Materials (http://www.mtnstopshiv.org/node/6560).

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

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

- The "Required at Visits" column indicates when the item is required per-protocol. Complete staff initials next to procedures completed.

- Staff are only to initial beside procedures in which they perform; not beside procedures performed by other staff members. If other staff members are not available to initial procedures in which they performed, staff completing the checklist can initial and date a note on the checklist documenting who completed the procedure, e.g., "done by {name}" or "done by nurse."

- 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. Bracketing procedures which are consecutive and all done on the same date is also acceptable.

- If a procedure listed on the checklist is not performed, enter "ND" for "not done" beside the item and record the reason why on the checklist or in chart notes; initial and date this entry.

The sequence of procedures presented on the visit checklists is a suggested ordering. In consultation with the MTN LOC (FHI 360), site staff are encouraged to modify the checklists to maximize the efficiency of site-specific study operations. Sites may alter the sequence of procedures, with the following exceptions:

- Informed consent must be obtained before any study procedures are performed. Study visit procedures are listed in protocol Sections 7.2-7.4.

- On the day of enrollment, random 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.

- Pelvic exam procedures must be performed in the sequence shown on the Pelvic Exam Checklist.

Notes:

- 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 in the event that the participant needs to abruptly leave the clinic or is short of time.

- IVRs should be removed immediately upon identification of conditions that require a hold or discontinuation.

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. See SSP Section 9 for more information on source documentation requirements for the lab.

2.3.4 Case Report Forms (CRFs)

The case report forms (CRFs) for this study are designed for use with the DataFax data management system described in Section 12 of this manual. As shown in Appendix 2-2, 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 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

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 folder/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 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 the 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 participant identification number (PTID) or the participant name. The PTID should be used whenever possible to maximize participant confidentiality. As a best practice, records that bear names or other personal identifiers, such as locator forms and informed consent forms, should be stored separately from records identified by PTID. 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 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 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 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 destruction of each unused study product. Separate accountability records must be maintained for each product, per instructions provided in the MTN-028 Pharmacy 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-028 Pharmacist Study Product Management Procedures Manual. Study clinic staff will contribute to the documentation of product dispensation and chain of custody as described in Section 7 of this SSP manual.

The specifications related to document security and participant confidentiality described in Section 2.3.5 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-028 Protocol
- Investigator Brochure for MK-2048A: current version and any subsequent updates
- Current FDA Form 1572
- Current list of authorized prescribers and staff authorized to sign Prescriptions and Intravaginal Ring Request Slip (names and signatures)
- Pharmacy Establishment Plan (MTN Director of Pharmacy Affairs Approved)
- MTN-028 Pharmacy Study Product Management Procedures Manual and applicable SOPs for investigational study product management and product Chain of Custody
- MTN-028 product shipping and receipt documentation, product storage temperature logs, and investigational product accountability records
- MTN-028 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-028 monitoring visit reports
- MTN-028 communications with site clinic staff, communications with the MTN Pharmacist, Merck, MTN LOC and/or the MTN SDMC or other MTN-028 communications or locally-required administrative, operational, and/or regulatory documentation

2.4 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 three years after completion or termination of the study. Study product records must be stored in site pharmacies. 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.

2.5 Protocol Deviations

In addition to the above, 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 should be referenced for complete guidance on protocol deviations.

For MTN-028 the Protocol Deviation Log (PDL-1) CRF will be used to document each protocol deviation. The PD Log CRF is completed and faxed to the SDMC for each reportable deviation identified. Like all CRFs, completed PD Log CRFs will be filed in the participant's study binder. Missed visits are considered protocol deviations per the MTN policy, however these will *not* be captured on the PD Log CRF for MTN-028 (the Missed Visit CRF will capture this information instead).

Corrective and preventive action plans are required components of protocol deviation documentation. Note that the corrective and preventive action plans documented on the PDL CRFs are not required to be completed in order to report the deviation. The PDL page should be transmitted to DataFax once the CRF is completed, even if all of the action plans are pending or in progress. It is important to ensure that documentation includes any associated counseling that was done to address the protocol deviation (e.g., counseling on the importance of retention for missed visit deviations, or reviewing 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-028 Management Team 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 faxed, the MTN Regulatory Department will follow up with the site if any clarifications or additional information on the CRF is needed. The study management team will follow up with the site regarding any next steps as needed.

Note: Some protocol deviations will 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. These documents can be accessed on the MTN Website under *Resources and Links (*http://www.mtnstopshiv.org/node/4535). The site OCSO Program Officer should be contacted with any questions related to critical events.

It is recommended that sites report in an expedited manner to IRBs/ECs 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.

Appendices

Section Appendix 2-1- Source Documentation of Study Procedures

Note that items in **bold are required source documents for listed study procedure/evaluation. Other source documents listed are recommended, but site should specify actual source document as needed in the Source Documentation SOP.

Evaluation /Procedure	Source Document(s)
ADMINISTRATIVE AND REGULATORY	
Obtain Informed consent(s)	**Signed and Dated Informed Consent form** Informed Consent Coversheet
Assess informed consent comprehension	**Informed Consent Comprehension Checklist**
Assign a unique Participant Identification (PTID) number	**MTN-028 PTID-Name Linkage Log**
Collect/review/update locator information	**Site locator documents (collect/update)** Visit checklist (review)
Obtain demographic information	**Demographics CRF**
Assess and/or confirm eligibility	**Behavioral Eligibility Worksheets** **Eligibility Criteria CRF** Eligibility Checklist
Randomization	**MTN-028 FSTRF Confirmation Email**
Reimbursement	Visit checklist, site-specific reimbursement log, and/or chart note
Record/ update AEs	Adverse Experience Log CRF (and/or chart notes)
Schedule next visit	Visit checklist (and/or chart notes)
Record Protocol Deviations	Protocol Deviation Log CRF
A record of all contacts, and attempted contacts, with the participant	Missed Visit CRF **Site-specific contact/outreach/retention logs and/or chart notes**
A record of all procedures performed by study staff during the study	Visit checklists, chart notes, and/or other site-specific flow sheets
BEHAVIORAL	
Adherence Assessment	**Ring Adherence CRF**
HIV pre- and post- test counseling	Chart note and/or site-specific counseling worksheet
HIV/STI risk reduction counseling	Chart note and/or site-specific counseling worksheet
Protocol requirements counseling (To include adherence, product use and contraceptive counseling, as needed)	Chart note and/or site-specific counseling worksheet
CLINICAL	
Medical and menstrual history, including pre-existing conditions	Adverse Experience Log CRF Baseline Medical History Questions **Pre-Existing Conditions CRF** (all baseline conditions including clinical evaluations will be summarized here) and/or Chart Notes
Concomitant medications	**Concomitant Medications Log CRF** and/or Chart Notes
Physical examination (full or modified)	**Physical Exam CRF**
Pelvic examination	Pelvic Exam CRF, Pelvic Exam Ring Assessment CRF, Pelvic checklist, Pelvic Exam Diagrams (non-Datafax) CRF, and/or chart notes
Provide available test results	Chart note and/or visit checklist

Treat or prescribe treatment for UTI/RTI/STIs or refer	Chart notes, prescription and/or referral documentation
Staff-initiated Study Product Holds and Permanent Discontinuations	**Clinical Product Hold/Discontinuation Log CRF**
LABORATORY	
Urine Samples	
hCG	Site specific testing logs, Follow-up Visit Summary CRF
Dipstick UA	Site specific testing logs Safety Laboratory Results CRF
Urine culture	Site specific testing logs Safety Laboratory Results CRF
Blood Samples	
CBC with differential and platelets	Safety Laboratory Results CRF Site-specific lab requisition form Lab result report
HIV-1 serology	HIV Results CRF HIV Confirmatory Results CRF Lab result report Site-specific lab requisition form
HBsAg	Site-specific lab requisition form Lab result report
INR	Site-specific lab requisition form Lab result report
Anti-HCV	Site-specific lab requisition form Lab result report
Chemistries (Creatinine, AST, ALT)	Site-specific lab requisition form Lab result report Safety Laboratory Results CRF
PK- Blood	Pharmacokinetics CRF
Syphilis serology	STI Test Results CRF Site-specific lab requisition form Lab result report
Plasma archive	Enrollment CRF LDMS Tracking Sheet
Pelvic Samples	
Vaginal fluid pH	Site specific testing logs Pelvic Exam CRF
Rapid Trichomonas test	Site specific testing logs STI Test Results CRF
KOH wet mount for candidiasis	Site specific testing logs STI Test Results CRF
Saline wet mount for BV	STI Test Results CRF Site specific testing logs
Vaginal NAAT for GC/CT	Site-specific lab requisition form Lab result report STI Test Results CRF
PK- Vaginal fluid	Pharmacokinetics CRF
PK- Cervical tissue	Pharmacokinetics CRF
Pap smear interpretation	Site-specific lab requisition form Lab result report

Gram stain collection	Specimen Storage CRF
STUDY PRODUCT	
Participants will receive study IVR, study IVR use instructions and will be instructed to self-insert the study IVR, followed by pelvic exam to check placement	Visit checklist or site-specific counseling worksheet (or chart notes) Clinic Study Product Accountability Log Enrollment CRF
Collect IVR	Ring Insertion and Collection CRF Clinic Study Product Accountability Log Clinic Study Product Destruction Log

Section Appendix 2-2: CRFs Used as Source Documents

Unless otherwise noted in the Comments column, the CRF may be used as source for all form items.

CRF Name	CRF Acronym	Comments
Adverse Experience Log	AE-1	
Clinical Product Hold/Discontinuation Log	PH-1	
Concomitant Medications Log	CM-1	
Demographics	DEM-1	
Eligibility Criteria	ECI-1	Form may be source for item 1. Eligibility Checklist and/or Screening and Enrollment Log may be source for all items
Enrollment	ENR-1	The informed consent form should be source for items 1 and 3. Form may be source for item 4 (or lab requisition). The FSRTF Randomization Confirmation Email should be source for items 5-6. This form may be source for item 7.
Follow-up Visit Summary	FVS-1	Form may be source for items 1-2. All other items should be completed based on source data recorded on source documents.
Missed Visit	MV-1	
Pelvic Exam	PE-1	Form may be source for all items except item 2. AE Log should be source for item 2
Pelvic Exam Diagrams	n/a	
Pelvic Exam Ring Assessment	PER-1	
Pharmacokinetics Specimens – Enrollment/Day 28	PKS-1	
Pharmacokinetics Specimens – Days 1, 2, 3, 7 14, 21, 29, 30, 31	PKS-1	
Physical Exam	PX-1	
Pre-existing Conditions	PRE-1	
Pregnancy Outcome	PO-1	Source if relevant medical records are not available.
Pregnancy Report and History	PR-1	
Protocol Deviation Log	PDL-1	
Ring Adherence	RA-1	
Ring Collection and Insertion	RCI-1	Form may be source for all items except item 3. Pharmacy dispensing records should be source for item 3
Safety Laboratory Results	SLR-1	All laboratory value items should be completed based on laboratory source documents. Form may be source for non-laboratory value items.
Specimen Storage	SS-1	
Social Impact Log	SIL-1	
STI Test Results	STI-1	Form may be source for item 1. Local laboratory reports are source for items 2-5.
Participant Replacement Log	PRL-1	
Termination	TM-1	

Section Appendix 2-3: CRFs Not Used as Source Documents

CRF Name	CRF Acronym	Comments
HIV Confirmatory Results	HRS-1	All items should be completed based on source data recorded on source documents.
HIV Results	HIV-1	All items should be completed based on source data recorded on source documents.