MTN-028 Study-Specific Procedures Manual
Overview of Section Contents and Identification of Current Section Versions

Section Number	Section Title	Version Number	Version Date	Updates and Comments
1	Introduction	1.0	24JUN15	
2	Documentation Requirements	1.0	24JUN15	
3	Accrual and Retention	1.0	24JUN15	
4	Study Visit Procedures	1.1	18AUG15	Version 1.1 • Sections 4.4.1, 4.5, 4.5.4.1, 4.5.7, 4.5.11: Updated per CM#1
5	Informed Consent	1.0	24JUN15	
6	Web Randomization	1.1	12OCT15	Version 1.1 • Section 6.4: Updated to clarify the meaning of the Eligibility Checklist Date listed on the Randomization confirmation notice
7	Study Product Considerations For Non-Pharmacy Staff	1.0	24JUN15	
8	Clinical Considerations and Safety Monitoring	1.2	1SEP15	Version 1.1 • Section 8.7: Updated per CM#1 Version 1.2 • Section 8.7.2: Updated to clarify documentation of pelvic findings due to biopsy
9	Laboratory Considerations	1.1	18AUG15	Version 1.1 • Table 9.1 and Section 9.6.7, 9.7.5: Updated per CM#1 • Table 9.3, Section 9.7.6: Updated to reflect current ring storage instructions and temperature
10	Counseling Considerations	1.0	24JUN15	
11	Data Collection	1.1	18AUG15	Version 1.1 • Table 1.1: Staff has been updated • Section 11.4: Name of PER CRF has been corrected
12	Data Communiqués	1.0	24JUN15	

13	Study Reporting Plan	1.2	16NOV15	Version 1.1: • MTN-028 Statistical and Data Management Center (SDMC) and DF/Net Research Staff table: Has been updated Version 1.2: • Section 13.2, item 11 (Missed Visit Report) has been updated to reflect current procedures.

Section 1. Introduction

This section specifies the sources of procedural information available to study staff, the responsibilities of the Investigator of Record (IoR) and the process by which each site will be approved to initiate implementation of MTN-028.

1.1 Current Protocol Specifications

The table below documents the history of the MTN-028 protocol, along with any Clarification Memos, Letter of Amendments, and Full Amendments, if applicable, all of which are considered Essential Documents. A copy of each document should be available to staff and a copy should be maintained in site essential files. It is not necessary for sites to file copies of the below-mentioned documents in this manual.

Document	Date
MTN-028 Protocol, Version 1.0	12 February 2015

Sites are expected to operate under the protocol version and associated Clarification Memos and/or Letters of Amendment that are currently approved by the local institutional review board/ethics committee (IRB/EC). To ensure this section reflects the current specifications of the protocol, upon issuance of any future protocol Clarification Memo (CM), Letter of Amendment (LoA), or Protocol Amendment, specifications listed above will be updated accordingly. These documents are available on the MTN-028 webpage (http://www.mtnstopshiv.org/studies/5923). Further information on the content and required handling procedures for these documents is available in Section 10.2 of the Microbicide Trials Network (MTN) Manual of Operational Procedures (MOP), which is located on the MTN webpage (http://www.mtnstopshiv.org).

1.2 Procedural Information

The Study Specific Procedures (SSP) Manual serves to supplement the protocol. It does not replace or substitute the protocol or its contents. In the event this manual is inconsistent with the information and guidance provided in the protocol, the specifications in the protocol will take precedence. In the event study implementation questions are not adequately addressed by the study protocol or this manual or if any inconsistencies between the two documents are identified, please notify the MTN-028 Study Management Team at mtn028mgmt@mtnstopshiv.org. This group consists of the MTN Director of Pharmacy Affairs and representatives from the Leadership and Operations Center (LOC)-University of Pittsburgh (Pitt) and FHI 360, the Statistical and Data Management Center (SDMC), and the MTN Laboratory Center (LC).

Contact details for all of the above listed individuals are listed in the MTN-028 protocol and are also available in the MTN Directory (http://www.mtnstopshiv.org/people/directory), which can be accessed via the MTN webpage.

1.3 Investigator of Record (IoR) Responsibilities

MTN-028 must be conducted in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization Consolidated

Guidance for Good Clinical Practice (GCP). In addition, MTN-028 must be implemented in accordance with all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Copies of all such regulations, policies, and guidelines should be maintained in on-site essential document files.

The Division of AIDS (DAIDS) policies '*Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*' and '*Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials*' are useful for interpreting and operationalizing the applicable regulations and guidelines in accordance with DAIDS expectations. These resources are available on the NIAID website (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/ClinicalSite.aspx) as well as on the MTN website under 'Resources and Links' (http://www.mtnstopshiv.org/resources).

The IoR at each study site must sign an Investigator Signature Form (protocol signature page) and a U.S. Food and Drug Administration (FDA) Form 1572 to formally indicate his/her agreement to conduct MTN-028 in accordance with the provisions of the study protocol, applicable US regulations, and MTN policies. An IoR may delegate their obligations and responsibilities for conducting MTN-028 to other study staff members. However, in doing so, this delegation does not relieve the IoR of his/her ultimate responsibility for all study procedures performed and all study data collected. Delegation of IoR responsibilities must be formally documented throughout the period of study implementation on the site's Delegation of Authority (DoA) log. The obligations and responsibilities assumed by the IoR when signing the FDA Form 1572 are listed on the form itself, which is available on the DAIDS Regulatory Support Center (RSC) website. Note that no staff member should fulfill the IoR role in the IoR's absence. Full responsibility and authority over the protocol by anyone other than the IoR may only take place if an additional 1572 is completed and submitted to DAIDS.

Consistent with the regulations, guidelines, and policies cited above, the site IoR must obtain and maintain IRB/EC approval of MTN-028 throughout the period of study implementation. Detailed information on IRB/EC submission, review, approval, and documentation requirements is located in Section 9.4 of the MTN MOP. All sites are encouraged to request an acknowledgement of receipt for all documents submitted to their IRBs/ECs and to request that IRBs/ECs note the effective and expiry dates of all approvals. Documentation of all correspondence to and from all responsible IRBs/ECs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in on-site essential document files. Documentation of all IRB/EC approvals may also be requested by the MTN LOC.

Note: Staff regularly involved in the source documentation of safety data or are delegated to perform critical trial related procedures should be included on the FDA Form 1572 as a sub-investigator. Such components may include, but are not limited to, adverse event (AE) assessment, collection of participant safety information, confirmation of participant eligibility, or dispensation of study product.

1.4 Study Activation Process

Prior to commencing active recruitment activities and undertaking any study procedures, each study site must complete the following:

- obtain approval to conduct MTN-028 from all required local regulatory authorities and IRBs/ECs,
- complete protocol registration procedures with the DAIDS RSC Protocol Registration Office (PRO), and
- complete study activation requirements in collaboration with DAIDS, MTN LOC and LC, and the SDMC and be issued a Site-specific Study Activation Notice.

Detailed information on these procedures can be found in Section 11 of the MTN MOP. MTN LOC will notify sites (on a site-by-site basis), when all activation requirements have been met by issuing a Site-Specific Study Activation Notice.

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.

Section 3. Accrual and Retention

This section provides information on requirements and procedures for recruiting participants in MTN-028. This section also presents information related to definitions, requirements, and procedures for participant retention.

3.1 Pre-Screening Procedures

Sites are encouraged to implement pre-screening procedures for MTN-028 as part of their outreach and recruitment strategy. Like all outreach and recruitment approaches, strategies and materials used during the pre-screening process must be submitted and approved by local IRBs/ECs. During pre-screening, staff may explain MTN-028 to potential study participants and ascertain elements of presumptive eligibility, which should be confirmed at an on-site screening visit. The information obtained during pre-screening activities cannot be considered for eligibility determination. Participants found to be presumptively eligible may also be provided the study informed consent or other IRB approved informed consent materials for review prior to their screening visit as part of the pre-screening procedures. SCHARP-provided PTIDs should not be assigned until after participants provide informed consent at the screening visit.

Note: No information collected from participants may be used for publication purposes unless written informed consent is provided from potential participants.

3.2 Participant Accrual

Approximately 18 participants will be recruited at one US site. The study-wide accrual period is 6-9 months. The accrual period is considered to begin on the first day of participant enrollment at the site. Site staff should make every effort to complete accrual at a rate of about 2-4 participants per month.

Screening and enrollment data will be captured on case report forms (CRFs) and submitted to MTN Statistical and Data Management Center (SDMC). The Eligibility Criteria CRF will be completed and faxed for all participants once they are enrolled or have screened out. The SDMC will provide information on the number of participants screened and enrolled based on data received and entered into the study database. Please see Section 13 of this manual for more details on SCHARP Enrollment Reports.

3.2.1 Accrual Tips

Sites should develop methods for tracking actual versus targeted accrual, including monitoring the expected screening to enrollment ratios and how these change over time.

Recruitment methods and venues should be assessed on an ongoing basis. The usefulness or "yield" of various recruitment sources should also be tracked over time. Routine team meetings should be held to identify recruitment sources of participants who screen and enroll and methods for timely evaluation of the usefulness of recruitment methods and venues. Discussion points should include the following:

- Of all participants contacted through a particular method or at a particular venue, how many eventually enroll in the study?
- If this number (percentage) is high, keep using that method or venue
- If not, move on to different methods or venues

Staff responsibilities include the following:

- Designate a Recruitment Coordinator who is responsible for tracking accrual rates and managing recruitment efforts over time.
- Hold weekly or biweekly meetings among staff involved in accrual activities – community educators, recruiters, outreach workers, peer educators, others – to discuss current and ongoing strategies
- Engage community representatives on accrual issues and strategies throughout the accrual period

Continue to discuss as a team, over time, the following characteristics of "good candidates" for study participation:

- Likely to be retained for the duration of the study
- Likely to use study product as indicated for the duration of the study

3.2.2 Participant Accrual SOP

Site staff are responsible for establishing a study-specific participant accrual plan in the form of a SOP on Participant Accrual; and updating the SOP and recruitment efforts undertaken if needed to meet site-specific accrual goals. The accrual SOP should contain, at minimum, the following elements:

- Site-specific accrual targets
- Pre-screening procedures (if applicable)
- Recruitment methods/venues and approaches for timely evaluation of the utility of recruitment methods/venues
- Methods for identifying the recruitment source of participants who present to the site for screening
- Methods for tracking actual accrual versus accrual targets
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

3.3 Participant Retention

The term "retention" generally refers to completion of follow-up visits and procedures as specified in a study protocol. This definition must be operationalized for any study, and operational definitions usually reflect the primary objectives and endpoints of a study. For MTN-028, two retention measures are planned to be used. Additional retention measures may be defined and used during the study if desired by the Protocol Chair and/or Protocol Statisticians.

- During the study, retention for each regularly scheduled follow-up visit will be defined based on whether participants complete the visit within the visit window. Participants who complete a regularly scheduled visit within the visit window will be considered 'retained' for that visit.
- Overall study retention is calculated as the percentage of the total number of visits completed by all participants (within their allowable visit window) divided by the number of visits expected for all participants. A visit is considered expected for a participant once the allowable window closes, regardless of whether or not a participant is lost to follow-up or terminated early from the study.

As indicated above, participants who do not complete a particular scheduled visit within the allowable window, but then complete the next scheduled visit (including any required make-up procedures that were missed), will not be considered retained for the missed visit. However, they will be considered retained for the next scheduled visit. Thus retention rates can fluctuate over time and across visits.

The MTN SDMC will post reports on their ATLAS portal presenting retention rates for key study visits designated by the Protocol Team. The SDMC also will generate a final end-of-study retention rate after the study is completed.

3.3.1 Retention Requirements

The study site will target retention of 100% of enrolled study participants for each scheduled follow up visit. The site should target retention of 95% of enrolled participants over the follow-up period. The purpose of the 95% retention target is to ensure the accuracy of study results by minimizing bias that can be caused by missing data.

Low retention rates can have serious impacts on the accuracy of the study results because it is unknown whether participants who do not return for scheduled study visits used the study product, liked the product or had adverse effects resulting from use of the product. Missed visits also result in missing laboratory evaluations (PK) at specified study time points. To avoid these problems, and thereby avoid bias in the study results, high participant retention rates must be maintained throughout the study.

3.3.2 Participant Retention SOP

Site staff are responsible for establishing a standard operating procedure (SOP) for Participant Retention to meet the study retention goal of 95%. This SOP should be re-evaluated and modified in response to lower than anticipated retention rates, or at any other time when retention strategies are modified. The SOP should minimally contain the following elements:

- Site-specific retention goals
- Methods for tracking actual retention versus retention goals and for the timely evaluation of the utility of retention methods
- Site-specific definition of "adequate" locator information (for purposes of determining participant eligibility) and procedures for obtaining and updating locator information

- Visit reminder methods and timeframes
- Methods and timeframes for identifying when a visit has been missed and planned retention methods
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

3.3.3 Locator Information

Provision of "adequate" locator information during screening is a study eligibility requirement and each site must specify its definition of adequate locator information in its Participant Retention SOP. This information should be maintained in an organized manner so that different staff members can easily review the information and contribute to re-contact efforts when necessary. All study participants will be asked to provide locator information during the study screening process. Information provided should be regularly reviewed/updated during follow-up. Each study site is encouraged to develop an exhaustive locator form to maximize contact effectiveness and participant retention.

During the informed consent process and when collecting locator information, study participants must be informed that their locator sources will be contacted if study staff are unable to locate the participant directly. Study staff will negotiate with the participant how they will identify themselves when locator sources are contacted. Arrangements agreed upon with the participant should be documented on the locator form.

Study staff should view every participant contact as an opportunity to update the participant's locator information. When updating locator information, actively review each item on the locator form to determine whether the information is still current (i.e., rather than simply asking "Has any of your information changed since your last visit?"). Site staff should also probe for additional information that the participant was not able or willing to provide at previous visits.

Study staff should document in chart notes that they reviewed the locator information with the participant at every visit. Any updates to the locator form should use standard GCP corrections with initials and date of the staff member making the changes.

3.3.4 Retention Tips

Some additional strategies for maximizing participant retention are as follows:

- Dedicate adequate staff time and effort to retention efforts.
- Emphasize the value of the participant's involvement in the study during the study informed consent process and subsequently at follow-up visits. When participants complete scheduled visits, acknowledge and compliment their commitment, time, and effort devoted to the study.
- Develop rapport and ensure participants feel welcome and comfortable during their visits.
- Consider comfort of the waiting area and clinic rooms, especially the area where participants will spend long days at the clinic providing PK samples.
- Make use of all available contact methods (e.g. phone, mail, e-mail, etc.). Also make use of other available locator information sources, such as phone and postal directories and other public registries.
- Use tracking systems to identify when participants' scheduled visits are due and/or overdue. Establish routine mechanisms to remind both study staff and participants of upcoming scheduled visits.

- Prepare a calendar of scheduled visits for each enrolled participant, based on his/her enrollment date, or offer a planner/calendar as an incentive and note all study appointments in the planner/calendar. Note the dates of all scheduled visits in the participant's file for easy reference. Confirm the scheduling of the next visit at each follow-up visit and give the participant an appointment card with the scheduled visit date and time noted.
- Pay close attention to the allowable visit window and prioritize retention efforts for participants nearing the end of the window. Organize daily caseloads and work assignments based on these priorities. For participants who demonstrate a pattern of late or missed appointments, schedule follow-up visits for the beginning of the allowable visit window (if applicable) to allow maximum time for re-contact and re-scheduling if needed.
- Follow-up on missed appointments with an attempt to re-contact/re-schedule within 24 hours (preferably on the same day). Continue these efforts per the local retention SOP until contact is made.
- Keep participants and community members up-to-date on study progress to foster a sense of partnership and ownership of the study, for example, site may choose to use participant newsletters or other IRB-approved method of communication with participants.
- Inform local service providers who interact with the local study population about the study, so that they also can express their support for the study.
- Host gatherings, parties and/or other social events for participants. Host social, educational, and/or other events for participants' partners.

Section 4. Study Procedures

This section provides information on requirements for study procedures in MTN-028, including screening, enrollment and participant follow-up visits.

4.1 Visit Location

Because of the nature of study procedures required to be performed during the MTN-028 study, all visit procedures are expected to be completed at the study clinic only.

4.2 Eligibility Determination and SOP

It is the responsibility of the site Investigator of Record (IoR) and other designated staff to ensure that only participants who meet the study eligibility criteria are enrolled in the study. Each study site must establish a standard operating procedure that describes how study staff will fulfill this responsibility. This SOP minimally should contain the following elements:

- Eligibility determination procedures, including:
  - During-visit eligibility assessment procedures
  - Post-screening visit eligibility assessment and confirmation procedures (i.e. review of laboratory results)
  - Final confirmation and sign-off procedures prior to enrollment/randomization
  - Documentation of each eligibility criteria (met or not met)
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures (if not specified elsewhere)

Should study staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR or designee should contact the MTN-028 Management Team (mtn028mgmt@mtnstopshiv.org) and the MTN-028 PSRT (mtn028psrt@mtnstopshiv.org).

All eligibility criteria are initially assessed at the Screening visit, and some are reconfirmed on the day of Enrollment (Visit 2). Prior to randomization, eligibility for study participation must be confirmed and documented on the MTN-028 Eligibility Checklist by designated staff. This checklist can be found on the MTN-028 webpage under Study Implementation Materials.

A second screening attempt will be allowed per the discretion of the IoR or designee. **Note:** When rescreening participants, all screening procedures need to be repeated, including the informed consent process.

In addition to the assessment of eligibility, the study informed consent should be reviewed with the participant to ensure that the participant clearly understands all information and is willing to participate in the study. Review of the informed consent must be documented in the participant's study files. See section 5 of this manual for additional information.

4.3 Screening Visit

The term "screening" refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MTN-028. The study eligibility criteria are listed in protocol Sections 5.2 and 5.3. Required screening procedures are listed in protocol Sections 7.2.

All protocol-specified screening and enrollment procedures must take place up to 45-days prior to enrollment/randomization, beginning on the day the potential participant provides written informed consent. In other words, the day the screening informed consent is signed is counted as "-45" and enrollment is counted as Day 0. For example, as shown below, a potential participant who provides written informed consent on 1 July 2015 could be enrolled on any day up to and including 15 August 2015.

The screening process starts as soon as the participant signs the informed consent form, even if no other screening procedures are conducted on that day.

If all screening and enrollment procedures are not completed up to 45 days of obtaining written informed consent, the participant must repeat the entire screening process, beginning with the informed consent process. Note, however, that a new participant identification number (PTID) is not assigned to the participant in this case. The term "screening attempt" is used to describe each time a participant screens for the study (i.e., each time the participant provides written informed consent for participation in the study).

4.3.1 Screening Visit Procedures

Required screening procedures are specified in the MTN-028 protocol section 7.2 and reflected in the visit checklists available on the MTN-028 webpage. Briefly, after providing informed consent, participants will be assigned a PTID and undergo a series of behavioral eligibility assessments, clinical evaluations, and laboratory tests. Locator and demographic information will also be collected during the screening visit. Participants will be reimbursed for their time, and scheduled for their enrollment visit if presumptively eligible.

Eligibility criteria which are based on self-report will be evaluated by administration of the Screening Behavioral Eligibility worksheet provided on the MTN-028 webpage under study implementation materials. It is suggested that staff administer this questionnaire early in the screening visit, so that more time-consuming clinical and laboratory evaluations can be avoided if the participant is determined ineligible due to behavioral criteria (unless sites decide to administer clinical and laboratory evaluations regardless of eligibility as a service to the participant). To maintain consistency across sites and participants, questions on this form will be asked verbatim.

Clinical screening visit procedures are described in detail in Section 8 of this manual, briefly:

- Clinical procedures include collection of medical/menstrual history, concomitant medications, physical exam, and pelvic exam.
- Participants will be evaluated for use of prohibited medications, STI/RTI/UTIs, genital signs/symptoms, and overall general health.
- Participants will also receive contraceptive counseling (as needed), and have discussion of pregnancy/breastfeeding history and future pregnancy intentions.
- Participants should receive all available test results and treatment or referrals for UTI/RTI/STIs if indicated.

The HIV testing algorithm for screening and testing considerations can be found in Section 9 of this manual. Participants will receive HIV pre- and post-test counseling as well as risk reduction counseling. Protocol and study product adherence expectations will be reviewed with participants. Counseling considerations are described in detail in SSP Section 10 of this manual.

Details regarding laboratory tests and sample collection at screening are provided in Section 9 of this manual. In summary:

- Participants receive testing for HIV, STIs (GC/CT, Trichomonas, and Syphilis), pregnancy, urine dipstick, HBsAg, Coagulation (INR), Anti-HCV, serum chemistries (creatinine, AST, ALT), and CBC with platelets and differentials.
- If indicated, participants may be tested for Bacterial Vaginitis, vaginal candidiasis, have vaginal pH measured, or have a Pap smear.

Per protocol Section 7.2, multiple screening visits (as part of the same screening attempt) may be conducted if needed, to complete all required procedures. In cases where the Screening visit is conducted over multiple days, all procedures are considered part of the same screening visit/screening attempt.

4.3.2 Assignment of Participant ID Numbers

The MTN SDMC will provide each study site with a listing of participant identification numbers (PTIDs) for use in MTN-028. As shown in Figure 4-1, the listing will be formatted such that it may be used at each site as the log linking PTIDs to participant names.

Figure 4-1
Sample Site-Specific PTID List for MTN-028

	Participant ID	Participant Name	Date	Staff Initials
1	XXX-00001-Z			
2	XXX-00002-Z			
3	XXX-00003-Z			
4	XXX-00004-Z			
5	XXX-00005-Z			
6	XXX-00006-Z			
7	XXX-00007-Z			
8	XXX-00008-Z			
9	XXX-00009-Z			
10	XXX-00010-Z			

Further information regarding the structure of PTIDs for MTN-028 can be found in Section 11 of this manual. PTIDs will be assigned to all potential participants who provide informed consent for screening, regardless of whether they enroll in the study. Only one PTID will be assigned to each potential participant, regardless of the number of screening attempts the participant undergoes. Study staff are responsible for establishing SOPs and staff responsibilities for proper storage, handling, and maintenance of the PTID list such that participant confidentiality is maintained, individual PTIDs are assigned to only one participant, and individual participants are assigned only one PTID.

4.3.3 Screening and Enrollment Log

The DAIDS policy *on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* requires study sites to document screening and enrollment activity on screening and enrollment logs. Screening and enrollment logs may be maintained separately or combined into one document. A sample screening and enrollment log suitable for use in MTN-028 is available on the MTN website under Study Implementation Tools. Study sites are encouraged to reference the eligibility codes listed at the bottom of the sample screening and enrollment log when recording the reason for screening failure/discontinuation.

4.3.4 Participants Found to be Ineligible (Screen Failures)

Screening procedures should be discontinued when the participant is determined to be ineligible. If the participant is found to be ineligible at the beginning of the screening visit, sites may choose to continue with clinical and laboratory evaluations as a service to the participant, per their site SOPs. If a participant screens out due to a clinical condition requiring follow-up, appropriate referrals should be provided to ensure well-being of the participant. Documentation of all referrals should be included in the participant chart. All lab results should be provided and explained to participants within a reasonable timeframe, regardless of eligibility determination. For all screened out participants, the following documentation should be in place:

- Completed ICF
- Reason(s) for ineligibility, with date of determination, as per the completed Eligibility Checklist
- Completed Eligibility Criteria CRF, updated with screen failure reason(s) and faxed to DF/Net
- Necessary referrals on file (as appropriate) and documentation that any clinically significant abnormalities (labs, etc.) were communicated to the participant (even if referral is not necessary)

- All source documentation complete up until the time that ineligibility was determined
- Chart notes complete up until the time ineligibility was determined
- Indication of what visit procedures were conducted (on visit checklists)

In addition, the Screening and Enrollment Log should be updated with date of discontinuation of screening and reason for screen failure (list item number as appropriate from the Eligibility Checklist).

4.4 Enrollment Visit

A participant will be considered enrolled in MTN-028 when a designated staff member requests a randomization assignment via the FSTRF web-based randomization system once the site has confirmed that the participant has met all eligibility requirements. The enrollment visit is considered Day 0. Further information on methods and materials for random assignment is provided in section 6 of this manual.

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the Investigator of Record or designee should contact the MTN-028 Protocol Safety Review Team (PSRT) for guidance on subsequent action to be taken. PSRT contact details are provided in Section 8 of this manual. Additionally, the MTN-028 Management Team and PSRT must be informed.

4.4.1 Enrollment Visit Procedures

The Enrollment/Visit 2 serves as the baseline visit for MTN-028. All procedures for this visit must be conducted on the same day, and cannot be split across multiple days. According to Protocol Section 7.3, menses must not coincide with a participants enrollment visit (Visit 2), and ideally with study visits 3-6 (Days 1, 2, 3, and 7). This should be taken into consideration when scheduling the enrollment visit. If a participant is menstruating on the day of enrollment, her entire visit should be rescheduled for after the completion of menses. If the participant is enrolled and subsequently starts her menses during days 1-7, the pelvic exam and sample collection should continue as long as the participant is comfortable (see also section 8.7 of this manual).

Study enrollment procedures are specified in Protocol Section 7.3 and reflected in the visit checklists available on the MTN-028 webpage. The following procedures will be completed as part of eligibility confirmation prior to randomization on the day of enrollment. The IoR or designated staff will reconfirm and document the criteria indicated on the Eligibility Checklist prior to proceeding with randomization/enrollment per site SOPs.

Before randomization, the participant will undergo the following procedures:

- Confirm 45-day screening window has not been exceeded
- Update and confirm adequacy of locator information
- Review informed consent and confirm participant is still interested in continued study participation
- Confirm behavioral eligibility criteria through administration of the Enrollment Behavioral Eligibility worksheet provided on the MTN-028 study webpage under Study Implementation Materials.
- Update medical/menstrual history since screening visit. Evaluate use of prohibited medications, STI/RTI/UTIs or reproductive tract signs/symptoms, conduct pregnancy testing, provide contraceptive counseling (if indicated) and evaluate overall general health. Document all pre-existing conditions.
- Collect blood for: Serum chemistries, CBC with differential and platelets, HIV testing and plasma archive (Note if site is not conducting finger stick HIV rapids: to reduce

participant burden, site should consider collecting plasma archive and HIV samples as part of a single blood draw, prior to randomization)

- In conjunction with HIV testing, participants will receive HIV pre- and post-test counseling as well as risk reduction counseling.
- Conduct a physical exam and pelvic exam
- If indicated, participants should be tested for STIs (GC/CT, Trichomonas, syphilis), bacterial vaginitis, or candidiasis
- Participants should receive all available test results and if indicated treatment or referrals for STI/RTI/UTIs.
- Protocol adherence and study product adherence counseling. NOTE: this may also be conducted after randomization, but it could be helpful to provide the participant with more information about the study product prior to her final decision to enroll in the study

Once the procedures above and final determination of eligibility has been completed by designated staff, the participant should be randomized per the procedures in Section 6 of this manual. The MTN SDMC will generate and maintain the study randomization scheme and MTN Pharmacy will produce any associated printed materials. The act of Randomization (i.e. assignment to a study treatment arm) is considered the effective act of enrollment in the study.

After randomization, participants will undergo the following procedures:

- Provision of study product instructions and site contact information
- Self-collection of vaginal swab for PK (hour 0 sample, prior to ring insertion)
- Insertion of IVR
- Pelvic exam to check IVR placement
- PK: Blood and vaginal fluid (Post ring insertion at time points: 1, 2, 4, 6)
- Reimbursement
- Schedule next visit

Detailed instructions on IVR use including insertion/removal procedures and first product use, exam to check ring placement, as well as IVR adherence counseling is provided in Section 10 of this manual.

4.5 Follow-up Visits

Throughout the study follow-up period, two types of follow-up visits may be conducted. **Scheduled visits** are those visits required per protocol. There are a total of 11 clinic follow-up visits, including the Final Clinic Visit

- Visits 3-8: (Days *1, *2, *3, *7, 14, 21)
    - *NOTE: Menses must not coincide with Study Visits 2 (Day 0) and ideally with Study Visits3-6 (Days 1, 2, 3, 7), therefore participant's menstrual cycle must be considered when scheduling Visit 2- Enrollment Visit (Day 0).). In the event a participant has her menses during Enrollment Visit, the visit should be postponed until termination of menses. If participants have menses during visits 3-6, it should be document but all procedures should be done. As much as possible, menses should be avoid during these visits.
- Visit 9 (Day 28) Ring Removal Visit
- Visits 10-12 (Days 29, 30, 31)
- Visit 13 (Day 35) Final Clinic/Early Termination Visit

For example, if a participant is enrolled on August 4, 2015, her clinic visits will be as follows:

August 2015

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						1
2	3	4 Day 0	5 Day 1	6 Day 2	7 Day 3	8
9	10	11 Day 7	12	13	14	15
16	17	18 Day 14	19	20	21	22
23	24	25 Day 21	26	27	28	29
30	31					

September 2015

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1 Day 28	2 Day 29	3 Day 30	4 Day 31	5
6	7 Labor Day	8 Day 35	9	10	11	12

Interim visits are those visits that take place between scheduled visits. More specifically, a visit is considered an interim visit when a participant presents for additional procedures or assessments beyond the required procedures for a scheduled visit. There are a number of reasons why interim visits may take place. Interim visits may be performed at any time during the study, for the following or other reasons:

- For product-related reasons, e.g., a participant may need a replacement vaginal ring or want to discuss problems with adherence to product use.
- In response to AEs. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care (see also Section 8).
- For interim STI counseling and testing in response to STI symptoms or interim HIV counseling and testing in response to presumed exposure to HIV or to provide participants with the results of confirmatory HIV test results.

All interim contacts and visits will be documented in participants' study records and on applicable CRFs. Site staff may be required to assign visit codes to interim visits for purposes of data management as described in Section 11.

4.5.1 Target Visit Dates and Visit Windows

Enrolled participants will be scheduled to complete follow-up visits throughout their participation in the study. For each participant, Day 1-28 follow-up visits (Visits 3-9) are targeted to take place based on the participant's enrollment date. Each participant's enrollment date is defined as the date upon which they were randomized to MTN-028. Follow-up visits for Days 29-35 (visits 10-13) are targeted to take place based on the date of a participant's actual Day 28 visit date. Sites can choose to enter the target date for the Day 28 visit when initially generating the visit schedule at Screening in order to generate visit dates for the full duration of follow-up (Visits 3-13/Days 1-35). In this case, the tool should be updated if the participant's actual Day 28/Visit 9.0 date differs from the target date, once known, so that accurate target dates for visits 10-13 are provided and scheduled accordingly.

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the MTN-028 protocol allows for certain visits to be completed within a visit window, if possible. For Days 3, 7, 14, 21, 28, 31, and 35, there are visit windows specifying on which study days the visit can be completed. All other visits do not have visit windows as they are completed on consecutive calendar days. A complete listing of visit windows is available in Section 11 of this manual.

Sites are encouraged to complete required study visits on the target day if at all possible. If this is not possible, the visit may be completed within the visit window (for visits with a window). Visits completed within the visit window will be considered completed ("retained") visits.

Although the visit windows allow for some flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at specific intervals, and every effort should be made to do so.

The MTN Statistical and Data Management Center (SDMC) will provide the site with a visit scheduling tool that can be used to follow-up visit schedules for enrolled participants. Every effort should be made to schedule participants within the allotted timeframes.

4.5.2 Visits Conducted Over Multiple Days: "Split Visits"

All procedures specified by the protocol to be performed at a particular follow-up visit, ideally, will be completed at a single visit on a single day. In the event that all required procedures cannot be completed on a single day (e.g., because the participant must leave the study site before all required procedures are performed), the remaining procedures may be completed on subsequent day(s) within the allowable visit window, if that visit had a window. When this occurs, the visit is considered a split visit. As described in Section 11 of this manual, all case report forms completed for a split visit are assigned the same visit code (even though the dates recorded on the case report forms may be different).

For study visits requiring collection of samples for PK, please ensure that these collections are done on the first day of the split visit to avoid complicating interpretability.

If all required procedures cannot be completed on a single day and that visit does not have a window, the remaining procedures are considered missed. Documentation of the rational for not completing the procedures should be included in participant's file.

4.5.3 Missed Visits

For participants who do not complete any part of a scheduled visit within the allowable visit window, the visit is considered "missed" and a Missed Visit case report form must be completed

to document the missed visit (see Section 11 of this manual for more information on completion of this form).

For participants that miss Visit 9 (Day 28), meaning that the visit window has closed, participants should be contacted and counseled to remove the ring and return to the clinic as soon as possible. In addition to protocol-specified procedures for the applicable visit, the following procedures related to safety and product accountability should be completed the next time the participant presents to the site:

Collection/Removal of IVR

CBC with differential and platelets

Chemistries (Creatinine, AST, ALT)

Pregnancy Testing

Urine Dipstick

Note that if a participant misses Visit 9.0/Day 28, the target date of the missed Visit 9.0/Day 28 visit should be entered into the visit calendar tool to generate the visit schedule for Visits 10.0-13.0. Should this occur, consult the management team for guidance on completing the remaining study visits and associated procedures.

Outside of what is outlined above for Visit 9 (Day 28), no other visit types or procedures will be made up for MTN-028 in the event a visit is missed.

4.5.4 Follow-up Visit Procedures

After participants enroll in the study, they are expected to complete 11 protocol-required clinic visits each. Required follow-up visit procedures are listed in Protocol Sections 7.4 and Appendix I. As a general guide during follow up:

- Locator information must be obtained/reviewed at every visit.
- Medical/menstrual history, physical and pelvic exams, AE assessment and documentation, assessment of concomitant medications, and provision of any available lab results, will be done at all study visits. Treatment and referrals for any diagnosed UTI/RTI/STIs will be provided if indicated.
- Blood and vaginal fluid will be collected for PK at all follow-up clinic visits at a single time point, except on Day 28.
- Participants will be reimbursed for their time at each visit, and scheduled for their next visit as applicable.
- Pregnancy test will be done at Days 14 and 28, and at any other time if clinically indicated.
- At Day 28, blood and vaginal fluid for PK will be collected at hours 0, 1, 2, 4, 6.
- Cervical tissue and Dipstick UA will be collected only at Day 28
- The IVR is collected and returned at the Day 28 visit.
- Gram stain is only done at Day 3, 28, and 35 (Final Clinic Visit/Termination Visit)
- Chemistries are only done at Day 28 and 35 (Final Clinic Visit/Termination Visit)
- CBC is only done at Day 28. At Day 35 (Final Clinic Visit/Termination Visit) is done only if clinically indicated
- HIV testing and counseling will be done at the Day 35/Final Clinic Visit/Termination Visit (and at any other time if clinically indicated).
- Vaginal fluid pH, rapid Trichomonas test, KOH wet mount for candidiasis, and saline wet mount for BV will be done only if indicated.

- Protocol, adherence, and contraceptive counseling will be provided at any visit, if indicated

4.5.4.1 Day 35 Final Clinic Visit/Termination Considerations

Note: For participants who terminate early from the study, procedures outline in Section 7.4.4 of the protocol should be followed. Please note that if the vaginal ring has been out for more than three consecutive days, no PK procedures will be done.

Although the Day 35 Final Clinic Visit/Termination visit is the last scheduled study visit, a final contact is required after this visit to provide the participants with their final study test results, post-test counseling, and treatment, if needed. Additional contacts also are required for:

- Participants who are pregnant during the study to obtain pregnancy outcome
- Participants with positive or indeterminate HIV rapid or confirmatory test results
- Participants with certain types of AEs that are ongoing at study exit (See detailed guidance in Section 8.6 of this manual)

For each participant, a final contact should be scheduled based on the participant's overall clinical picture at study exit, as well as the time required to obtain all final study test results. It is recommended that final contact plans be documented on chart notes or a site-specific tool (e.g. worksheet). All final contacts must be documented in participant study records, but no case report forms are completed for these contacts.

After completing their Day 35 Final Clinic Visit/Termination visits and final study contacts, participants will no longer have routine access to services provided through the study such as HIV counseling and testing or contraceptive provision. Participants should be counseled about this — ideally before and during their Day 35 Final Clinic Visit/Termination visits — and provided information on where they can access such services after study exit. It is recommended that all study sites develop a written referral sheets that can be given to participants at their Day 35 Final Clinic Visit/Termination visits.

All participants will be contacted post-study to be informed of the study results and their random assignments. It is currently expected that study results and any additional unblinding information will be available within approximately 6 months after the study end date. Participant preferences for methods to be used for contacting them when unblinding information and study results are available should be documented in participant study records.

Lastly, for participants whom study staff may wish to contact regarding participation in future studies, permission for such contact should be sought from the participant and documented. It is recommended that participant permission (or lack thereof) for future studies be documented on a study exit worksheet or other site-specific documentation that can be easily accessed by study staff.

4.5.5 Participants Who Become Infected with HIV

Per protocol section 7.5.1, study product use must be held immediately for participants with a reactive rapid HIV test result (this includes participants with discordant rapid results from the same visit).

If a participant becomes infected with HIV-1 after the Enrollment Visit, she will be referred to local care and treatment services and may return to the research clinic for additional counseling and other support services, as needed per site SOP. Once HIV status is confirmed, study follow-up visits will be discontinued and the participant will be considered terminated from the study.

Participants who seroconvert after randomization may be offered additional laboratory testing (such as HIV RNA and HIV drug resistance testing), as clinically indicated per site SOP.

4.5.6 Participants Who Become Pregnant

If a participant becomes pregnant, follow-up visits and procedures will be discontinued and the participant will be considered terminated from the study (see Protocol Section 7.5.2). Participant will be referred to local health care services and may return to the research clinic for additional counseling, as needed per site SOP.

Site should develop a plan with participant to attain pregnancy outcome. One contact to obtain this information is sufficient. For example, participant could call or e-mail the site to inform the site of the outcome.

4.5.7 Participants Who Permanently Discontinue Study Product for Other Reasons

For participants who permanently discontinue study product use for any other clinician initiated reason (other than HIV seroconversion or pregnancy), site investigators may, after consultation with the PSRT and MTN-028 Management Team, decide to discontinue study participation (see Protocol Section 7.5.3).

If a participant is permanently discontinued from product use due to an AE, they must continue to be followed until the resolution or stabilization of the AE is documented.

In the event study follow-up is continued, participants will have the protocol-specified weekly visits through Day 35, specifically those visits at Day 7, Day 14, Day 21, Day 28 and Day 35. Protocol-specified procedures will continue except the following:

- Pelvic exams*
- Collection of blood for safety assessments*
- Protocol counseling will be modified
- PK specimen collection

* (Unless required for AE follow-up)

The above procedures should be collected/conducted at either the scheduled or interim visit in which study product is discontinued and omitted thereafter, unless the participant was previously on a temporary hold.

NOTE: Participants that miss more than three consecutive visits or have the ring out for more than three consecutive days will be permanently discontinued from study product. If the participant undergoes early termination, guidance in Section 7.4.4 of the protocol and Section 4.5.4.1 of this manual should be followed.

4.5.8 Follow-up Procedures for Participants Who are on a Temporary Clinical Study Product Hold

All protocol-specified study visits and procedures will continue except the following (see Protocol Section 7.6):

- Pelvic exams*
- Provision of product use/protocol adherence counseling
- PK specimen collection for participant that are on product hold for more than three consecutive days

*Unless required for AE follow-up

The collection of samples for PK should be collected/conducted at either the scheduled or interim visit in which study product is temporarily held and omitted thereafter. Completion of these procedures will resume at the visit following resumption of study product use.

4.5.9 Follow-up Procedures for Participants Who Decline Study Product Use

In the event that a participant declines further use of study product during follow-up, the MTN-028 management team should be informed. See Section 7.6 of this manual for information on how to document participant-initiated declines on the study product request slip. Counseling should explore the reasons for the self-initiated decline, and work with the participant to develop a plan for product resumption. If in the opinion of the IoR/designee the participant is unlikely to resume study product use during study follow-up, early termination for noncompliance with required study procedures should be considered after consultation with the PSRT (see Section 4.5.10 below). As always, participants may withdraw consent and exit the study for any reason at any time. Note that all protocol-specified procedures should continue in the interim (unless the participant declines) until the participant is terminated or decides to withdraw from the study.

NOTE: As mentioned in Section 4.5.7 above, participants that have the ring out for more than three consecutive days will have permanent discontinuation of product use. Guidance for permanent product discontinuation applies.

4.5.10 Replacing Participants

Participants will be replaced if:

- If the participant is terminated early for any reason (e.g. pregnancy, HIV status, clinician discretion, permanent product discontinuation, participant voluntary withdraw)
- If the participant has had the ring out for more than 3 consecutive days, voluntarily or by site's decision.
- If the participant misses 3 (consecutive) visits

NOTE: Participants that have had the ring out for longer than three consecutive days will be permanently discontinued from product use and replaced. Participants may remain in the study if the ring has been out and re-inserted within three days (including the third day).

NOTE: If the ring is removed on Day 26 or if participant misses three consecutive visits after Day 26, it is not necessary to replace that participant.

The purpose of replacing participants is to compensate for the potential data loss due to loss of follow-up and/or on temporary hold or permanent product discontinuation. If a participant discontinues study participation or is placed on hold (and the ring has been out for longer than three consecutive days) and needs to be replaced contact the MTN-028 Management Team immediately (mtn028mgmt@mtnstopshiv.org). Please refer to Section 6 Web Randomization for more information on the process of replacing participants.

In the event that a replacement participant terminates early or is placed on product hold for longer than three consecutive days, the replacement participant will need to be replaced and the PTID for the original participant that is being replaced should be recorded on the Enrollment CRF. The MTN-028 Management Team should also be contacted immediately (mtn028mgmt@mtnstopshiv.org) and the steps described in Section 6 of this manual for replacing participants should be followed.

4.5.11 Criteria for Early Termination of Study Participants

As outlined in Protocol Section 9.8, participants may voluntarily withdraw from the study for any reason at any time. The IoR/designee also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the PSRT. Participants also may be withdrawn if Merck & Co., NIAID, MTN, government or regulatory authorities, including the FDA and Office for Human Research Protections (OHRP), or site IRBs/ECs terminate the study prior to its planned end date.

If the participant is terminating early from the study for any reason, staff should complete the following:

- Ask participant if she is willing to complete one last visit, during which visit procedures for the Day 35/Final Clinic/Termination visit should be completed; with the addition that the IVR should be collected. Please note, PK procedures will not be conducted for participants that have the ring removed for three or more consecutive days.
- Record the reason(s) for the withdrawal in participants' study records.
- Consultation with the PSRT regarding early terminations per IoR decision should be printed and filed in the participant chart. PSRT consultation is not required for voluntary withdrawals.
- Update participant locator form, and document how the participant would like to receive any follow up test results (as needed), and be informed of study results.

Although the protocol allows for participants who voluntarily withdraw from the study to reverse their decision and re-join the study during their planned follow-up period, according to their original visit schedule, the investigator should weight the benefits of having the participant rejoin the study. As noted in Section 4.10.5 above, participants that have their rings removed for longer than three consecutive days, will have product permanently discontinued, thus they will not contribute to the safety and PK endpoints in the study. Resumption of study procedures and follow-up are subject to the investigator's discretion, pending PSRT consultation. If such cases arise, study staff are advised to contact the MTN-028 Management Team for additional guidance on how to manage various aspects of protocol implementation and data collection as the participant resumes participation in the study. In general, however, the following instructions and requirements should be adhered to:

- The participant's original PTID and follow-up visit schedule will remain unchanged.
- Prior to performing any study procedure, the participant must provide written informed consent to document that she voluntarily rejoined the study. For re-consenting procedures, refer to Sections 5 of this study manual.
- An interval (since the last visit) medical and medication history should be taken and HIV and safety laboratory testing should be done as soon as the participant resumes study participation. Product use will be resumed only among participants who are confirmed HIV-uninfected per the MTN-028 HIV testing algorithm, are not pregnant, and ring has not been out for longer than three consecutive days.
- A pelvic exam should be performed as soon as possible, and prior to re-instating IVR use. IVR use will be reinstated (if applicable) only after any genital symptoms have resolved, any STIs/RTIs requiring treatment per CDC guidelines have been treated.
- After the above procedures are performed, the IoR or designee should include the results and findings of these procedures, and any other relevant participant history information, in a PSRT query form, and should submit the form to request PSRT consultation on resumption of study participation.

- If vaginal ring has not been out for more than three consecutive days and if resumption of study product use is endorsed by the MTN SDMC and PSRT, site clinic staff will communicate this decision to site pharmacy staff in writing, using the MTN-028 Intravaginal Ring Request Slip. A copy of the final PSRT query form should be filed in the participant's study notebook.
- Site staff should thoroughly document, in the participant's chart notes, resumption of study follow-up and study product use.

Section 5. Informed Consent

This section provides information on informed consent procedures for MTN-028. MTN-028 utilizes one study informed consent (Screening, Enrollment, and Long-term Storage), which consists of:

- Informed consent for screening and enrollment
- Informed consent for the following optional activities: long term specimen storage and possible future research testing.

Depending on IRB/EC requirements, the site may choose to use a separate informed consent form specifically for the consent of long term specimen storage and possible future research testing; however, if this is done, all required elements of the informed consent must be contained on the form.

5.1 Overview of Informed Consent Requirements and Procedures

Informed consent is a process by which an individual voluntarily expresses their willingness to participate in research, after having been informed of all aspects of the research that are relevant to their decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process, involving information exchange, comprehension, voluntariness, and documentation. Each of these aspects of the process is described in greater detail below. Please refer to Section 4.8 of the *International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice* (GCP) and the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* for further guidance on the informed consent process and documentation requirements.

US regulations (45 CFR 46.116) specify the elements of informed consent that must be conveyed to research participants through the informed consent process. It is the responsibility of the Investigator of Record (IoR), and all delegated study staff involved in the informed consent process, to deliver all required information to potential study participants.

Based on the technical and regulatory reviews that are completed as part of the MTN protocol development and study activation processes, there is adequate assurance that once the MTN

LOC (FHI 360) has activated a site for study implementation, site-specific informed consent forms specify all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate informed consent form. It is the responsibility of the IoR and designated study staff to perform the following:

- Deliver all required information in a manner that is understandable to potential study participants
- Assure that informed consent is obtained in a setting free of coercion and undue influence
- Confirm that the participant comprehends the information
- Document each step of the process

5.2 Site-Specific Informed Consent Forms

A sample informed consent form (ICF) is provided in the MTN-028 study protocol. Sites are responsible for adapting the sample as needed for local use. Local adaptation may include reformatting the consent forms in accordance with local IRB/EC requirements. Sites are responsible for following the procedures in the MTN Manual of Operations (MOP) Section 11.2 and the DAIDS Protocol Registration Manual when adapting site-specific ICFs. All must be reviewed and approved by MTN LOC (FHI 360) prior to IRB/EC submission. After regulatory approval is obtained, the approved ICF must be submitted to the DAIDS Protocol Registration Office (DAIDS PRO) prior to its initial use.

Each site is responsible for preparing bulk supplies of their approved ICFs and only using the currently approved versions of the ICFs at all times during the study. It is recommended that all sites consider the use of color-coding or other techniques to ensure that the various study informed consent forms are easily distinguished and used appropriately. A system for tracking version control and approvals the ICF is also recommended. Upon receiving final IRB/EC and any other applicable regulatory approval(s) for an amendment to the informed consent form, sites should implement the consent form immediately and submit the updated version to DAIDS PRO per the timelines outlined in the protocol registration manual.

5.3 SOP for Obtaining Informed Consent

As a condition for study activation, each site must establish an SOP for obtaining informed consent from potential study participants. At each site, the informed consent process will be conducted according to site SOPs. This SOP should minimally contain the elements listed below.

- The minimum legal age to provide independent informed consent for research at the study site
- Procedures for determining participant identity and age
- Procedures for determining participant literacy.
- Procedures for providing all information required for informed consent to the participant
- Procedures for determining participant comprehension of the required information
- Procedures to ensure that informed consent is obtained in a setting free of coercion and undue influence
- Procedures for documenting the informed consent process
- Storage locations for blank informed consent forms
- Storage locations for completed informed consent forms
- Procedures (e.g., color-coding) to ensure that different versions of the study informed consent forms are easily distinguished and used appropriately
- Procedures for implementing a change in the version of the informed consent form used

- Staff training requirements
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

5.4 Informed Consent for Screening and Enrollment

Informed consent must be obtained before performing any "on-study" procedures at the Screening Visit. For participants who do not consent to study participation, no procedures should be performed and no data that can be linked to the participant's name or other personal identifier(s) should be recorded.

Informed consent should be reviewed with the participant at the Enrollment visit to ensure that the participant clearly understands all information and is still willing to participate in the study. Review of the informed consent must be documented in the participant's study files.

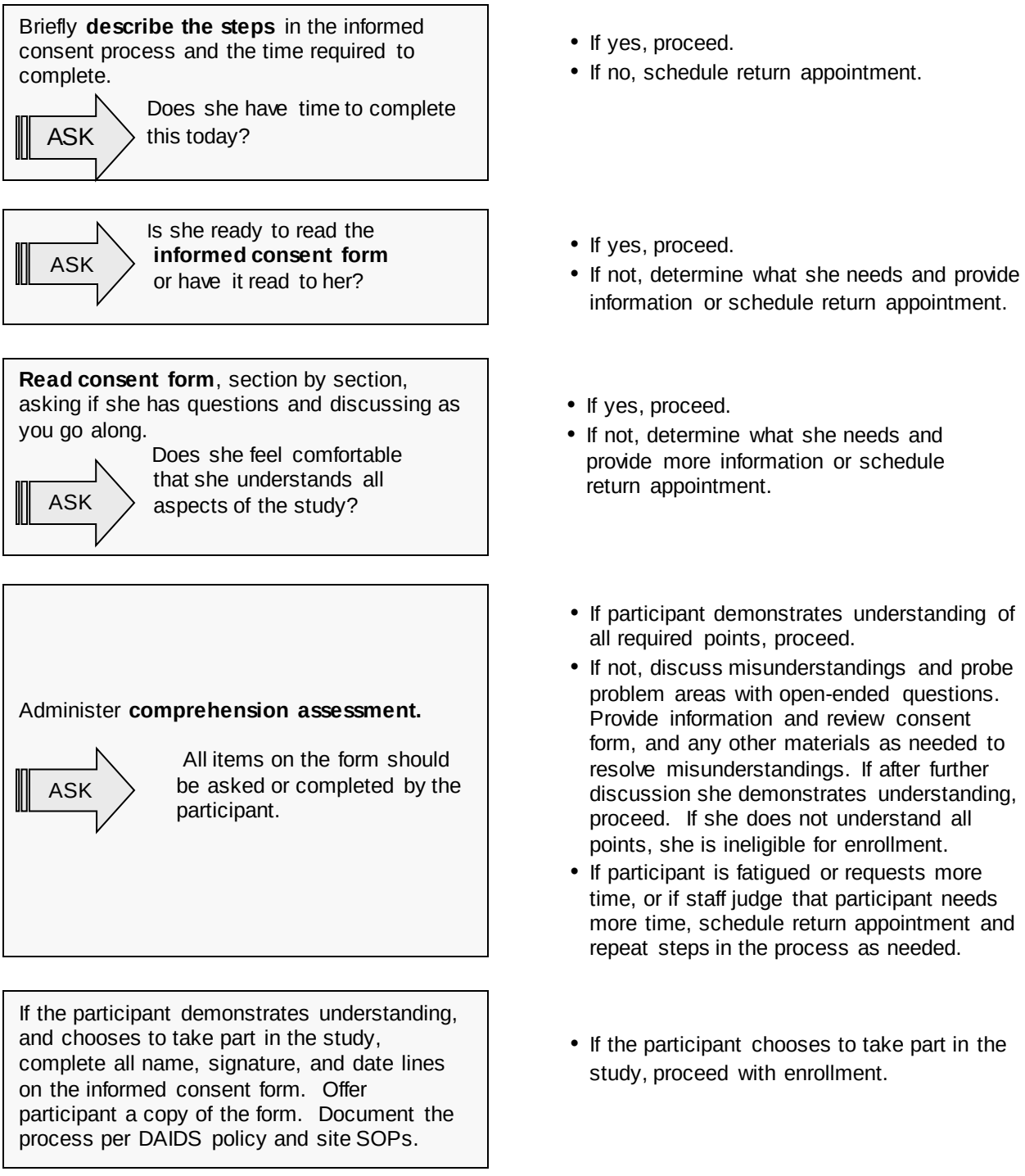
An overview of the standardized approach to the informed consent process is provided in Figure 5-1. Additional details related to key steps in the process are provided in the remainder of this section.

5.4.1 Informed Consent for Specimen Storage and Possible Future Research Testing

Study participants are asked to provide informed consent for long term storage of biological specimens and related health data for possible future research testing. Related health data may include demographic information such as race, ethnicity, sex, and medical conditions. Participants may choose to not have their specimens or health data stored for possible future research testing or withdraw their consent for specimen storage at any time and still remain in the study.

For participants who do not consent to specimen and health data storage and possible future research testing, all specimens are still collected and stored on-site per protocol requirements. These specimens will be retained until the study is completed and all protocol-specified testing has been done. Thereafter, any remaining specimens already collected from these participants will be destroyed. Participants who provide consent to specimen and health data storage and possible future research testing are allowing for the remaining (leftover) samples along with their demographic information to be kept and not destroyed at the end of the study.

Figure 5-1
Overview of MTN-028 Informed Consent Process



5.5 Informed Consent Support Materials

5.5.1 Other Informed Consent Visual Aids

Use of visual aids are encouraged throughout the informed consent process to facilitate participant comprehension. Each site should determine the most appropriate visual aids for its study population and ensure that a "kit" containing each of these aids is available in each room where informed consent discussions take place. Sample study products and supplemental IVR illustrations have been provided to each site to use as visual aids. In addition to the visual aids decided upon at the site, it may be helpful to point out such things as a locked file cabinet, a referral clinic across the way, or a calendar on the wall. It may not be necessary to use each visual aid with each participant. Study staff should use their best judgment of each participant's information needs and how best to address those needs.

Suggested visual aids for the site to consider using are as follows:

- Calendar with study visit schedule
- Sample IVR
- Urine specimen cup
- Blood collection tubes
- 5 L jug (to demonstrate the total blood volume in the human body)
- IVR insertion instructions
- MTN-028 Study Information Booklet
- Other randomization explanation visual aids (e.g., sack or box containing two items of different colors)

5.6 Comprehension Assessment

The participant must not be asked to agree to take part in the study, or to sign the informed consent form, until she fully understands the information contained in the informed consent, including visit procedures. Site SOPs should explain the procedures that study staff members are responsible for implementing to ensure that each participant understands the screening process and the study prior to signing the study informed consent form, respectively, and undertaking any study procedures.

Various methods (either oral or written) to assess comprehension may be utilized. One method is to use a written assessment tool that participants must complete prior to signing the informed consent form. Another approach is the use of open-ended questions to ascertain participant understanding during the informed consent discussion.

5.6.1 Comprehension Assessment Tools and Scoring System

Templates of two assessment tools (open-ended, and multiple choice) are available as separate electronic files on the Study Implementation Materials section of the MTN-028 webpage. Sites may use the tools as provided or may choose to adapt for their local use.

- Multiple Choice Assessment Tools:

  This assessment tool is structured around questions that correspond with the required elements of informed consent for research. Sites choosing to utilize the multiple choice assessment tool should incorporate a scoring system into the assessment and re-review the contents of the informed consent until the potential participant can answer all questions correctly. For example, if a participant answers less than 80% correctly, she should be re-counseled and the entire assessment should be repeated. This process should be repeated until it is determined the participant is unable to demonstrate adequate understanding. For participants that answer over 80% correctly, the questions not understood should be reviewed with the participant to ensure understanding of the information. The review and proper understanding of the information should be documented on the assessment tool, in the participant's chart notes or other site-specific source document.

- Open-Ended Assessment tool:

  The open ended-assessment tool is also structured around 11 open-ended questions that correspond with the required elements of informed consent for research. Each question should be read to the potential participant, giving her time to respond to each one.

  Each question should be satisfactorily answered by the participant before moving to the next question. For each question, the checklist specifies particular points that must eventually be included in the participant's response. These are identified on the tool as "Required Points of Comprehension."

Regardless of the method used to assess comprehension, if the assessment results indicate misunderstanding of any aspect of the study, site staff should review those aspects again until the participant fully understands them. Site staff should ensure 100% understanding of the IC prior to the participant providing written informed consent. If after all possible efforts are exhausted, the participant is not able to demonstrate adequate understanding of the study, do not ask them to sign the informed consent form or screen/enroll in the study. Similarly, if the participant has concerns about possible adverse impacts if they were to take part in the study, or indicates that they may have difficulty adhering to the study requirements, do not ask them to sign the informed consent form to screen/enroll in the study.

5.6.2 Administration of Comprehension Assessment

The comprehension assessment tool will be administered to each potential participant after they have completed the informed consent discussion described above and before they are asked to sign the informed consent form. It is expected that study staff administering the informed consent and assessing comprehension will be sufficiently knowledgeable about MTN-028 to make good judgments about the potential participants' understanding of the required information.

The comprehension assessment tool is considered a study source document that should be completed, handled, and retained in the participant's study file like any other source document. After administering the assessment tool, study staff should carefully review the form to verify that all required points have been satisfactorily addressed by the participant and that this is adequately documented. Consideration should be given to having two study staff members complete this verification because failure to document comprehension of all required points will be considered an informed consent process protocol deviation.

Comments may be recorded in a designated area on the form (and on the back of the form if additional space is needed) or on an informed consent coversheet (refer to section 5.7 below); however, this is not required. All required points must be satisfactorily addressed by the

participant, before proceeding to the final informed consent decision and signing of the informed consent form (s).

After the informed consent process is completed, the final outcome of the process should be recorded directly on the assessment tool (or in a chart note) and the staff member who completed the checklist should ensure his or her signature is recorded in the space provided.

All comprehension assessment tools should be submitted to local IRB/ECs for approval prior to use. Detailed instructions for use of all comprehension tools must be specified in the site SOP for obtaining informed consent.

5.7 Documenting the Informed Consent Process

US FDA regulations and ICH E6 guidelines require that informed consent be documented by "the use of a written informed consent form approved by the IRB/EC and signed and dated by the subject or the subject's legally authorized representative at the time of consent."

To fulfill this requirement, complete all signature and date lines on the informed consent form in dark ink. Legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a participant's full surname, and it is strongly recommended that initials not be used in place of a participant's full first name. However, if a participant commonly signs their name using an initial for their first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

On the study informed consent form, in addition to completing signature requirements as described above, the participant must indicate on the form whether they agree to storage and future testing of biological specimens. The participant may decline any of these options and still enroll in MTN-028.

The DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials lists detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS policy must be met. In order to also meet some of the suggestions listed in the DAIDS policy, site staff are strongly encouraged to use an Informed Consent Coversheet similar to the sample included on the MTN-028 webpage under Study Implementation Materials . Sites choosing to use a coversheet should list the coversheet as a source document in their SOPs for source documentation for MTN-028 and should use the coversheet consistently to document all informed consent processes with all participants. The first half of the coversheet (items up to and including "Start time of informed consent discussion:") should be completed at the start of the IC session. The remainder should be completed at the end of the informed consent session. If a site chooses not to utilize the Informed Consent Coversheet, all elements of each informed consent process must be documented in detail in a signed and dated chart note per site SOP.

It is essential that all informed consent documentation (e.g., the informed consent form, the coversheet) document that informed consent was obtained before any study procedures were conducted.

Regulations require that participants be given a signed copy of the informed consent forms. If a participant opts not to receive a copy, document this on the cover sheet or chart note and offer the participant an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full informed consent form.

5.8 Informed Consent Process for Participants who Resume Study Participation After Voluntary Withdrawal

In the event a participant voluntarily withdraws from MTN-028 and wishes to re-join the study, she must undergo a re-consenting process to restart participation in the study regardless of any

previously documented written informed consent. Written informed consent must be obtained prior to any study procedures, including clinical procedures, and prior to any procedures to determine product use eligibility. Refer to SSP Section 4.7.7.1 for specific procedures related to study resumption.

Written informed consent for storage and future testing of biological specimens is optional for participants re-joining the study. Participants may choose not to re-consent to storage and future testing of biological specimens and still re-join the study.

The documentation requirements for the re-consenting process are the same as the requirements for participants joining the study for the first time (see Section 5.7).

5.9 Ongoing Assessment of Participant Comprehension

For enrolled participants, informed consent also must be understood as an ongoing process that continues throughout the study follow-up period. Periodically, at study visits, staff should assess participants' comprehension using a discussion style similar to the enrollment assessment. The key elements of informed consent also should be reviewed at study follow-up visits. Sites may choose to review key elements of informed consent with individual participants, or in group sessions. Elements of informed consent can be reviewed at every visit, or periodically, as per site SOPs. Reviewing key elements of informed consent during follow-up visits may focus on the remainder of study participation. These informal assessments will help to identify aspects of the enrollment informed consent process that are, and are not, optimally effective for study participants. The assessments also may identify rumors or misperceptions about the study that require a response by the Protocol Team. This discussion should be noted in the participant's chart note for that visit date.

Section 6. Web Randomization

This section provides information on the process for randomization to study group for MTN-028 study participants using the Frontier Science & Technology Research Foundation (FSTRF) randomization system.

6.1 Participant Randomization Overview

Randomization is the process whereby a participant is assigned to a study treatment arm.

There are two main steps in the randomization process:

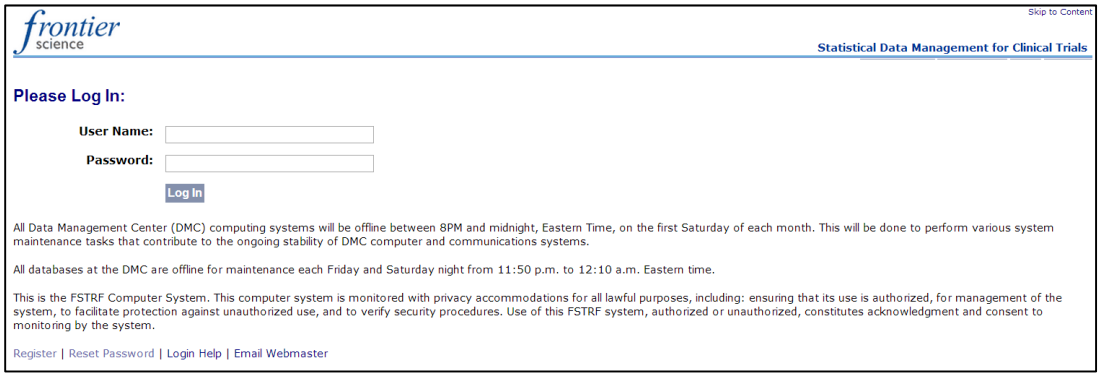
- request randomization using the MTN-028 Frontier Science & Technology Research Foundation (FSTRF) Randomization system
- receive and print randomization confirmation notice

6.2 Requesting FSRTF User Accounts

Staff must have FSTRF user account in order to access the system and randomize participants. Follow the below steps in order to create an account.

- Go to the FSTRF Portal:
  https://www.fstrf.org/apps/cfmx/apps/common/Portal/index.cfm
- Click on the link for "Register"

Figure 1. Log in page of the FSTRF Randomization System



- Enter your information (e.g. first name, last name, institution, e-mail address)
- Create a password
    - **NOTE**: This is the password you will use to access the system moving forward once an account has been created.
- If you are a staff member (for example, the clinic coordinator) requesting an account for one of your staff, please enter your own information under "Person completing this form". If you are entering information for yourself, you can check the box for "same as above".
- Click "Next"
- Choose the project "MTN" from the drop down menu and click "Other- Non-Laboratory Staff" for your position from the menu. In the comments, please enter "MTN-028" and your site name.
- Click "Next"
- For "Web/Data Access for Lab(s)", click "No"
- For "Randomization Access", click "Yes"
    - Click "Institution number not available"
    - Click both "Access to Randomization Checklists" and "Access to Randomize Patients"
- Review your information for accuracy and click "Submit"

NOTE: If you or your staff member already has a FSTRF account, for example, due to participation in another clinical trial, you must still request an account via the FSTRF Portal in order to randomize for MTN studies. Use the same e-mail and password of the existing account to request the MTN account.

6.3 Requesting Participant Randomization Using the FSRTF System

CRS staff will request randomization for a participant via the MTN-028 FSTRF web-based randomization system once the participant has met all eligibility requirements at the participant's Enrollment Visit (Visit 2.0).

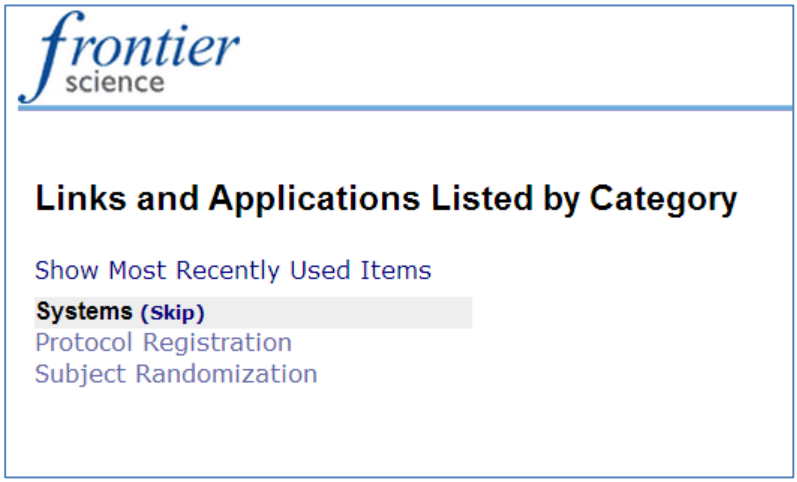
To request randomization for a participant:

1. Log onto the FSTRF system at www.fstrf.org/Portal (see Figure 1) and log in using your FSTRF Randomization System username and password

NOTE: You must request a FSTRF user account – see above section 6.2

2. Once logged on, you will arrive at the welcome page (see Figure 2). From the welcome screen, click on "Subject Randomization"

Figure 2. Links and Applications Listed by Category Page of the FSTRF Randomization System



3. From the Randomization Screen, use the drop down menus provided to select your institution and study, then click "Continue" (see Figure 3a). You can disregard (e.g., leave blank) the check box for "Blank Eligibility Checklist", since it does not apply to MTN-028. Click "OK" in the confirmation pop-up box (see Figure 3b).

Figure 3a. FSTRF MTN Subject Randomization System Part 1

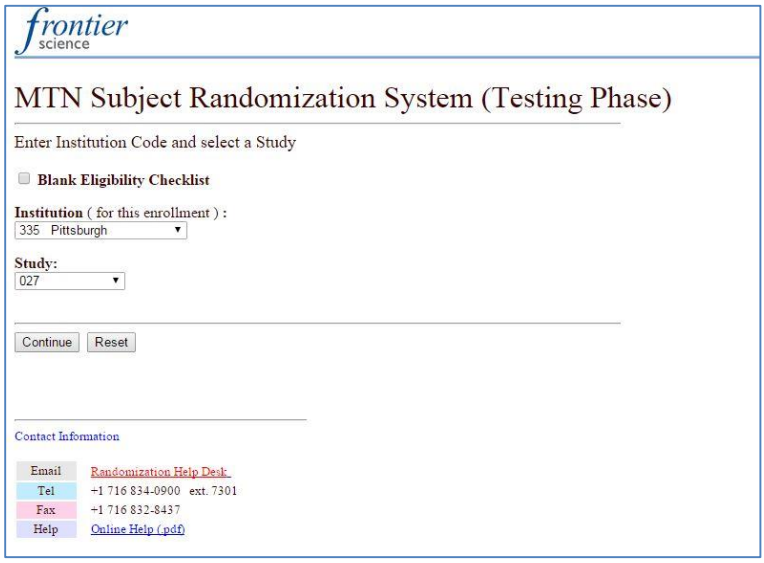
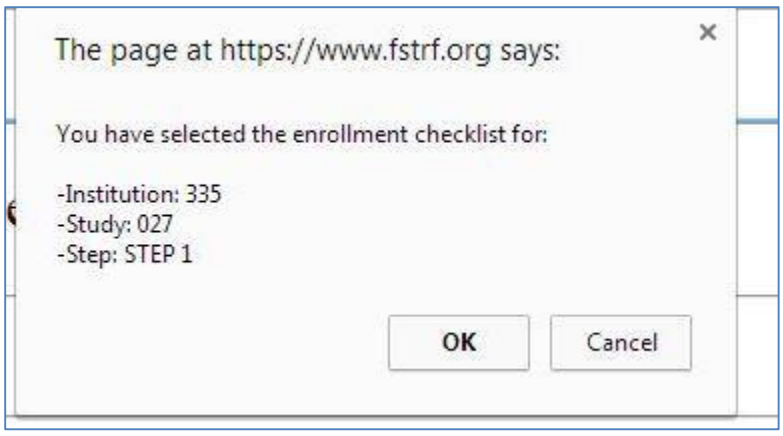


Figure 3b. FSTRF MTN Subject Randomization System Part 1 Pop-up Box



4. The next page is pre-filled so you do not need to edit or complete anything on this page. Click "Continue" (Figure 4a). Click "OK" in the confirmation pop-up box (see Figure 4b).

Figure 4a. FSTRF MTN Subject Randomization System Part 2

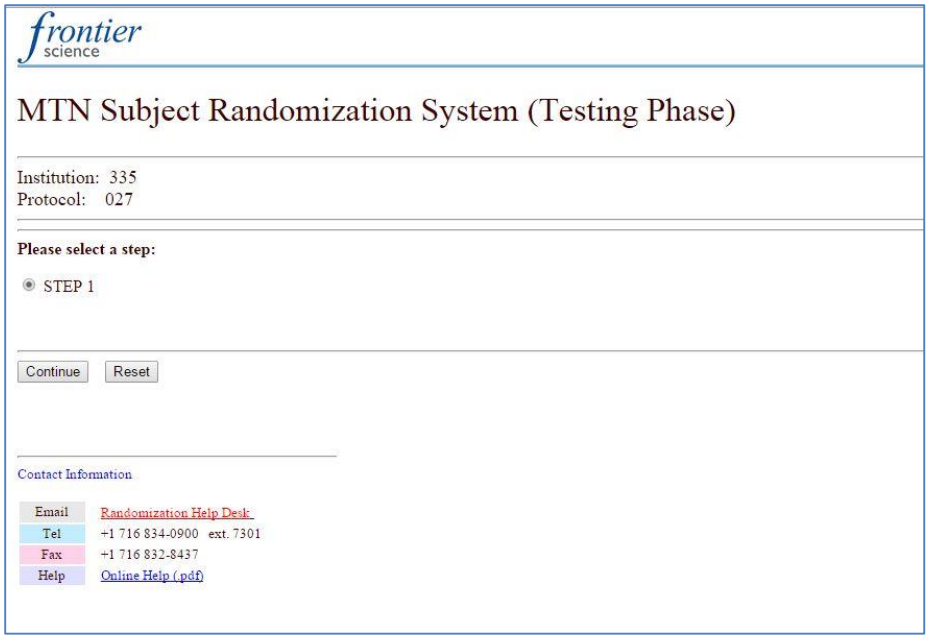
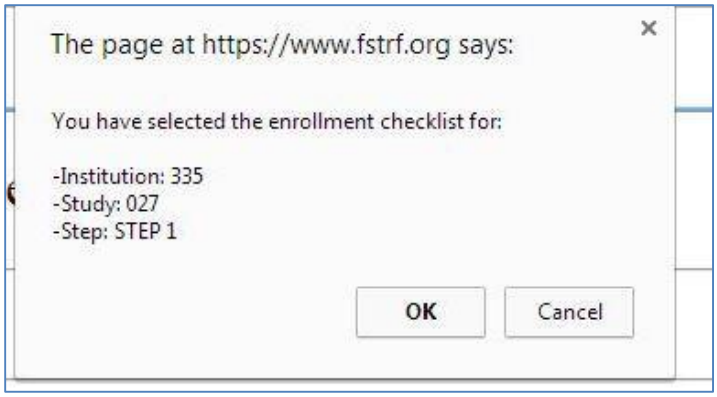


Figure 4b. FSTRF MTN Subject Randomization System part 2. Pop-up Box



5. On the next screen, select the box for "Click here to continue!" Enter the participant's Participant ID Number (e.g. PTID), without dashes, in the space provided and hit the "Enter" key on your keyboard. You must enter a valid PTID to proceed (See Figure 5a). Click "OK" in the confirmation pop-up box (figure 5b).

Figure 5a. FSTRF MTN Subject Randomization System Randomization Page

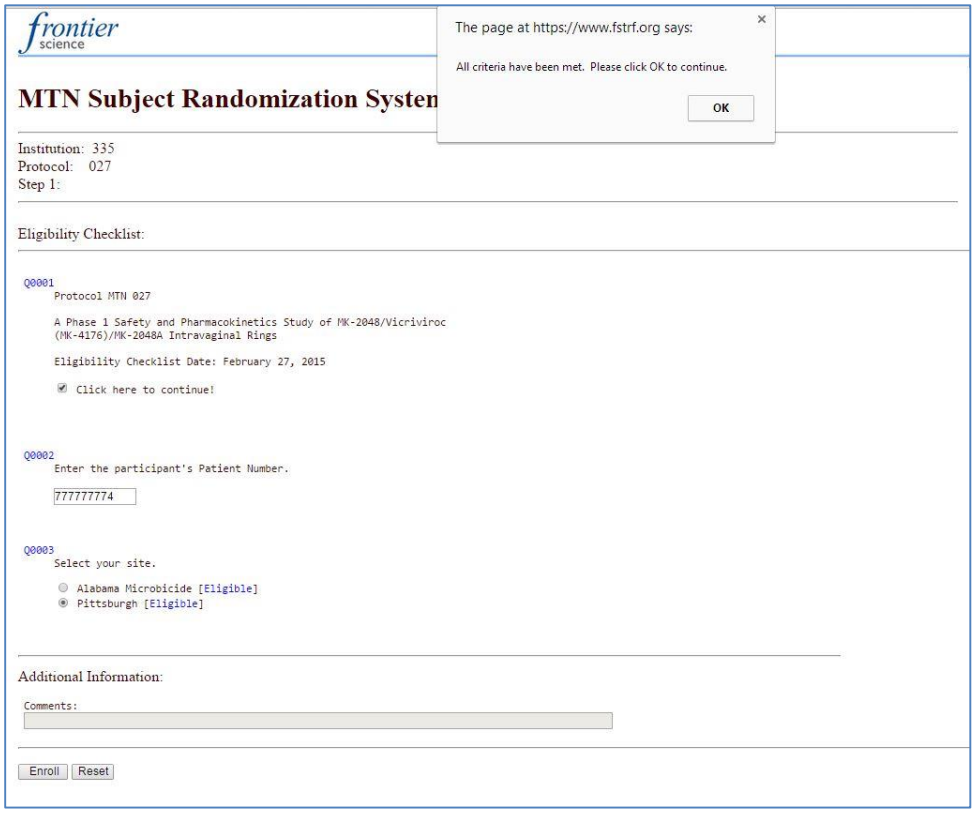
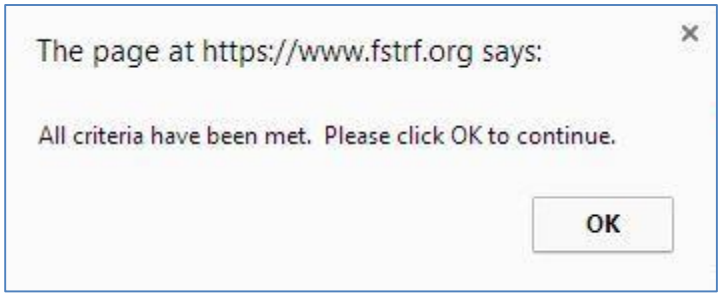


Figure 5b. FSTRF MTN Subject Enrollment System Randomization Page Pop-up Box



6. Click "Enroll" at the bottom of the page and "OK" in the confirmation pop-up box (See Figures 6a and 6b). This will confirm the request to randomize the participant.

Figure 6a. FSTRF MTN Subject Enrollment System Randomization Page

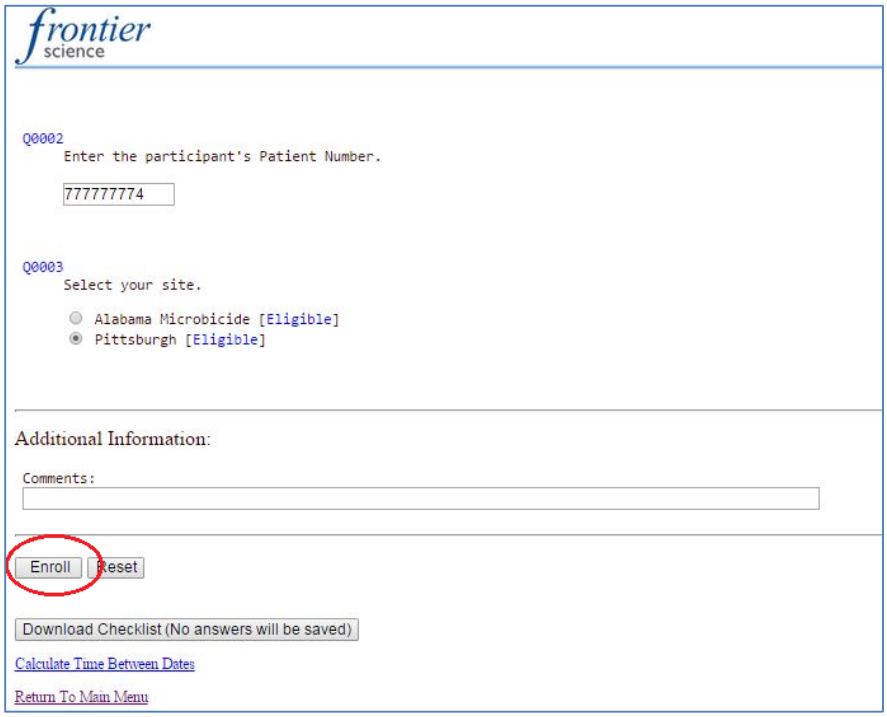
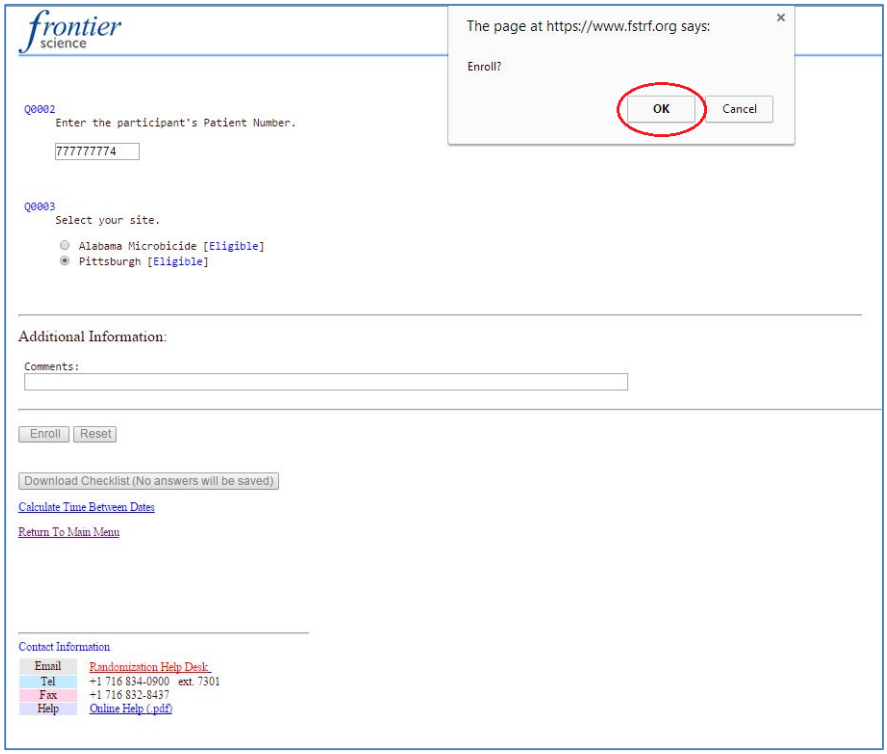


Figure 6b. FSTRF MTN Subject Enrollment System Randomization Page



6.4 Randomization Confirmation Notices

When a participant has been successfully randomized, you will see the following web message (Figure 7). A notification of randomization will also be sent via e-mail to:

- CRS Clinic Coordinator and CRS Pharmacist aliases
- Randomization confirmation notices will include date of randomization, CRS clinic staff member name, DataFax site number (Inst.), study number, PTID, site location, and the randomization number (Code).
- NOTE: The Eligibility Checklist Date listed on the Randomization confirmation notice refers to the date that this item was last modified by FSTRF when configuring the web randomization interface. This date does not signify the date that each participant's eligibility for the study was confirmed. Rather, the date provided on the MTN-028 Eligibility Checklist word document should be used as the date that each participant's eligibility was confirmed.
- Once the randomization confirmation notice is received, CRF staff must complete the following steps:

1. Write the randomization number (code) on the MTN-028 prescription before sending to the pharmacy.

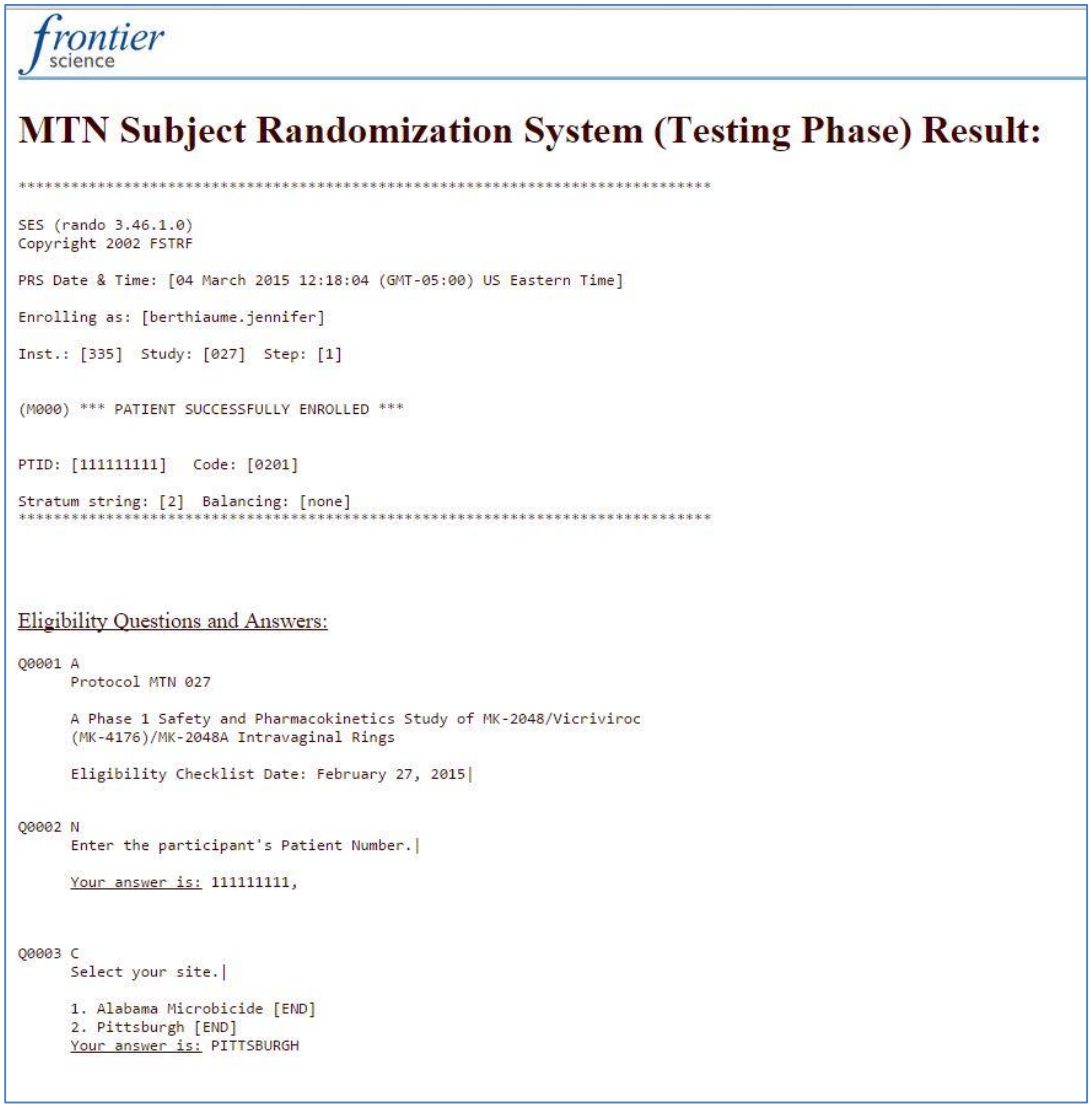
NOTE: The randomization number (Code) provided by FSTRF will be displayed as a 4-digit number with a leading 0. When transcribing the randomization number onto the MTN-028 Prescription and Enrollment (ENR-1) CRF, the leading "0" should be transcribed.

2. Print two copies of the randomization confirmation email – one to keep in the participant's study binder and the second to send with the study prescription to the pharmacy.

3. All randomization notices should be kept in a secure location

4. Please refer to SSP Section 7 for additional guidance on study product dispensation considerations for clinic staff.

Figure 7. FSTRF MTN Randomization Notice



frontier science

MTN Subject Randomization System (Testing Phase) Result:

```
**************************************************************************

SES (rando 3.46.1.0)
Copyright 2002 FSTRF

PRS Date & Time: [04 March 2015 12:18:04 (GMT-05:00) US Eastern Time]

Enrolling as: [berthiaume.jennifer]

Inst.: [335]  Study: [027]  Step: [1]


(M000) *** PATIENT SUCCESSFULLY ENROLLED ***


PTID: [111111111]   Code: [0201]

Stratum string: [2]  Balancing: [none]
**************************************************************************
```

Eligibility Questions and Answers:

```
Q0001 A
      Protocol MTN 027

      A Phase 1 Safety and Pharmacokinetics Study of MK-2048/Vicriviroc
      (MK-4176)/MK-2048A Intravaginal Rings

      Eligibility Checklist Date: February 27, 2015|


Q0002 N
      Enter the participant's Patient Number.|

      Your answer is: 111111111,


Q0003 C
      Select your site.|

      1. Alabama Microbicide [END]
      2. Pittsburgh [END]
      Your answer is: PITTSBURGH
```

6.5 Randomization Codes and Randomization Time

- Randomization confirmation notices will include 4-digit randomization number (codes). This 4-digit randomization number will be used by the pharmacist to identify which study product sub-lot code should be dispensed. Randomization numbers (codes) will appear on confirmation notices that are sent to both CRS Pharmacists and Clinic Coordinators.
- The randomization time within the confirmation email is provided in Eastern Standard Time (EST). When completing item 5 on the Enrollment CRF, convert the time of randomization according to the site's local standard time zone.

6.6 Replacing Participants

If a participant discontinues study participation or is placed on hold (and the ring has been out for longer than consecutive three days) the participant needs to be replaced, and the following steps should be completed:

1. Inform the MTN-028 Management Team immediately (mtn028mgmt@mtnstopshiv.org)
2. Once the site receives confirmation from the SCHARP Project Manager that the participant does need to be replaced, the site must contact FSTRF (sdac.random.desk@fstrf.org; user.support@fstrf.org) to let them know that there is a participant that needs to be replaced. The email to FSTRF should include the PTID for the participant that needs to be replaced.
3. Once FSTRF notifies the site that the randomization system is ready to replace the participant, the next eligible participant will be enrolled as a replacement participant. The replacement participant will be assigned a new PTID and the site clinic staff will complete the steps for randomization using the FSTRF website. The replacement participant will be assigned to the same product as the participant being replaced via the FSTRF website.
    - NOTE: FSTRF's operating hours for assistance with randomization are 6AM – 5PM Eastern. If it is determined that a participant must be replaced after 5PM Eastern (2PM Pacific) and another patient is already scheduled to be randomized that afternoon, that patient can be randomized. Site staff should still email FSTRF informing them that a participant needs to be replaced and the next day when FSTRF informs the site that the randomization system is ready to replace the participant, the next eligible patient randomized will be assigned the same product as the discontinued participant.
4. The reason that the participant is being replaced should be recorded on the Participant Replacement Log CRF.
5. The PTID assigned to the participant that is being replaced should be documented on the replacement participant's Enrollment CRF.

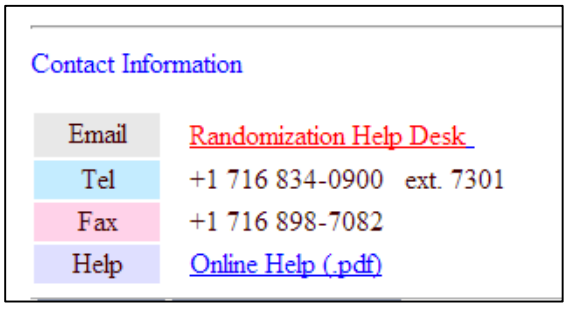
6.7 Logging Out

To log out of the FSTRF system, click on "skip to content" in the upper right corner of the screen. This will reveal a menu bar with a logout option (see Figure 8).

Figure 8. Signing out of FSTRF

6.8 Randomization Technical Support

In circumstances where CRS staff need to randomize a participant, but are unable to access the FSTRF system due to technical problems, have any issues with the FSTRF randomization, or do not receive the randomization confirmation email, the CRS staff should contact FSTRF via the contact information provided at the bottom of the portal.



For operational issues, contact the MTN-028 SCHARP Project Manager and the Statistical Research Associate.

Section 7. Study Product Considerations for Non-Pharmacy Staff

This section provides information and instructions for non-pharmacy staff (i.e., clinic staff) related responsibilities regarding blinding, transport, receiving the MTN-028 intravaginal ring (IVR) from pharmacy (dispensation of IVR from pharmacy staff to clinic staff), and delivery of the IVR to study participants (provision of IVR from clinic staff to study participant). Record keeping requirements for clinic staff are also provided. Associated instructions for pharmacy staff are provided in the MTN-028 Pharmacy Study Product Management Procedures Manual, which will be made available to each MTN CRS Pharmacy by the MTN LOC Pharmacist. Please refer to section 10 of this SSP manual for product use instructions and guidance on study product adherence counseling.

7.1 Responsibilities and Obligations with Regard to Blinding

MTN-028 Investigators of Record (IoRs), and by delegation all MTN-028 study staff, are responsible for maintaining the integrity of the study's single blind design. to which Each participant is randomly assigned study product (combination low dose VCV 91mg/MK-2048 10mg IVR or combination original dose VCV 182mg/MK-2048 30mg IVR) in a double-blinded manner, meaning that neither study participants nor study staff — including all members of the Protocol Team — will be provided information on the identity of the specific study product to which each participant has been assigned. However, if staff or participants were to visually compare study IVR types, then they might be able to discern that there are differences in

appearance, and therefore, differences in study IVR type. For this reason, this study is deemed as single-blind.

Designated clinic staffwill generate the randomization number to which each participant has been assigned, through an online randomization system. Study documentation maintained by pharmacy staff — who are excluded from ascertaining primary and secondary study endpoints —will include blinded coded information indicating the specific sub-lot code(s) for the study IVR to which participants have been assigned, based on randomization number.

Blinding will be maintained throughout the study and until all study endpoint data have been verified and are ready for final analyses. There are no circumstances under which it is expected that unblinding a participant study product regimen assignment will be necessary to protect the safety of that individual. In the event that study staff becomes concerned that a participant may be put at undue risk by continuing use of study product, the IoR may temporarily hold or permanently discontinue product use by the participant. However, knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow-up and/or treatment.

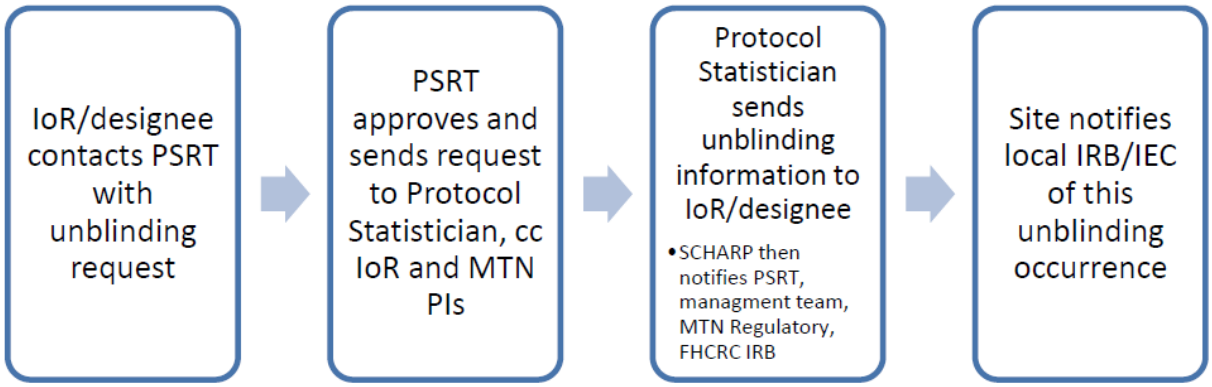
7.1.1 Emergency Unblinding Process

During the trial, an IoR/designee may request that a participant's study product regimen assignment be provided (unblinding), if it is essential to protect a participant's safety.

To request the unblinding for a specific participant, the following steps are required:

1. IoR/designee must contact the Protocol Safety Review Team (PSRT) (mtn028psrt@mtnstopshiv.org).
2. If the PSRT rules that unblinding is required, the PSRT will send the unblinding request to the Protocol Statistician (Barbra Richardson; barbrar@scharp.org), and cc the IoR/designee from the site so that the statistician can send the information to the correct person at the site. The MTN PI and co-PI should also be copied on this request from PSRT.
3. The Protocol Statistician will provide the study product regimen assignment to the IoR/designee and will then notify the following: MTN PI and Co-PI, PSRT, the protocol management team and protocol chairs, MTN Regulatory and the Fred Hutchinson Cancer Research Center IRB that this has occurred.
4. The site IoR/designee must notify the local IRB in an expedited manner of this occurrence of unblinding.

Figure 7-1. Flow Chart of Emergency Unblinding Process



7.2 Randomization Assignment

The MTN Statistical Data Management Center (SDMC) will generate and maintain the study randomization scheme and associated materials, which consist of MTN-028 Pharmacy Randomization List.

MTN SDMC will conduct participant randomization via an online system with the Frontier Science & Technology Research Foundation, Inc. (FSTRF). After a participant has been confirmed as eligible and has provided written informed consent to take part in the study, a clinic staff member will submit on the FSTRF website the required participant information for enrollment and randomization. After online submission, designated clinic staff and pharmacy staff will receive email notification that the participant has been randomized for this study – this email will include information that is necessary for clinic staff to complete a prescription (i.e., randomization number). Please refer to SSP Section 6 for detailed instructions for randomizing participants using the FSTRF randomization system.

Clinic staff will print the randomization email notification and place in the participant clinic binder. The act of assigning a Randomization Number to a participant is considered the effective act of enrollment and randomization into the study. Once a Randomization Number is assigned, the participant is considered enrolled in the study.

Prescriptions (Appendix 7-1) will be produced as two-part no carbon required (NCR) forms. A bulk supply of prescriptions will be provided to the clinic staff by MTN LOC Pharmacy. Sites will identify the individual responsible for receiving the slips and for contacting the MTN LOC Pharmacist should additional slips be needed during the study.

After recording CRS Name, CRS ID, CRS Location, PTID, Randomization Number, and other details on the prescription, clinic staff will separate the two sheets of the form, and the white original will be delivered to the pharmacy (in batches). The clinic staff may fax the prescription and the pharmacy will dispense the study product. The yellow copy (bottom) will be retained in the participant's study notebook in the clinic. Only one prescription will be used for each participant. A prescription must be signed by an authorized prescriber as designated on FDA Form 1572.

7.3 Dispensing Study Product

Each participant is assigned to combination low dose VCV 91mg/MK-2048 10mg IVR or combination original dose VCV 182mg/MK-2048 30mg IVR based on the randomization number provided in the randomization email notification from FSTRF.

Each IVR will be dispensed from the pharmacy in its original sealed pouch. The pharmacist/designee will also dispense a white participant IVR return bag. On the return bag label, the pharmacist/designee will complete the PTID and dispensation date, and clinic staff will complete a contact name and phone number. Clinic staff must be sure to provide the participant with the correct IVR and return bag. Clinic staff should instruct the participant that the IVR should be rinsed and dried and placed in the bag if the used IVR is removed prior to the next scheduled visit so that it can be returned to the clinic. Although participants are encouraged to not remove the ring, they may also rinse and dry the ring and place it in this bag for storage if there is a need to temporarily remove the ring. The ring should always be rinsed with clean water before reinsertion. Participants may request a new bag at clinic visits, as needed, if the bag is used or misplaced.

7.3.1 Chain of Custody

For MTN-028, the IVR and white return bag will only be dispensed from the pharmacy directly to a designated transport staff member (runner or courier). If transported by a courier, the courier will deliver the study product to a clinic staff member. A clinic staff member will then provide the participant-specific study product and bag to the participant. The pharmacist will record the PTID and date/time that the IVR is dispensed on the IVR pouch label. The study product will be transported in a manner that will maintain the required storage temperature of 2-8C. The MTN-028 Chain of Custody (Pharmacy) SOP provides documentation regarding who receives the vaginal ring from the pharmacy. Responsibilities and procedures from the time of product receipt from the pharmacy until delivery to participant, including procedures for participant identity verification prior to ring provision, should be outlined in the Clinic Study Product Accountability and Destruction SOP. This clinic SOP should be developed with input from both pharmacy and clinic staff to ensure smooth on-site clinic flow. This SOP must be approved by the MTN LOC Pharmacist prior to study activation and may only be modified after consultation with the MTN LOC Pharmacist.

The IVR should be vaginally inserted within 24 hours of the date/time indicated on the IVR pouch label. If administration does not occur within this time frame, the unused IVR must be returned to the pharmacy. Clinic staff can request another IVR for the given participant by marking RE-SUPPLY on an MTN-028 Intravaginal Ring Request Slip.

7.3.2 Initial Vaginal Ring Dispensing - Prescription Overview

All prescriptions will have the assignment “MTN-028 Intravaginal Ring (MK-2048A (Low Dose): 91mg of VCV (MK-4176) + 10mg of MK-2048 or MK-2048A (Original Dose) 182mg of VCV (MK-4176) + 30mg MK-2048)”, as all participants will be randomized to intravaginal ring. The randomization number pre-printed on participant’s randomization email notification from FSTRF will indicate to the pharmacy which IVR sub-lot code(s) can be dispensed to that given participant (MTN-028 Pharmacy Randomization List). Note that only one IVR may be dispensed at each visit.

The in-clinic procedures are listed below.

In Clinic (procedures C1-C5):

C1. Conduct participant randomization via the online FSTRF system. A randomization number will be generated for this participant. Complete an MTN-028 Prescription accordingly. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed/marked and dated informed consent form for enrollment prior to recording his/her initials beside these boxes.

C2. The middle section of the prescription must be completed by a study staff member designated in the site's delegation of duties as an authorized prescriber of study product. This person also must be listed as an investigator (either the Investigator of Record or Sub-Investigator) on the current FDA Form 1572.

C3. The bottom section of the prescription requires clinic staff initials and the date once all of the above is completed. This should be completed by the clinic staff member who verifies that the participant signed the informed consent form and completed the top part of the prescription.

C4. Double-check the accuracy of all entries and then separate the two parts of the completed prescription. Retain the yellow (clinic) copy in the participant study notebook.

C5. Deliver the white (pharmacy) original prescription to the study pharmacy.

In Pharmacy (procedures P1-P3):

P1. Upon receiving the completed MTN-028 Prescription (at enrollment), the pharmacist will review the document for completion and accuracy. The pharmacist will print the FSTRF randomization email notification in order to double check prescription completeness and accuracy. This hard copy of the email will be placed in the participant pharmacy binder. In the event that pharmacy staff identifies possible errors on the original prescription, they will return the original prescription to clinic staff for clarification or correction. If corrections are required, corrections must be made on both the white original prescription and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both copies. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Corrections to original study prescriptions should only be made by an authorized prescriber and fully documented in the participant's chart notes.

P2. Participant randomization and receipt of the MTN-028 Prescription will be documented on the Pharmacy Randomization List. Two pharmacy staff members (at minimum one pharmacist), will verify (by initialing and dating) the linking of the participant's randomization number and possible IVR sub-lot codes. The PTID provided on the Prescription and verified on the FSTRF confirmation email will be entered on the Pharmacy Randomization List.

P3. Following review of the signed MTN-028 Prescription, pharmacy staff will dispense the study product for participants per instructions in the MTN-028 Pharmacy Study

Product Management Procedures Manual and in accordance with the site pharmacy Chain of Custody SOP.

7.4 Study Product Accountability

Study product will be dispensed to clinic staff and provided to the participant in the clinic. **Used** study product will be returned by the participant and given to the clinic staff (rather than the pharmacy). Therefore, accommodation must be made to allow for documentation of distribution, collection, and removal of study product at the site clinic. A standardized process of tracking and accountability must be followed by all MTN-028 sites. A sample Participant-Specific Clinic Study Product Accountability Log is available on the MTN-028 website under Study Implementation Materials. This log includes tracking the date that the IVR is provided to the study participant, the date of IVR return to the clinic, and the final status of each ring (used ring for storage, used ring for destruction, unused ring to pharmacy, or ring not returned). Sites will be provided an SOP template which should be modified to reflect the specific processes at the site.

7.4.1 Documentation of Ring Provision and Ring Collection

Participant-Specific Clinic Vaginal Ring Accountability Log
This log should be maintained and completed as outlined in the SOP for Clinic Vaginal Ring Accountability and Destruction (template is available on the MTN-028 website under Study Implementation Materials). This SOP should define who is responsible for updating this log, when it is updated, where it is stored, how and when it will be QC'd, and who is responsible for the QC procedures. It must be updated when the IVR is provided to the participant or returned to the clinic and indicated in the Source Document SOP whether any of the data points will collect source data.

Ring Collection and Insertion CRF
Site staff must document all IVR returns on the Ring Collection and Insertion CRF, as well as the Participant-Specific Clinic Study Product Accountability Log described above.

After documenting the return of used or unused rings on the CRF and clinic log, clinic staff should proceed to follow the directions outlined in SSP Section 9.7.9 (Testing of Intravaginal Ring (IVR)). The placement of the used ring in the biohazard bag (supplied by Network Lab) that is to be stored is also documented on the Participant-Specific Clinic Study Product Accountability Log.

In the unusual event that a vaginal ring was dispensed but never inserted, the returned (unused) vaginal ring must be returned to the clinic and documented by study staff on the Ring Collection and Insertion CRF and the Participant-Specific Clinic Study Product Accountability Log. The unused vaginal ring should be returned to the pharmacy for quarantine. Only unused vaginal rings may be returned to the pharmacy; this can include study product in which the overwrap pouch was opened but the IVR was never vaginally inserted. Clinic staff and pharmacy staff will complete the MTN-028 Record of Return of Site-Specific Unused Intravaginal Rings.

Clinic Study Product Destruction Log
In the rare event that a ring must be destroyed, the Clinic Study Product Destruction Log (also available on the MTN-028 website under Study Implementation Materials) must be completed to document the destruction of the specific biohazard waste container/bin that contained the IVR to be destroyed. This will be the final documentation required for recording the accountability of any used ring that is not destined for further testing. If a ring is inserted in the clinic and then removed, during the same visit, due to an adverse event or error subsequently discovered, the ring would be placed in the specified biohazard container for destruction.

7.5 Duration of Use of Each IVR

Participants should be counseled to refrain from removing the IVR until scheduled Visit 9/Day 28 (approximately 28 days of IVR insertion), unless instructed otherwise by the study clinic. No replacement IVR is scheduled, given the protocol design.

Participants will receive an IVR to insert at their Enrollment Visit (Visit 2). Participants will be instructed to refrain from removing the IVR during the 28 day period, unless instructed otherwise by the study clinic. Ring removal is scheduled to occur at the participant's Day 28 visit. In the rare event a participant is not available to return to the clinic for the Day 28 visit to have the IVR removed, site staff should reschedule the visit within the visit window (i.e. no later than Day 29). If the participant is not able to return to the clinic within the Visit 9.0/Day 28 visit window, site staff should instruct the participant to remove the ring, rinse the ring with clean water (no soap), dry with a paper towel, and place in the re-sealable plastic bag provided or suitable substitute, until the participant is able to return to the clinic. All attempts made to contact the participant and retrieve the study product must be documented in the participants chart and the PSRT must be informed.

7.6 Vaginal Ring Re-supply During Follow-up or Interim Visits

While conducting all visit procedures for each scheduled visit is ideal, it is acknowledged that this might not always be possible. At a minimum, all of the following procedures must be conducted in order to dispense study product:

- AE assessment and clinical management, in accordance with section 8 of the protocol (verbal report of symptoms is acceptable; if symptoms indicate that further evaluation is necessary, this must be conducted prior to dispensing study product).
- If indicated based on clinical discretion (e.g. participant reports risk behaviors and/or shows signs/symptoms of HIV or pregnancy), a pregnancy test and/or HIV test may be performed and must be negative prior to dispensing study product.
- Collection of used vaginal ring (and unused, if applicable), if available.
- Adherence Counseling/Vaginal Ring Use Instructions, as needed.

The MTN-028 Intravaginal Ring Request Slip, which will be produced as two-part NCR forms, (see Appendix 7-2) will be used by clinic staff to communicate to pharmacy staff that a new IVR should be resupplied to a participant. [**NOTE**: Once the initial IVR has been vaginally inserted, the participant should not require additional IVRs. However, for example, in the unusual circumstance that the IVR has been expelled in such a way that the participant feels that it is not retrievable (e.g., during menses, in the toilet, etc.), then the participant should be instructed to notify the clinic, and a new IVR will be dispensed. The used IVR should be brought back to the clinic by the participant and given to clinic staff, preferably in the white IVR return bag. The slip is also used to communicate clinic staff decisions to temporarily hold, permanently discontinue, or resume (after a temporary hold) IVR use. Further, the slip is used to communicate to the pharmacy of a participant's refusal to accept a new vaginal ring and to communicate when the product use period is completed. At minimum, one MTN-028 Intravaginal Ring Request Slip should be completed (white top sent to pharmacy and yellow copy stored in participant clinic binder) for each participant when she has completed use of study product – MTN-028 Intravaginal Ring Request Slip marked PRODUCT USE PERIOD COMPLETED.

A Bulk supply of the slips will be provided to the clinic staff by MTN LOC Pharmacy. Sites will identify the individual responsible for receiving the slips and for contacting the MTN LOC Pharmacist should additional slips be needed during the study. Instructions for completion of the MTN-028 Vaginal Ring Request Slips are printed on the slips themselves. Additional guidance for clinic staff is as follows:

- The participant's ID number (PTID) and the Randomization Number assigned to the participant in the boxes provided at the top of the slip.

- Mark the box for RESUPPLY, HOLD, RESUME, PARTICIPANT DECLINE, PERMANENT DISCONTINUATION, or PRODUCT USE PERIOD COMPLETED.

- If RE-SUPPLY or RESUME is marked, only one (1) vaginal ring is dispensed.

- Mark RESUME only after a HOLD has been lifted.

- Only mark the HOLD or PERMANENT DISCONTINUATION box for clinical (site-initiated) hold/permanent discontinuations. This includes any time the participant is directed by the clinician to remove the ring. Additionally, PERMANENT DISCONTINUATION should be marked for participants who decide to terminate from the study early. Record the reason for the hold or discontinuation on the line provided.

- If a participant declines to be issued a new vaginal ring for any reason, mark the PARTICIPANT DECLINE box. For participants who decline study product, a ring request slip should be completed in order to document the refusal. If the participant agrees to start receiving product again, mark the RE-SUPPLY box to indicate she is restarting product.

- At the scheduled Ring Removal Visit (Visit 9/Day 28), mark the PRODUCT USE PERIOD COMPLETED box. This will indicate that no more vaginal rings will be provided for the participant.

- The clinic staff printed name, signature, and signature date must be completed by a clinic staff member authorized to order study product for participants during follow-up. When marking RESUME, this clinic staff member must be an authorized prescriber. In all other circumstances, the slips do not need to be signed by an authorized prescriber; however site-specific pharmacy regulations and procedures may be more stringent. All sites must comply with their local requirements.

- Double-check the accuracy of all entries. The MTN-028 Intravaginal Ring Request Slip is a two-part NCR form. Retain the yellow copy in the participant study notebook, and deliver the white original to the pharmacy.

- The pharmacist must review the slip for completion and consistency. In the event that pharmacy staff identify possible errors on the slip, they will return the original slip to clinic staff for clarification or correction. If corrections are needed, the corrections must be made on both the white original sheet and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both copies. Identical corrections and notes should be recorded on both copies, on the same date, by the

same person. Corrections should only be made by study staff authorized to complete the requested action on the original request slip. See above.

Once an IVR is provided to a participant, clinic staff will document on the Ring Collection/Insertion CRF the needed details regarding the provision of the vaginal ring. (S)he will also document this action on the Participant-Specific Clinic Vaginal Ring Accountability Log as outlined in the SOP for Clinic Vaginal Ring Accountability and Destruction.

7.6.1 Vaginal Ring Hold and Resumption

Protocol Section 9 (Clinical Management) and SSP Section 8 (Clinical Considerations and Safety Monitoring) specify the circumstances under which use of study product may be temporarily held or permanently discontinued. A product hold can occur for a number of reasons, as described throughout Protocol Section 9. Holds may be placed either in the clinic or over the phone.

If a product hold is instituted **during a clinic visit or over the phone**, an MTN-028 Intravaginal Ring Request Slip marked HOLD should be completed and delivered to the pharmacy, and a Product Hold/Discontinuation Log CRF should also be completed and faxed to DF/Net Research. A Product Hold/Discontinuation Log CRF should be completed for each clinical product hold, even if the participant is already on a hold for another reason. There is no need to send pharmacy an additional MTN-028 Vaginal Ring Request Slip if a product hold is already in place.

If product hold is instituted **over the phone**:

- Request that the participant remove the vaginal ring and place it in the study-provided white IVR return bag until further instructions are available.
- Follow-up as clinically appropriate per protocol, SSP and/or site SOPs.
- The participant should not resume IVR use until it is determined safe by the IoR/designee. IVR use may be resumed by asking the participant to come to the clinic for a new IVR.

An IVR should not be removed for a hold and later reinserted for reuse.

Once an MTN-028 Intravaginal Ring Request Slip is completed and a “HOLD” is marked, regardless of the reason or duration, no further rings will be dispensed for that participant until another slip is marked “RESUME” and signed by an authorized prescriber.

For the first dispensation after a hold, complete an MTN-028 Vaginal Ring Request Slip marked RESUME. The Product Hold/Discontinuation Log CRF documenting the hold should be updated and re-faxed to DF/Net Research when the participant resumes study product.

7.6.2 Permanent Discontinuation

If it is determined by the site clinician that IVR use will be permanently discontinued, site staff will complete an MTN-028 Intravaginal Ring Request Slip marked PERMANENT DISCONTINUATION. No further Request Slips need to be completed for this participant after this visit. A Product Hold/Discontinuation Log CRF must also be completed and faxed to DF/Net Research. If the participant opts to remain in follow-up, follow guidance per SSP Section 4

(Study Procedures) regarding visit procedures for participants who have discontinued use of study product.

7.7 CYP3A4 Inhibitors and Inducers

VCV (MK-4176) is a CYP3A4 substrate – it is extensively metabolized by CYP3A4. Despite only two of the four study products containing VCV, study stuff must promote the avoidance of certain scheduled/routine CYP3A4 inhibitors and inducers (prescription medications, over-the-counter medications, herbal supplements, and nutritional supplements) via any route of administration, since this study is blinded. Appendix 7-3 outlines CYP3A4 inhibitors that participants should avoid using concomitantly in this study. Appendix 7-4 outlines CYP3A4 inducers to be avoided. **NOTE:** single dose oral fluconazole for the treatment of vaginal fungal infections is permitted.

Information in Appendices 7-3 and 7-4 is adapted from:
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#4

If drug-drug interaction questions arise during the study that cannot be answered by any of the study-related materials provided (protocol, SSP, SOPs), please contact the MTN-028 PSRT (mtn027psrt@mtnstopshiv.org). Medications with unknown interactions will be dealt with on a case-by-case basis with input from the PSRT, as needed.

Other prohibited medications and practices can be found in Protocol Section 6.6 and SSP Section 8.5.

7.8 Study Product Retrieval

Protocol Section 6.4.4 specifies the circumstances under which study product must be retrieved from participants who are required to hold or discontinue vaginal ring use. Because participants are expected to have the vaginal ring in place at the time of their clinic visit, the need for product retrieval is expected to be rare. When product retrieval is required, retrieval may occur by the participant returning the product to study staff. Only unused vaginal rings are brought to the pharmacy for quarantine.

Table 7-3 specifies the circumstances and timeframes with which vaginal rings must be retrieved. If the vaginal ring cannot be retrieved (i.e., participant disposed of it or product was lost after removal) this must be documented on the Ring Collection and Insertion CRF and the related details and counseling on the need to ensure return of product to site should be detailed in the participant's chart notes.

Table 7-3. Retrieval of Study Product

	Retrieve Study Product Within:
Permanent discontinuation or temporary hold due to potential HIV seroconversion	24 hours
Permanent discontinuation for any other reason or IoR discretion	5 working days
Temporary hold for reasons with	7 working days

expected duration of greater than 7 days	
End of Study (Visit 13/Day 35; Final Clinic Visit)	2 working days

For all product holds requiring product retrieval, if the IVR is not retrieved within the time frame listed in Table 7-3, the PSRT must be informed. The retrieved IVR must be documented by clinic staff on the Ring Collection and Insertion CRF and on the Participant-Specific Clinic Vaginal Ring Accountability Log as outlined in the SOP for Clinic Vaginal Ring Accountability and Destruction.

7.9 Study Product Complaints

During the study, a problem or concern may be observed with an IVR. A problem may be noted by the pharmacy staff, clinic staff, or the participant. These complaints may be about the dosage form (ring), packaging (overwrap pouch), or other aspects of the study product. Clinic staff should make thorough record of complaints of participants and clinic staff. The clinic staff member will notify (via email) the site PoR and other designated site pharmacy staff of the study product complaint. This notification should include as much detail as possible and pictures (if necessary). The following information should be provided in the email: date of the observed issue, date that the issue was reported, date IVR was dispensed, did an adverse event occur, description of the nature of the issue, and any other details deemed necessary.

The site PoR will forward (via email) this information to the MTN LOC Pharmacist. The MTN LOC Pharmacist will forward the study product complaint to Merck. If the complaint/issue is concerning an unused IVR, then the unused IVR should be quarantined in the pharmacy. If the complaint/issue is concerning a used IVR, then the clinic staff should process this IVR per standard operating procedures for used IVRs.

Appendix 7-1: MTN-028 Prescription

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

CRS Name:		**CRS ID:**	
CRS Location:		**Randomization #:**	☐☐☐☐

Participant ID: ☐☐☐ – ☐☐☐☐☐ – ☐

Did the participant provide written informed consent for enrollment into MTN-028? . . . . . Yes ☐ No ☐ Clinic Staff Initials _____

MTN-028 Intravaginal Ring
(MK-2042A: 91mg VCV and 10mg MK-2048 or 182mg VCV and 30mg MK-2048)

Sig: Insert one ring into the vagina.

Quantity: One intravaginal ring. May be refilled as needed per request by designated clinic staff on MTN-028 Intravaginal Ring Request Slip for duration of participation in the study.

Authorized Prescriber Name (please print): _____

Authorized Prescriber Signature: _____

Date: ☐☐ – ☐☐☐ – ☐☐
dd *MMM* *yy*

Clinic Staff Instructions: Complete all items on this prescription. After initialing and dating below, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Clinic Staff Initials: _____ Date: ☐☐ – ☐☐☐ – ☐☐
dd *MMM* *yy*

Appendix 7-2: MTN-028 Intravaginal Ring Request Slip

CRS Name:

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Randomization Number: ☐☐☐☐

Clinic Staff Instructions: Mark whether this is a study intravaginal ring re-supply, clinical hold, resume (after a clinical hold), clinical permanent discontinuation, participant decline, or product use period completion notification. Only an authorized prescriber can indicate product resumption. Deliver the original white copy (labeled "Pharmacy") to the pharmacy. File the yellow copy (labeled "Clinic") in the participant's study notebook.

☐ **RE-SUPPLY** → **Pharmacy:** Dispense 1 intravaginal ring.

☐ **HOLD** → **Reason:** _____

Pharmacy: Do not dispense further intravaginal rings to the participant until another MTN-028 Intravaginal Ring Request Slip marked "RESUME" is received.

☐ **RESUME** → **Pharmacy:** Dispense 1 intravaginal ring. Only an authorize prescriber can indicate RESUME.

☐ **PARTICIPANT DECLINE** → **Pharmacy:** Do not dispense at this visit – participant is refusing intravaginal ring.

☐ **PERMANENT DISCONTINUATION** → **Reason:** _____

Pharmacy: **Do not** dispense any further intravaginal rings to the participant.

☐ **PRODUCT USE PERIOD COMPLETED** → **Pharmacy:** Do not dispense any further intravaginal rings to the participant.

Clinic Staff Name (please print): _____

Clinic Staff Signature: _____

Date: ☐☐–☐☐☐–☐☐

dd *MMM* *yy*

Appendix 7-3: CYP3A4 Inhibitors to Avoid

Strong Inhibitors ≥ 5-fold increase in AUC or > 80% decrease in CL	**Moderate Inhibitors ≥2 but < 5-fold increase in AUC or 50-80% decrease in CL**	**Weak Inhibitors ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL**
Antibiotics: clarithromycin, telithromycin Antidepressants: nefazodone Azole Antifungals: ketoconazole, itraconazole, posaconazole, voriconazole Pharmacokinetic Enhancers: cobicistat Protease Inhibitors: ritonavir, indinavir, lopinavir/ritonavir, nelfinavir, saquinavir, boceprevir, telaprevir Reverse Transcriptase Inhibitors: delavirdine Vasopression Receptor Antagonists: conivaptan	Antiarrhythmics: dronedarone Antibiotics: erythromycin, ciprofloxacin Antiemetics: aprepitant Antineoplastics: imatinib Azole Antifungals: fluconazole, miconazole Calcium Channel Blockers: verapamil, diltiazem Protease Inhibitors: atazanavir, darunavir/ritonavir, fosamprenavir	Antiandrogens: bicalutamide Antianginals: ranolazine Antiarrhythmics: amiodarone, quinidine Antibiotics: azithromycin Antidepressants: fluoxetine, fluvoxamine Antihyperlipidemics: atorvastatin Anti-inflammatory (asthma): zileuton Antineoplastics: nilotinib Antituberculars: isoniazid Anxiolytics: alprazolam Calcium Channel Blockers: amlodipine, felodipine Herbal Supplements: ginkgo biloba, goldenseal Histamine H2 Antagonists: cimetidine, ranitidine Immune Suppressants: cyclosporine Platelet Aggregation Inhibitors: cilostazol Protease Inhibitors: tipranavir/ritonavir

Appendix 7-4: CYP3A4 Inducers to Avoid

Strong Inducers **≥ 80% decrease in AUC**	**Moderate Inducers** **50-80% decrease in AUC**	**Weak Inducers** **20-50% decrease in AUC**
Anticonvulsants/Mood Stabilizers: phenytoin, carbamazepine Anticonvulsants/Barbiturates: primidone Antituberculars: rifampin Barbiturates: phenobarbital, butalbital Glucocorticoids: dexamethasone Herbal Supplements: St. John's wort^ Protease Inhibitors: tipranavir (alone)	Antibiotics: nafcillin Antihypertensives: bosentan Antituberculars: rifabutin CNS Stimulants: modafinil Reverse Transcriptase Inhibitors: efavirenz, etravirine, nevirapine	Anticonvulsants: oxcarbazepine, rufinamide Antidiabetics: pioglitazone CNS Stimulants: armodafinil Glucocorticoids: prednisone Herbal Supplements: echinacea^ Protease Inhibitors: amprenavir

^The effect of St. John's wort and echinacea varies widely and is preparation-dependent.

AUC: Area under the curve in a plot of concentration of drug in blood/systemic circulation versus time. AUC (from zero to infinity) represents the total drug exposure over time.
CL: Clearance

Section 8. Clinical Considerations and Safety Monitoring

This section presents information on clinical procedures and safety monitoring performed in MTN-028. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 9. Instructions for completing data collection forms associated with clinical procedures are provided in Section 12.

8.1 Baseline Medical and Menstrual History

The participants' baseline medical and menstrual history is initially collected and documented at the screening visit; and then actively reviewed and updated, as necessary, at the enrollment visit. The purpose of obtaining this information is to:

- Assess and document participant eligibility for the study

- Assess and document the participant's baseline medical and menstrual conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up (i.e. adverse event identification)

In order to obtain a complete, accurate, and relevant participant self-reported medical and menstrual history, it will be necessary to ask the participant about significant past medical conditions as well as any current conditions. It is recommended that sites use the MTN-028 Baseline Medical History Questions sheet (Word version available on the MTN-028 web page under *Study Implementation Materials*) in conjunction with the Pre-existing conditions CRF and/or chart notes to guide and document medical history taking. Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit complete and accurate information from the participant. This is especially important with regard to details about severity and frequency of pre-existing conditions.

At the enrollment visit, a participant's medical and menstrual history should be reviewed and updated as needed. Record the start and stop dates of the participant's last menstrual period in item 1 of the Pharmacokinetics Specimens—Enrollment CRF. Only record dates of menstrual period bleeding (including expected monthly bleeding on OCPs). If a participant has not had a menses in the past 30 days, mark the 'none' box.

The baseline medical and menstrual history should explore in detail any medical conditions or medications that are deemed exclusionary for this study. Refer to protocol section 5.2 and 5.3 for complete listing of study inclusion and exclusion criteria. Further guidance about select clinical eligibility criteria is as follows:

- **History of adverse reactions to any of the components of the study products:** The 3 components of the IVR are the two drugs, VCV (MK-4176) and MK-2048, and ethylene vinyl acetate (EVA) copolymer 28. Women who have a hypersensitivity/allergy to any component of the IVR should not be enrolled. For example, if a potential participant states that she has an allergy to NuvaRing (contains EVA) or Implanon/Nexplanon (contains EVA), she may have an allergy to EVA. However, EVA is generally well-tolerated.
- **Regular use and/or anticipated regular use during the period of study participation of CYP3A inducer(s) and/or inhibitor(s):** Clinical staff should review the list of prohibited CYP3A inducer(s) and/or inhibitors available in SSP section 7 with the participant.
- **Chronic and/or recurrent candidiasis**: defined as 4 or more symptomatic episodes within the past year.
- **PEP/PrEP use for HIV exposure or prevention within 6 months prior to Enrollment:** These criteria are intended to exclude participants who may be high-risk for HIV acquisition or may have an undectectable HIV infection due to PEP or PrEP use. Potential participants that have had an investigational exposure to drugs used for PrEP/PEP may be enrolled as long as other exclusion criteria do not apply (e.g. participation in other investigational studies within the past 60 days.).

8.2 Pre-existing Conditions

Details of all relevant conditions identified during the baseline medical and menstrual history taking at screening should be recorded on the Pre-Existing Conditions CRF. Relevant conditions include (but are not limited to): hospitalizations; surgeries; allergies;

conditions requiring prescription or chronic medication (lasting for more than 2 weeks); and any conditions currently experienced by the participant.

In addition to participant-reported conditions, record the following on the Pre-Existing Conditions CRF:

- Grade 1 and higher lab values
- Medically-relevant physical exam abnormalities
- Pelvic exam abnormal findings
- Any identified STIs

The clinician should record as much information as possible about the severity and frequency of any pre-existing condition in the comments field of the Pre-existing Conditions CRF to best describe the condition at the time the participant enters the study. Severity of each pre-existing condition should be assessed per the DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT). If the condition is not listed in the Female Genital Grading Table for Use in Microbicide Studies, refer to the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events (hereafter referred to as the "DAIDS Toxicity Table"). See Section 8.14 for further clarifications, guidelines, and tips for severity grading in MTN-028. The purpose of grading the pre-existing condition is to determine whether abnormal conditions, symptoms, signs and findings identified during follow-up are adverse events (AEs). By definition, pre-existing conditions are present prior to or at enrollment and are, therefore, not considered AEs. New conditions identified during follow-up that were not present at enrollment, and pre-existing conditions that increase in severity (increase to a higher grade) or frequency during follow-up, are considered AEs.

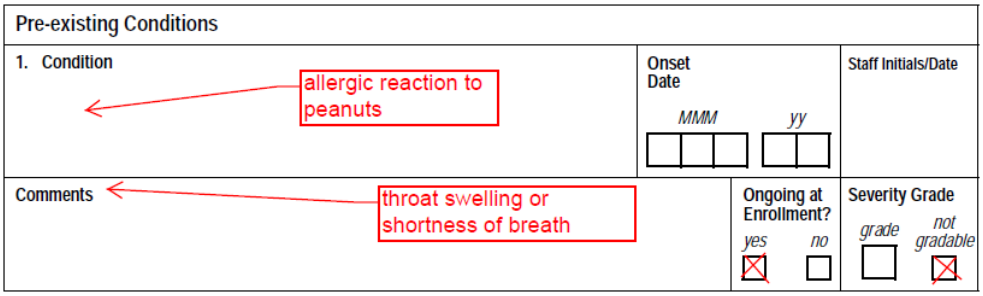
At Enrollment, each pre-existing condition entry should be reviewed, updated as needed, and have the status for 'ongoing at enrollment' indicated. Note that recurrent chronic conditions should be marked as 'ongoing' at enrollment, even if the participant is not currently experiencing an acute event (e.g. intermittent headaches). For severity grading, the highest severity experienced for the condition should be used. In the comments section, note the typical severity for outbreaks/acute episodes of the condition.

Note that any menorrhagia, metrorrhagia, or menometrorrhagia events ongoing at the time of randomization should be marked as "not gradable" on the Pre-existing log CRF. This is because the FGGT grades these bleeding events relative to each participant's baseline bleeding pattern. In the "Comments" field of the ongoing PRE entry, include text similar to what is in the FGGT row to describe the severity and frequency of the condition.

Any past resolved (not ongoing at the time of randomization) menorrhagia, metrorrhagia, or menometrorrhagia events documented on the PRE CRF should be assigned a grade from 1-4 per the FGGT.

During screening, if a volunteer reports having a history of anaphylactic reactions (such as difficulty in breathing or severe hives after eating peanuts), even it has happened once before in her lifetime, it is still important for the site clinician to document these events as pre-existing conditions on PRE-1 Log CRF. Record the condition in Item 1 as "allergic reaction to peanuts" and note types of symptoms in the comments field including severity grade (per the 'acute allergic reaction' row of the DAIDS toxicity table) when this event occurred. Please see the example below.

In this example, note that the condition is listed as "allergic reaction to peanuts" and the comments field provides a more detailed narrative of signs or symptoms that occurred, e.g. 'throat swelling or shortness of breath', and the severity grade.. At the Enrollment Visit, check 'yes' for the 'ongoing at enrollment?' box and check 'not gradable' box (as participant was not experiencing an anaphylaxis event at the time of enrollment). An AE submission for an anaphylactic reaction is required if this same event occurs after enrollment or during the study follow-up.



8.3 Follow-up Medical History

It is necessary to update the participants' medical history at all follow-up clinic visits to determine whether previously reported conditions remain ongoing and whether new symptoms, illnesses, conditions, etc. have occurred since the last medical history was performed. Any symptoms reported by the participant should be further probed and evaluated. Study clinicians should follow-up on any ongoing baseline conditions as well as any previously reported adverse events that are continuing.

Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit complete and accurate information from the participant. As an example, follow-up interim history taking could be approached as follows:

- General questions about current health and medications (e.g. How are you feeling today? Any current symptoms, or issues since your last visit? Have you been to your doctor or hospital outside the study clinic since the last time we spoke? Changes to any medications you are currently taking?)
- Targeted gynecological questions (e.g. When was your last menstrual period? Would you say this is typical for you? Have you experienced any gynecologic problems since your last visit, for example, have you been bothered by abnormal discharge, pain, or bleeding?)
- Targeted questions about ongoing pre-existing conditions and previously reported AEs (e.g. At your last visit you reported X was ongoing, how are you feeling now? You reported that you occasionally experience X, have you had any recent episodes?)

If during follow-up a baseline condition resolves or increases in severity or frequency, this update should be documented in chart notes. Such information should not be added to the Pre-Existing Conditions CRF as that form represents a snapshot of the participant's medical status at baseline. As a reminder, if a condition increases in severity or frequency, this should be reported as a new AE and documented as such (see Section 8.2).

Review of the medical history must be documented; this can be done in chart notes or in a site-specific tool if desired. If no new symptoms, illnesses, conditions etc., are reported, and if ongoing conditions remain unchanged, the participant chart should reflect this.

Note that during follow-up, sites should record the start and stop dates of the last vaginal bleeding of any type experienced in item 1 of the respective Pharmacokinetics Specimens CRF. This includes menstrual period bleeding, withdrawal bleeding, or expected breakthrough bleeding experienced while the participant is on Depo, Mirena, or other continuous contraceptive method where a women does not experience a monthly menstrual period.

All newly-identified participant-reported symptoms and conditions, that meet the definition of a reportable AE per protocol section 8, will be documented on the Adverse Experience Log (AE-1) CRF (see SSP section 8.11 for further details on AE reporting).

If during follow-up, a condition is identified as being present at baseline and the participant inadvertently did not report it in her baseline medical history, the clinician should add the newly-identified information to the Pre-existing Conditions CRF. A chart note should also be documented to explain why the newly-identified information is recorded on the Pre-existing Conditions CRF retrospectively.

8.4 Concomitant Medications

The MTN-028 protocol requires site staff to document all medications taken by study participants beginning at screening and continuing throughout the duration of the study. This includes any preventive medications and treatments (e.g., allergy shots, flu shots, and other vaccinations), prescriptions (including contraceptives), over-the-counter preparations, vitamins and nutritional supplements, medications taken for pre-exposure (PrEP) or post-exposure prophylaxis (PEP), and herbal and naturopathic preparations. If silver nitrate and/or monsel solution is used during the collection of cervical biopsies, this should be recorded on the concomitant medications log form.

It is helpful to ascertain the baseline medication information in the context of the baseline medical history. Site staff should ask open-ended questions to elicit participant report of current medications, and use the information obtained in the medical history to probe for additional medications that the participant may otherwise forget to report.

At follow-up visits, or during an interim visit, retrieve the participant's previously completed Concomitant Medications Log form, record any new medications provided to the participant by study staff, and actively ask the participant whether she is still taking all previously-recorded medications, at the same dose and frequency. Also actively ask whether the participant has taken any new medications since the last medical history was taken. Add all new information to the form in log fashion, using additional form pages as needed. To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring a list of all medications to study visits.

8.5 Prohibited Medications and Practices

Certain medications and practices are contraindicated during MTN-028 study participation because they may be harmful to the participant, impact product safety, confound adverse event determination or impact pharmacokinetic parameters. Prohibited medications and practices for MTN-028 include:

- Receptive intercourse (vaginal, anal, or oral intercourse, finger simulation and the use of sex toys) for duration of study and for 5 days preceding Enrollment, i.e., participants should be sexually abstinent.
- CYP3A inhibitors and CYP3A inducers (see SSP Section 7) with the exception of single dose fluconazole (diflucan) for the treatment of vaginal fungal infections
- Female-to-male transition medications (i.e. cross gender hormonal therapy)
- Non-study vaginal products and other devices. This includes, but is not limited to: spermicides, female condoms, diaphragms, contraceptive intravaginal rings, vaginal medications, menstrual cups, cervical caps, douches, lubricants, and sex toys (e.g., vibrators, dildos, etc.).
- Tampons during the first week of study participation (starting at the enrollment visit) and for 24 hours prior to each clinic visit following enrollment.
- Participation in other research studies involving drugs, medical devices, or vaginal products for the duration of study participation

As outlined in SSP Section 10.2.4, participants will be counseled on avoiding these medications and practices during study participation. Use of any prohibited medications will be recorded on the concomitant medications log CRF and all prohibited medications and practices should be reported to the MTN-028 Management Team. Note that use of prohibited medications will also result in a temporary product hold and the PSRT should be notified (see SSP section 8.10).

NOTE: Use of topical PrEP is not approved by the FDA as a prevention method; therefore it is not available to the general population. If a participant reports its use, the MTN-028 Management Team should be immediately consulted for further guidance as the participant may be co-enrolled in another investigational study. Furthermore, in addition to protocol outlined prohibited medications, study product should be held in response to reported use of PEP or PrEP, and the PSRT should be notified.

8.6 Physical Exam

Protocol Section 7.10 outlines the required physical exam assessments. A comprehensive physical examination is required at Screening and Enrollment. A modified/targeted physical examination (to include at a minimum assessment of general appearance, weight, and vital signs) is required at all other follow-up visits, and at interim visits if clinically indicated. Site clinicians may use their discretion to determine whether or not to conduct a more comprehensive physical exam in response to reported symptoms or illnesses present at the time of the exam.

The Physical Exam CRF will be provided to the site to document the comprehensive physical exam at the Screening and Enrollment Visits and to document the conduct of all targeted physical examinations during follow-up.

Physical exams may identify additional baseline medical information that participants inadvertently do not report in their baseline medical history. For example, the clinician may identify a skin condition during the physical exam and upon further inquiry learn that the participant has had this intermittent chronic condition since age 16. In such situations, the clinician should add the information to the Baseline Medical History Questions Sheet and the Pre-existing Conditions form as well, since the condition was present at the time of enrollment.

8.7 Pelvic Exam Overview

Pelvic exams are required at all study visits starting with the Screening visit. These exams are necessary to evaluate protocol exclusion criteria, to collect detailed information on baseline vaginal conditions, and to ensure the ongoing safety of study participants during each follow-up visit.

Pelvic exam procedures must be performed in the order shown on the Pelvic Exam checklist and from the area specified on the checklist, if specified (e.g. from the lateral vaginal wall). The order of specimen collection is critical to ensure that first specimens collected do not affect subsequent specimens. Collect specimens away from apparent abnormalities and exclude swabbed areas from subsequent examination. See SSP sections 9.7.8, 9.8.1-9.8.3, and 9.10.1 of this manual for additional details regarding vaginal and cervical samples for PK collection and analysis. The IVR should ideally remain in place during the pelvic exams. There may be instances when inserting the speculum with the ring in place causes discomfort or visually impairs the evaluation; in these instances it is acceptable for the clinician to remove the ring during exams. If applicable, IVR removal and re-insertion during pelvic examination and duration of removal should be documented on the Pelvic Exam Ring Assessment CRF.

Exams During Vagnial Bleeding: Pelvic exams should ideally not be performed if the participant is experiencing vaginal bleeding as this may interfere with visualization of the vagina and cervix, elevate the vaginal pH, affect vaginal PK samples, and complicate interpretation of wet prep findings. However, given the frequency of scheduled exams it is recognized that vaginal bleeding may coincide with some study visits. See below for special circumstances in the event a participant is experiencing her menses or any vaginal bleeding at the time of an exam:

- During screening, if the participant is experiencing any vaginal bleeding, reschedule the exam and associated sample collection to be completed within the 45 day screening window.
- At enrollment, the participant should be rescheduled if any vaginal bleeding is reported or observed on exam. Note per protocol section 7.3, menses should not coincide with a participant's Enrollment visit and ideally Days 1-7; this should be taken into consideration when scheduling enrollment. Every effort should be made to avoid scheduling these visits while particpants are on her menses; however, if Days 1-7 study visit take place while participant is on menses, all study procedures and sample collection should continue per particiapnt's conform level.
- During a scheduled follow-up visit, the pelvic exam and associated sample collection, and vaginal swabs for PK, should still be completed as long as the participant is comfortable. Notify the MTN-028 management team if vaginal bleeding coincides with Days 1-7, or if the participant declines the exam or any sample collection.

- If a participant presents for an interim visit complaining of genital symptoms, perform a pelvic exam to evaluate her symptoms at that time. If she is not comfortable with completing an exam, she should be scheduled to return for a pelvic exam as soon as possible after vaginal bleeding stops.

General Technique:

- Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to ensure participant comfort and accurate documentation of exam findings.
- Use clean hand/dirty hand technique, and/or assistants, to avoid contamination. Keep extra gloves available as two hands may be needed at different time points during the exam.
- Use a speculum of appropriate type and size to permit adequate visualization of the vagina and cervix. For most participants, a Graves speculum is preferred to enable visualization of all anatomic areas and tissues. At Screening, record the type and size of the speculum used on the Pelvic Exam Diagrams form for reference at subsequent exams. If during follow-up the speculum type and size changes, site may record the new information on the Pelvic Exam Diagram form. Prior to insertion, ensure that the speculum functions properly and has no rough edges.

8.7.1 Detailed Procedural Instructions for Pelvic Exams

Prior to the Exam: Prepare all required equipment, supplies, and paperwork; label specimen collection supplies as needed. Review documentation of prior exams and other relevant documentation from the current visit and prior visits. While the participant is clothed, explain the procedure to her and answer any questions she may have.

Position the Participant: Drape the participant and establish a comfortable examination position that allows for the perineum and vulva to be inspected. Adjust stirrups and back elevation as needed.

Examine the External Genitalia:

- Do not insert the speculum before examining the external genitalia.
- Relax the participant's knees as far apart as is comfortable for her.
- Palpate the inguinal lymph nodes to assess for enlargement and/or tenderness.
- Perform naked eye examination of the external genitalia including the perineum, and perianal area

Examine the Cervix and Vagina:

- The speculum may be lubricated with warm water if needed. No other lubricant may be used. Gently insert the speculum and open it once past the pelvic floor muscles, using gentle downward pressure, so as to avoid trauma while enabling visualization of the cervical face and upper vagina.
- If the cervix is poorly visualized, to avoid iatrogenic injury, remove the speculum and use a gloved finger (lubricated with warm water if needed) to establish the position of the cervix. Then re-insert the speculum.
- Perform naked eye exam of the cervix and vagina, noting any abnormal findings.

Removal of Visual Obstruction: After collection of vaginal and endocervical specimens, any obstruction (e.g., mucus, cellular debris) may be removed using a large saline-moistened swab (scopette) in a gentle dabbing fashion to remove the obstruction. Avoid twisting or rolling the swab over the surface of epithelium. Do not use a dry swab to remove any obstruction at any time, as this may cause trauma to the epithelium. If saline is not available, a swab moistened with water will also suffice.

Examination of the Cervix and Vagina: To complete the naked eye examination of the vagina, slowly withdraw the speculum with the blades moderately open, re-focusing as needed. Alternatively, the speculum may be rotated ninety degrees to allow visualization of the anterior and posterior vaginal walls; retract the speculum away from the cervix and close the blades to rotate.

Perform Bimanual Exam: Required at Screening and Enrollment and when clinically indicated. After completing all of the above-listed tissue examinations and specimen collection and removing the speculum, perform a bimanual exam for adnexal or fundal masses and/or tenderness.

8.7.2 Documentation of Findings

All exam findings (normal and abnormal) should be documented using the non-DataFax Pelvic Exam Diagrams CRF. All abnormal findings must be thoroughly documented (e.g., to include type, size, location, and severity) to ensure appropriate assessment can be provided during the next pelvic exam.

All abnormal findings during screening will be documented on the Pelvic Exam CRF and the Pre-existing Conditions CRF. All abnormal findings identified during follow-up will be documented on the Pelvic Exam CRF and Adverse Experience Log (AE-1) CRF, as appropriate. The results of laboratory test results performed using specimens collected during pelvic exams are recorded on the STI Test Results CRF.

All pelvic exam findings consistent with the "grade 0" column of the FGGT are considered normal. The following also are considered normal:

- anatomic variants
- gland openings
- Nabothian cysts
- mucus retention cysts
- Gartner's duct cysts
- blood vessel changes other than disruption
- skin tags
- scars
- cervical ectopy

Intrauterine contracetive device (IUCD) strings may be visible upon exam and are also considered a normal finding. If present, they should be documented on the non-DataFax Pelvic Exam Diagrams form. Sites may determine whether they choose to consistently document the presence of IUCD strings (best practice) or not. It is recommended that if a

participant has an IUCD but the string is not visible upon exam, this be documented and followed up on.

Normally-healing biopsy sites, per clinician's discretion, including blood expected from the procedure, are considered normal findings. If noted, please document as such on the non-DataFax Pelvic Exam Diagrams form and further information can be added to chart notes. If the biopsy site is not healing normally or there is more blood than expected, per clinician's discretion, the non-DataFax Pelvic Exam Diagrams form and Pelvic Exam CRF should document the abnormal finding and an AE Log CRF should be completed.

Abnormal findings will be classified according to the state of the epithelium and blood vessels associated with the finding, as follows:

Epithelium

Integrity:

- Intact
- Disrupted:
  - Superficial
  - Deep (complete disruption is considered deep and exposes stroma and possibly blood vessels; a bleeding area is often but not always deep)

Color:

- Normal
- Slightly red
- Red
- White
- Other (includes "pale")

Blood Vessels

Integrity:

- Intact
- Disrupted

Pelvic exam findings should be documented using terminology corresponding to the FGGT and the study-specific pelvic exam case report forms. For findings in which the finding term marked on the pelvic exam case report form is more specific than the corresponding term on the FGGT, use the more specific term. Figure 8-1 below provides further information to guide and standardize terminology used to describe abnormal pelvic exam findings.

Figure 8-1
CONRAD/WHO Terminology for Pelvic Exam Findings

Term	***Status of* Epithelium**	***Status of Blood Vessels***	***Comments***
Erythema	*Intact*	*Intact*	*Distinguished by color (erythema being redder than normal, edema either normal or paler than normal. May be sharp or diffuse.*
Edema	*Intact*	*Intact*	

Term	*Status of* Epithelium	*Status of Blood Vessels*	*Comments*	
Petechiae	*Intact*	*Disrupted*	*≤ 3 mm*	*Color of finding is red or purple.*
Ecchymosis	*Intact*	*Disrupted*	*> 3 mm*	
Peeling	*Disrupted, superficial*	*Intact*	*Fragment of disrupted epithelium may remain attached to the area from which it has peeled off. Generally has well demarcated outline. Underlying epithelium looks normal*	
Ulcer	*Disrupted, superficial or deep*	*Intact or disrupted*	*May include sloughing at base. Generally round or oval with sharply demarcated outline. Superficial ulcers are more accurately called erosions.*	
Abrasion	*Disrupted, superficial or deep*	*Intact or disrupted*	*Distinguished from other findings in this class by diffuse or poorly demarcated outline.*	
Laceration	*Disrupted, superficial or deep*	*Intact or disrupted*	*Sharply demarcated linear finding. Includes fissures. Lacerations appear to be the result of trauma. Fissures appear to be linear "pulling apart" or wearing away of tissue.*	

Note: Superficial epithelial disruption does not penetrate into subepithelial tissue. Deep epithelial disruption penetrates into and exposes the subepithelial tissue and possibly blood vessels. If bleeding from the finding is present, the disruption is often but not always deep.

8.9 STI/RTI/UTI Evaluation, Management and Treatment

Clinical and laboratory evaluations are performed in MTN-028 to diagnose the following STIs and RTIs:

- Chlamydia infection
- Gonorrhea infection
- Syphilis infection
- Trichomoniasis
- Bacterial vaginosis (BV) (if indicated)
- Candidiasis (if indicated)

Infections should be considered "symptomatic" when a participant self-reports or complains of symptoms associated with the infection. Symptoms should not be confused with "signs" of infection that may be observed during clinical examinations performed by study staff.

Urinary tract infections (UTIs): Suspected UTIs may be clinically managed based solely on the presence of symptoms indicative of a possible UTI, including the following:

- Frequent urge to urinate
- Passage of only a small volume of urine
- Pain and burning during urination
- Lower abdominal pain and/or uncomfortable pressure above the pubic bone
- Milky/cloudy, reddish, or bloody urine

Urine dipstick may be performed per site SOP, but sites are expected to send a urine culture for definitive diagnosis when a UTI is suspected. The results of the urine culture do not need to be returned before presumptive treatment, but the results of the culture will influence how the AE is captured. When the participant initially reports symptoms suggestive of a urinary tract infection, capture each symptom as a separate AE. If urine culture results are positive, update the AE CRFs to reflect a single AE for grade 2 Urinary Tract Infection per UTI criteria defined in the FGGT. If urine culture is negative, the AE (s) will remain reported as symptoms only. Record the results of any dipsticks performed on the Safety Laboratory Results CRF; urine culture results must be documented in chart notes and/or other site-specific source documents.

Note that urine dipstick testing is required at screening and Day 28/Visit 9.0. Document results (protein, glucose, LE, and nitrites) on the Safety Laboratory Results CRF. At the screening visit, positive dipstick results do not directly impact eligibility, but abnormal protein and glucose parameters should prompt further evaluation or consideration pending IoR review. Abnormal protein and glucose uncovered at the screening visit should be captured on the Pre-Existing Log CRF. In follow-up, findings of abnormal protein and glucose on the dipstick should be reported on the AE log CRF as indicated. Grade the severity of the urine glucose value according to the "Proteinuria, random collection" row of the Toxicity Table. Note that findings of LE/nitrites are not gradable per the DAIDs toxicity table, and like other non-gradable labs should not be reported as pre-existing conditions or AEs.

STI/RTIs will be treated in accordance with current CDC guidelines available here: http://www.cdc.gov/std/treatment/ and site SOPs.

When clinically appropriate, investigators should use oral or parenteral medications when at all possible to avoid intravaginal medication use. Observed single dose treatment should be provided whenever possible, per clinician discretion.

8.10 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for product hold and discontinuation (Section 9.3), guidance on product hold and discontinuation in response to observed AEs (Section 9.4), management of other clinical events (Sections 9.5), HIV infection (Sections 9.6), pregnancies (Section 9.7), and early study termination (Section 9.8).

All specifications of protocol Sections 6 and 9 must be followed; IoRs are encouraged to consult the PSRT with any questions related to proper interpretation of the protocol and proper management of study product use in particular. Conditions requiring product hold or permanent discontinuation are summarized in Figure 8-1 below. Flow charts for product

use management are available in the study implementation materials section of the MTN-028 webpage.

The protocol specifies that a hold should be initiated should a participant report prohibited medication use. When possible, treatment options that are not prohibited by the protocol should be pursued; however, clinical management of the participant should be prioritized if alternative treatment is not available. Product use may be resumed when use of the prohibited medication has ended. Consult the PSRT regarding the timeframe for product resumption in the event that a single dose prohibited medication is used. Note that in addition to protocol outlined prohibited medications, study product should be held in response to reported use of PEP or PrEP, and the PSRT should be notified.

Note that per protocol, product should be temporarily held in response to grade 3 unrelated AEs and the PSRT should be notified. Sites are encouraged to request a quick response in the body of the email in these cases, to minimize potential unnecessary time off product.

All clinical and product use management must be fully documented in participant study records. When the PSRT is consulted in relation to clinical and product use management, completed PSRT query forms (including a response from the PSRT) must be printed and filed in participant study records. Unless otherwise specified in protocol section 9, the IoR/designee should immediately consult the PSRT for any product holds, for further guidance on resuming study product, continuing the hold temporarily, or progressing to permanent discontinuation of study product. Product holds and discontinuations must be communicated to site pharmacy staff using the Vaginal Ring Request Slip, as described in Section 7 of this manual. Product holds and discontinuations also must be documented on Product Hold/Discontinuation CRFs.

Following temporary holds or permanent discontinuation from study product, some study procedures will be modified or discontinued. See SSP sections 4.5.5 to 4.5.9 for details.

Figure 8-1
Conditions Requiring Product Hold or Permanent Discontinuation

Condition	Temporary Hold	Permanent Discontinuation
Report of use of prohibited medications and medications to be avoided (including the use of PEP/PrEP) as described in protocol Section 6.6	X	
Unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee.	X*	
Exposure to or acquisition of HIV infection		X
Pregnancy		X
Breastfeeding		X
Grade 3 AE **unrelated** to Study Product not addressed in Section 9.5	X	
Grade 3 AE **related** to Study Product not addressed in Section 9.5		X
Grade 4 AE not addressed in Section 9.5 (regardless of relationship)		X

Condition	Temporary Hold	Permanent Discontinuation
Superficial epithelial disruption (abrasion/peeling) **which has worsened** after re-evaluation in 3-5 days	X	
Deep epithelial disruption (ulceration)	X	
Symptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) **which has worsened** after re-evaluation in 3-5 days	X	
Asymptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) **which has worsened** after re-evaluation at the next scheduled visit	X	
Generalized erythema or severe edema (area >50% of vulvar surface or combined vaginal and cervical surface)	X	
Unexpected genital bleeding **due to deep epithelial disruption**	X	
Vaginal ring has been out for **longer than three consecutive days**		X
Particiapnt has missed **more than three consecutive study visits**		X

See Protocol Section 9 for complete guidelines on clinical management and study product holds.
**After consultation with PSRT, participants may progress to permanent discontinuation from study product.*

8.11 Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-028. Please also refer to Section 8 of the MTN-028 Protocol and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004, (Clarification dated August 2009) (DAIDs Toxicity Table)
- Addendum 1, Female Genital Grading Table for Use in Microbicide Studies dated December 2004 (FGGT)
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, January 2010
- DAERS Reference Guide for Site Reporters and Study Physicians
- Investigators Brochure for VCV (MK-4176) IVR and MK-2048A IVR

8.11.1 Adverse Events

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines an adverse event (AE) as any untoward medical occurrence in a clinical research participant administered an investigational product and that does not necessarily have a causal relationship with the investigational product. As such, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

For MTN-028, the ICH-E6 definition is applied to all participants in all study groups, beginning at the time a participant is randomized through when they terminate from the study. Study staff must document <u>all</u> AEs reported by or observed in study participants,

regardless of severity and presumed relationship to study product on Adverse Experience Log (AE-1) case report forms (CRF).

Ongoing medical conditions, problems, signs, symptoms, and findings identified prior to random assignment are considered pre-existing conditions. Such conditions should be documented on the Pre-Existing Conditions case report form. If a pre-existing condition worsens (increases in severity or frequency) after randomization, the worsened condition is considered an AE. If a pre-existing condition resolves after randomization, but then recurs at a later date, the recurrence is considered an AE.

Each site's SOP for source documentation should define the extent to which the AE Log CRF will be used as a source document. Site-specific delegation of duties documentation should designate study staff authorized by the Investigator of Record (IoR) to complete AE Log forms. Regardless of who initially completes these forms, a clinician listed on the site's FDA Form 1572 should review them to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

8.11.2 Serious Adverse Events (SAEs) / Expedited Adverse Events (EAEs)

ICH-E6 defines a serious adverse event (SAE) as any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

  NOTE: *The term "life threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. A grade 4 severity grading on the Toxicity Table does not necessarily mean that an event is life-threatening. For example, when determining whether a grade 4 laboratory event meets the ICH definition of "life threatening", consider the event in the context of any related symptoms the participant may have experienced.*
- Requires in-patient hospitalization or prolongs an existing hospitalization,

  The following types of hospitalizations are not considered Adverse Events, serious or otherwise:
  - *Any admission unrelated to an AE (e.g., for labor/delivery)*
    Admission for diagnosis or therapy of a condition that existed before randomization AND has not increased in severity or frequency since baseline.
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above

ICH guidance (E2A) also states that medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious.

SAEs are a subset of all AEs. For each AE identified in MTN-028, an authorized study clinician must determine whether the AE meets the definition of SAE. The Adverse Experience Log CRF includes an item (item 8) to record this determination.

All AEs that meet the definition of "serious" (SAEs), regardless of relationship to study product, are expedited adverse events (EAE). EAEs require additional reporting for rapid review and assessment by DAIDS.

8.11.3 Reporting Adverse Events in an Expedited Manner (EAE Reporting)

Expedited Adverse Events (EAEs) should be reported per the Manual for Expedited Reporting of Adverse Events to DAIDS, version 2.0; January 2010. For MTN-028, the "SAE (Serious Adverse Event) Reporting Category" will be used to report EAEs.

All EAEs must be reported to the DAIDS Regulatory Support Center (RSC) using the internet-based DAIDS Adverse Experience Reporting System (DAERS). All EAEs must be reported within three reporting days of site awareness of the EAE.
All EAEs must also be reported on the AE Log CRF. The AE Log case report form includes an item to record if the AE is also being reported as an EAE. When completing AE Log CRF and DAERS report or EAE form, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness and consistency. All AE descriptions and details (e.g., onset date, severity grade, relationship to study product) must be recorded consistently across all documents. All EAEs submitted to the DAIDS Safety Office will be compared with AE Log CRFs received at the MTN SDMC to ensure that all reports that should have been received by both DAIDS Safety Office and the SDMC have been received and that the details recorded on each form are consistent. If an EAE that was previously reported to the DAIDS RSC resolves and then later recurs at a level requiring expedited reporting, the second occurrence must be reported as a new EAE report (and a new AE-1 CRF, if not already completed).

8.12 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in MTN-028. The guidance below should be followed when assigning AE terms/descriptions:

- Whenever possible, a diagnosis should be assigned. Document associated signs and/or symptoms related to a diagnosis in the comments section of the AE Log CRF.
- When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, each individual sign and symptom must be identified and documented as an individual AE.
- Whenever possible, use specific terms to indicate the anatomical location of the AE (e.g., "vaginal" instead of "genital" or "uterine cervix" instead of "cervical").
- Use medical terms (e.g. "ulcers" instead of "sores")
- Ensure correct spelling
- Do no use abbreviations, unless the abbreviations are for accepted laboratory findings (e.g. "AST increased", "SGOT decreased")

Procedures per se should not be reported as adverse events; rather the underlying condition which leads to a procedure may be considered an adverse event. Any associated procedures may be considered treatments for the adverse event. For example, while "appendectomy" would not be considered an adverse event, "appendicitis" would, with "appendectomy" documented as a treatment provided for the adverse event. In addition, any event that occurs as a result of a study-related procedure should be recorded as an AE. Specify in AE text description (item 1) if the AE is related to a procedure (iatrogenic). For example, if a participant experiences cervical bleeding that is more than expected as a result of the

cervical biopsy, then "cervical bleeding due to cervical biopsy" should be submitted as an AE. "Cervical bleeding" maps to "Reproductive system and breast disorders" System/Organ Class (SOC) whereas "Cervical bleeding due to biopsy" maps to "Injury, Poisoning, and Procedural Complication" SOC.

Do not include information on relatedness to study product or timing of study product use in the AE term/description if the AE is **not** due to the act of study ring insertion or removal. Limit the AE text to the medical description and anatomical location, when needed. Including text such as "after ring insertion" or "at site of ring placement" affects the way the AE will appear in safety reports.

When reporting AEs which are due to ring removal or insertion, please follow the guidance below:

- If the AE is **due to the act** of study ring insertion or removal, include this information in item 1. For example, use AE text of "pelvic pain due to ring removal" or "vulvar laceration due to ring insertion" rather than just "pelvic pain" or "vulvar laceration."

  It is important to clearly identify in item 1 AEs that are **due to the act** of study ring insertion or removal, as these AEs are assigned unique coding terms within the standardized MedDRA coding system.

  If the AE is **not due to the act** of study ring insertion or removal, do not include mention of the ring in item 1 or in the Comments section of the AE log CRF when providing rationale for relationship to study product.

- If text is present in the "Comments" field that the AE is due to the act of ring insertion or removal, this same text needs to be in item 1. If not, this may result in a Clinical Query asking that this information be added to item 1 so that the AE is described completely and accurately.

When reporting an AE that is associated with an underlying condition, include the underlying condition in the AE term or description. For example, if a participant is experiencing pain related to an underlying cancer diagnosis, include the cancer diagnosis in the AE term or description.

8.12.1 Reporting Genital, Genitourinary, and Reproductive System AEs

- Vaginal Discharge: Vaginal discharge by participant report and vaginal discharge as observed by the clinician should be graded per the appropriate rows in the FGGT. The verbatim term from the FGGT should be used to distinguish if vaginal discharge was clinician observed versus participant reported.

** Note – if vaginal discharge is present both by history and on examination, only report the one with the most severe grade. (Grade 3 and 4 vaginal discharge is listed as "NA" in the FGGT.) If they are the same grade, report 'vaginal discharge by participant report' as the AE term.

Vaginal bleeding: For MTN-028, the following types of genital bleeding events are reportable as adverse events on an AE Log CRF:

- each new instance of heavy or prolonged menstrual bleeding, intermittent vaginal bleeding, or unexplained infrequent vaginal bleeding (as compared to the participant's baseline), unless judged to be related to a participant's contraceptive use
- postcoital bleeding (bleeding associated with sexual intercourse) if not present at baseline

New events of infrequent bleeding during follow-up for unknown reasons or delay of menses for more than one month should be documented on an AE Log CRF using the appropriate term below:

- For missed menses events of 1-3 months in duration, use the term "missed menses"
- For missed menses events of 4-5 months in duration, use the term "oligomenorrhea"
- For missed menses events of 6 months or longer, use the term "amenorrhea"

If the newly-identified bleeding episode is determined to be different from her baseline (i.e. longer, heavier, more/less frequent) and not related to her current contraceptive method, record the episode on an Adverse Experience Log CRF. Grade and term the episode per the applicable "Abnormal Uterine Bleeding Unrelated to Pregnancy" or the "Unexplained Infrequent Bleeding" row of the DAIDS Female Genital Grading Table (menorrhagia, metrorrhagia, or postcoital bleeding). Note that *shorter* than baseline menses is not included in the FGGT, and should not be considered an adverse event.

Note that IVR use can continue in the presence of unexplained genital bleeding per the clinician's discretion, but ongoing events should be further investigated by a pelvic exam. If evaluation determines bleeding is due to deep epithelial disruption, the IVR should be held per protocol section 9.5.

When reporting genital bleeding events, reference should be made to the points below, which standardize the terminology that should be used when reporting AEs involving genital bleeding.

- Bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the IoR or designee is not considered to be an AE. For example, Monsel's discharge and/or minimal bleeding related to specimen collection should not be considered an AE. If the bleeding exceeds the amount considered normal by the clinician, it should be considered an AE and should be documented and reported if applicable using the term cervical friability. The severity of cervical friability should be graded per the cervical edema and friability row of the DAIDS Female Genital Grading Table.

- If both Menorrhagia and Metrorrhagia are present, a single adverse event should be reported as "Menometrorrhagia" and graded per the Menorrhagia row of the FGGT.

- Bleeding that is associated with an observed abnormal pelvic exam finding should be considered an AE and should be documented and reported if applicable using the term associated with the exam finding, with the anatomical location noted. For example, if a vaginal laceration is observed on exam, with blood emanating from the finding, the term vaginal laceration should be used to document the AE. The fact that blood or bleeding was present should be documented on the Pelvic Exam Diagrams form and the pelvic exam case report form, and may also be noted in the

comments section of the Adverse Experience Log CRF, but the term metrorrhagia should not be used to document the AE.

- Non-menstrual bleeding that is not associated with an observed pelvic exam finding, i.e., for which no source of blood or bleeding is observed on exam, should be considered an AE and should be documented and reported if applicable using the term metrorrhagia. This term refers to bleeding of variable amounts occurring between regular menstrual periods and should be used to report non-menstrual bleeding such as spotting between menses, ovulation bleeding, and breakthrough bleeding. This term should also be used to report blood-tinged discharge and blood observed in the vagina with no identified source.

- If a participant reports genital bleeding after sexual intercourse, this event should be recorded as "postcoital bleeding" and graded per the "Postcoital Bleeding" row of the DAIDS Female Genital Grading Table.

STI/RTI

The following terminology should be used only if STI diagnosis is based on clinical evaluation and confirmed, when appropriate/possible, by laboratory result(s). For example, symptomatic bacterial vaginosis and symptomatic vulvovaginal candidiasis should not be reported as AEs based on participant symptoms alone.

- Bacterial vaginosis: Only report symptomatic infections that are confirmed with saline wet mount testing and fulfilling Amsel's criteria (see section 9.7.2 of this manual for definition of criteria) as AEs, using the term "symptomatic bacterial vaginosis."

- Candidiasis: Only report symptomatic infections that are confirmed with KOH wet prep and/or culture as AEs, using the term "vulvovaginal candidiasis."

- Chlamydia: Report all infections using the term "genitourinary chlamydia infection."

- Gonorrhea: Report all infections using the term "genitourinary gonorrhea infection."

- Suspected genital herpes outbreaks: Because herpes testing is not required in MTN-028, each suspected genital herpes outbreak should be reported using the term marked on the Pelvic Exam CRF describing the lesion together with the anatomical location (e.g., vulvar ulceration, vaginal blister).

- Genital herpes:Use the criterion for diagnosing genital herpes per the FGGT. Note that laboratory testing is required in order to use the term "genital herpes" for AE reporting. Such testing is not required per protocol and should only be done if clinically indicated. Any new lesion/ulcer observed during the study should be reported as an AE even if it thought to be due to prior herpes diagnosis/infection.

- Genital warts: Report all outbreaks of genital warts as AEs, regardless of whether infection with HPV was known to be pre-existing before enrollment/randomization. Report the AE using the term "condyloma" and include the anatomical location of the

warts (e.g., cervical, vaginal, vulvar, perianal). Grade according to the "Condyloma" row of the FGGT.

- Syphilis: Per the FGGT, a Grade 2 Syphilis adverse event is defined as a positive treponemal test along with a positive non-treponemal test and no previous treatment OR a four- fold rise in titer on the non-treponemal test after previous treatment regardless of symptoms or non-oral lesions positive by darkfield exam for treponemes. Report all syphilis adverse events, using the term "syphilis infection" (no anatomical location is required when reporting syphilis infections). Contact the MTN-028 PSRT in the event a participant has a positive treponemal test and a negative non-treponemal test as this could represent late latent syphilis.

- Trichomoniasis: Report only Grade 2 infections per FGGT, using the term "vaginal trichomoniasis". Trichomoniasis may be diagnosed by positive wet mount, culture, PCR, rapid Trichomoniasis or other licensed test (excluding Pap smear), showing T. vaginalis, regardless of symptoms.

In the absence of a laboratory-confirmed STI or RTI diagnosis, use the term "vulvovaginitis" when 2 or more of the genital/vaginal signs or symptoms listed below are present. Comment on the individual signs/symptoms in the "Comments" field of the AE Log CRF.

- pain
- itching
- erythema
- edema
- rash
- tenderness
- discharge

Similarly, use the term "cervicitis" when 2 or more of the genital/vaginal signs or symptoms listed below are present in the absence of a laboratory-confirmed STI/RTI. Comment on the individual signs/symptoms in the "Comments" field of the AE Log CRF.

- dyspareunia
- erythema
- edema
- tenderness
- discharge

8.12.2 Reporting Abdominal Pain as an AE

When reporting abdominal pain as an AE, pain that is gastrointestinal in nature must be differentiated from pain that is genitourinary or reproductive in nature.

If abdominal pain is assessed as gastrointestinal in nature and no other overarching or unifying diagnosis is available, the term "abdominal pain" or "lower abdominal pain" should be used on item #1 on the AE Log CRF.

If the pain is assessed as genitourinary and a specific anatomic location is known, the term reported on the AE Log CRF should be described as such (i.e., "bladder pain" or "adnexal tenderness").

If the pain cannot be localized to a specific organ but it believed to be gynecologic in origin it should be described on the AE Log CRF using the term "pelvic pain"

8.12.3 Reporting Laboratory Abnormalities as AEs

If an abnormal laboratory test result is reported as an AE, separate from any clinical diagnosis associated with the result, the type of test performed and the direction of the abnormality should be reported (e.g. elevated ALT). The specific value or the severity grade of the result should not be reported as part of the AE term. Laboratory values that fall outside of a site's normal range but are below severity grade 1 are not considered AEs. These out of range but below grade 1 values are not documented as pre-existing conditions or adverse events on the PRE-1 CRFs unless requested by the Investigator of Record (IoR) or designee. When assigning severity grades, note that some sites may have normal reference ranges that overlap with the severity grade ranges. Thus, it is possible for a participant to have a result that falls within the site's normal range, but is still gradable per the Toxicity Table. Assign the severity grade based on the Toxicity Table severity grade ranges, regardless of whether or not the lab result falls within the site's normal reference range.

The IoR or designee should carefully review all laboratory abnormalities relevant to the participant's health to identify any adverse events or health problems. Documentation of this review is required by initialing and dating each page of lab results. The severity of all lab abnormalities will be graded and recorded in the source documentation. Results of protocol-specified local laboratory results will also be reported on the Laboratory Result DataFax CRF. Sites should document other results if any, in visit chart note, or in other designated site-specific documents. Through the participant's study involvement, lab abnormalities that meet the criteria for expedited reporting to DAIDS will be reported separately on the AE Log CRF and reported to DAIDS via the DAERS Reporting System.

8.12.4 HIV and AE Reporting

HIV infection is not included in the DAIDS Toxicity Table, and is not considered an AE for data collection or reporting purposes. Thus, if a participant seroconverts during study participation, HIV infection should not be reported as an AE or written anywhere on an AE Log CRF.

However, primary HIV infection is often symptomatic. If a participant seroconverts and develops one or more signs or symptoms of acute HIV-infection, it is appropriate to report each sign and symptom (e.g. fatigue, pharyngitis) as a separate AE on its own AE log CRF. If item 5 is marked 'not related', record 'due to alternative etiology' as the rationale in the Comments section of the AE log CRF. Do not write "HIV" or "HIV infection" anywhere on the AE Log CRF.

8.13 Adverse Event Severity Grading

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in MTN-028 must be graded on a five-point scale:

- Grade 1 = Mild
- Grade 2 = Moderate

- Grade 3 = Severe
- Grade 4 = Potentially life-threatening
- Grade 5 = Death

Severity is not the same as seriousness, which is based on the outcome or action associated with an event, as described in Section 8.1.3.

The severity of all AEs identified in MTN-028 will be graded using:

- DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT)
- If not identified there, the DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table), dated December 2004 (Clarification dated August 2009) will be utilized.

The DAIDS Toxicity Tables can be accessed on the DAIDS RSC web site (http://rsc.tech-res.com/safetyandpharmacovigilance/).

AEs listed in both the FGGT and the Toxicity Table should be graded according to the FGGT. AEs not listed in the FGGT should be graded according to the Toxicity Table. AEs not listed in the FGGT or the Toxicity Table should be graded according to the "estimating severity grade" row of the Toxicity Table.

Further clarifications, guidelines, and tips for grading the severity of AEs are as follows:

- Genital petechiae and genital ecchymosis should be considered Grade 1 as neither requires treatment.
- If the severity of an AE falls into more than one grading category on the Toxicity Table, assign the higher of the two grades to the AE.
- If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, and the diagnosis is not specifically listed in the Toxicity Table, assign the AE the highest severity grade among each of the associated signs and symptoms. Record the diagnosis as the AE term and record each associated sign and symptom in the AE Log comments section.
- Seasonal allergies should be graded according to the "Estimating Severity Grade" row of the Toxicity Table (not the "acute systemic allergic reaction" row).
- When grading using the "general infection" row of the Toxicity Table, note that if the condition requires systemic antimicrobial treatment, it must automatically be graded at Grade 2 or higher.
- When the participant initially reports symptoms suggestive of a urinary tract infection, capture each symptom as a separate AE. Once the culture results are available, update the AE CRFs to reflect a single AE for 'Urinary Tract infection' if the laboratory evaluation meets UTI criteria defined in the FGGT.
- Grade the severity of the urine glucose value according to the "Proteinuria, random collection" row of the Toxicity Table.
- It is preferable that abnormal Pap smear findings are reported and graded based on results of a biopsy, using the "Intraepithelial Neoplasia by biopsy" row of the FGGT (below). However, if further evaluation of the Pap smear finding is not performed, or is scheduled to be performed at a later date, then abnormal Pap smear findings that represent an increase in severity should be reported as AEs and graded according to the "Pap" row of the FGGT (see below).

Note: Atypical glandular cells (AGC) and AGC-favor neoplastic are not specifically mentioned in the "Pap" row, but should be assigned severity grades 1 and 2, respectively.

If a biopsy is performed at a later date, update the AE-1 CRF to indicate the results of the biopsy (item 1 - AE Diagnosis) and update the severity grade (item 3), as appropriate, per the "Intraepithelial Neoplasia by biopsy" row of the FGGT.

8.14 Adverse Event Relationship Assessment

One of the following relationship categories must be assigned to each AE:

- Related: There is a reasonable possibility that the AE may be related to the study product.
- Not related: There is not a reasonable possibility that the AE is related to the study product.

When assessing relationship, the study products that should be considered are the two study drugs and the vaginal ring. Any AEs thought to be related to the vaginal ring should be documented as such by choosing "related" and using descriptive text, to indicate that the presumed relationship is with the ring. For example, if the ring stretched the vaginal introitus in the process of insertion and caused a laceration, then the AE should be assessed related to study product and reported as such. However, if the AE cannot be directly attributable to the ring (e.g. fingernail scratch during ring insertion) the AE should be assessed not related to the study product.

Please note that when no other etiology for the event is apparent, the relationship does not automatically default to "related". There must be at least a reasonable possibility of a causal relationship.

Study staff should provide a reason for their determination of the relationship of the AE to the study product in the "Comments" section of the AE Log CRF. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required. When recording an AE that is the result of a study-related procedure, mark the "Relationship to study product" as "Not Related" and provide an explanation in the "Comments" section that the event is a 'result of a study-related procedure'.

8.15 Adverse Event Outcomes and Follow-Up Information: During Study Participation

All AEs identified in MTN-028 must be followed clinically at each scheduled visit until they resolve (return to baseline) or stabilize (persist at the same severity grade above baseline for 1 month).

At each follow-up visit, an authorized study clinician should review all previously identified ongoing AEs and evaluate and document its current status. Outcomes must also be reported on the AE Log case report form. In many cases, the final outcome of an AE will not be available when the AE Log CRF is first completed and faxed to DataFax. In such cases, the form should be updated when the final outcome becomes available and re-faxed to DataFax at that time.

As noted above, "resolution" of an AE is generally defined as returning to the condition or severity grade that was present at baseline (i.e. at the time of randomization) and

"stabilize" is defined as persistence at a certain severity grade (above baseline) for one month. For clinical events that are AEs, clinical management and follow-up of the AE should proceed per the specifications of section 9 of the protocol. If, however, a clinical AE is not addressed in section 9 of the protocol, at a minimum, follow-up evaluations should be performed at scheduled study visits until resolution or stabilization has been documented. More frequent evaluations may be performed at any time if required to properly monitor and/or manage participant safety, at the discretion of the IoR or designee. It is acceptable for AE follow-up/evaluation to be conducted over the phone, as clinically appropriate.

If an AE increases in severity or frequency (worsens) after it has been reported on an AE Log CRF, it must be reported as a new AE, at the increased severity or frequency, on a new AE Log CRF. In this case, the outcome of the first AE will be documented as "severity/frequency increased" and the new AE page number should be recorded. The outcome date of the first AE and the onset date of the new (worsened) AE will both be the date upon which the severity or frequency increased.

8.16 Adverse Event Outcomes and Follow-Up Information: After Study Termination

All AE Log forms completed for each participant should be reviewed at the Day 35 Final Clinic Visit/Termination visit to confirm they were evaluated by qualified and designated staff, and that the relationship status, AE grade, and outcome are accurately documented in the participant record. For AEs that are ongoing at the termination visit, the status/outcome of the AE should be updated to "continuing at end of study participation" and the AE Log CRF should be re-faxed to DataFax.

A subset of AEs must be followed after a participant's termination visit. AEs that require reassessment after the participant's termination visit include the following:

- AEs that are found to have increased in severity at the termination visit
- AEs deemed related to study product
- All Grade 3 or higher AEs that are ongoing at the termination visit
- SAEs/EAEs

The IoR or designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the AE must be re-assessed by study staff within 30 days after the termination visit; additional evaluations also may take place at the discretion of the IoR or designee.

For AEs that are continuing at the termination visit but do not meet the criteria above, it is left to the discretion of the IoR or designee as to whether the AE needs to be followed. Sites may notify the Protocol Safety Physicians (mtn028safetymd@mtnstopshiv.org) team for guidance in such situations. The requirements for submission of follow-up information on EAEs are specified in Section 4.3 of the *Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0 dated January 2010).*

If not resolved or stabilized at the time of reassessment, additional assessments should occur at the following frequency:

- If the study is ongoing, continue to reassess at least once per month while the study is ongoing until resolution/stabilization
- If the entire study has ended (not only participant participation), all AEs requiring re-assessment will be re-assessed at least once within 30-60 days after the study end date. The site is to send an informational query regarding the case to the PSRT at the

time of reassessment. The MTN-028 PSRT also may advise on whether any additional follow-up is indicated on a case by case basis.

For AEs that are re-assessed after the termination visit, information on the status of the AE at the time of re-assessment will be recorded in chart notes, and may be communicated to the PSRT, if applicable; however, no updates should be made to any case report forms based on the re-assessments.

8.16.1 Reporting Recurrent Adverse Events

If an AE previously reported on an AE CRF resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new AE CRF.

8.17 Social Harms

In addition to medical AEs, participants may experience social harms — non-medical adverse consequences — as a result of their participation in the study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends. They also could experience stigma or discrimination from family members and members of their community.

In the event that any social harms occur, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section. Social harms will also be reported on a Social Impact log CRF. The IoR will report any social harm, in his/her judgment, to be serious or unexpected to the PSRT and IRB according to local requirements. For example, social harms that result in serious adverse events (SAEs) should be considered 'serious or unexpected'. Social harms that are not SAEs may also be considered serious or unexpected, for example serious threats of physical harm, significant psychological duress, or discontinued provision of food, housing or financial support. Determination of whether a social harm is serious or unexpected is ultimately based on the discretion of the investigator; the MTN-028 PSRT can always be consulted as needed. Study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm.

Prior to study initiation, study staff teams at each site should discuss as a group what issues and problems are most likely to be encountered by participants at their site, and should agree upon how these issues and problems should be handled if reported. Roles and responsibilities should be defined for all staff members, such that each staff member is aware of what actions he/she can appropriately take, and what actions should be referred to other members of the team.

During study implementation, staff teams at each site should continue to discuss actual participant experiences, successful and unsuccessful response strategies, and other lessons learned among themselves and with community representatives. Based on these discussions and lessons learned, procedures for responding to issues and problems should be reassessed and updated as needed throughout the study.

The following are suggested strategies for responding to social harms that may be adapted and tailored to best meet participant needs at each site:

- When first responding to an issue or problem, actively listen to the participant's description of the problem and ask questions to elicit as much detail as possible about the problem, including the participant's perception of the severity of the problem. Record all pertinent details in signed and dated chart notes.
- Ask the participant to articulate her thoughts on what can/should be done to address the problem, including what she would like study staff to do in response to the problem (if anything).
- Discuss with the participant any additional or alternative strategies that you might suggest to address the problem and collaborate with her to develop a plan to try to address the problem. Document the plan in signed and dated chart notes.
- Take all possible action to try to address the problem, per the plan agreed upon with the participant. Document all action taken, and outcomes thereof, in signed and dated chart notes.

- As with medical AEs, follow all problems to resolution or return to baseline.
- Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.
- If the reported social harm is associated with an AE, report the AE on an AE Log CRF. If the social harm is associated with an AE that meets criteria for expedited reporting to the DAIDS RSC, report it as an EAE. Also report the issue or problem to all IRBs/ECs responsible for oversight of MTN-028, if required per IRB/EC guidelines.
- Consult the Protocol Safety Review Team (PSRT) for further input and guidance as needed. As is the case with medical AEs, data collected on social harms will be monitored by the PSRT.

8.18 Safety Distributions from DAIDS

Study sites may receive product- and safety-related information throughout the period of study implementation. This information will be distributed by DAIDS, through its RSC and/or the MTN Coordinating and Operations Center, and may include:

- Updated Investigators Brochures
- IND Safety Reports
- Other safety memoranda and updates

Each distribution will include a cover memo providing instructions on how the document is to be handled. In all cases, a copy of the distribution must be filed in on-site essential document files. Also in all cases, study staff responsible for clinical oversight of study participants should be made aware of any newly available safety information. In many cases, the distribution will need to be submitted to site IRBs/ECs. Safety distributions do not require IRB/EC approval; however acknowledgement of receipt is desirable. Submission letters/memos for IRB/EC submissions should specify the name and date of all documents submitted.

8.19 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-028 protocol for a complete description of the participant safety monitoring procedures in place for MTN-028. Section 14 of this manual is a reference for a description of the reports prepared by the MTN SDMC in support of MTN-028 safety monitoring procedures.

Participant safety is of the utmost importance in MTN-028. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study staff, under the direction of the IoR. The IoR and designated study staff also are responsible for submitting case report forms to the MTN SDMC and EAE reports to the DAIDSsuch that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- Clinical Affairs staff at the MTN SDMC will review clinic and laboratory data received at the SDMC and apply clinical data quality control notes (queries) to data requiring confirmation, clarification, or further follow-up by site staff. These queries will be issued to site staff for resolution on an ongoing basis throughout the period of

study implementation. In addition, Protocol Safety Physicians may contact site staff directly, if needed, for additional clarification of safety data.

- The DAIDS RSC, DAIDS RAB Safety Specialist, and DAIDS PSB Medical Officers will review all EAE Forms received for MTN-028 and follow up on these reports with site staff, the MTN-028 Protocol Team, and drug regulatory authorities when indicated.

- The Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared by the SDMC for the study. The PSRT will meet monthly conference call to discuss cumulative study safety data and any potential safety concerns.

- The MTN Study Monitoring Committee (SMC) also will conduct interim reviews of study progress, including rates of participant accrual and retention, completion of study endpoint assessments, study or lab issues, and in a closed report, safety data by arm of the study. While site staff are not typically involved in these reviews, site staff should be aware that the SMC may make recommendations to DAIDS and/or the MTN leadership that could affect the study and sites in significant ways. These decisions are based on a detailed review of the available study data and careful consideration of ongoing participant safety.

Section Appendix 8-1
MTN-028 Protocol Safety Review Team Plan

Roles and Responsibilities of the PSRT

The roles and responsibilities of the MTN-028 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports. Once the SDMC begins receiving follow-up safety data, the PSRT will convene via regularly scheduled monthly conference calls. The frequency of calls may be adjusted throughout the period of study implementation as agreed upon by the PSRT. Should any safety concerns be identified by the PSRT, these will be referred to the Protocol Team and MTN Study Monitoring Committee (SMC) as appropriate.

2. Respond to queries regarding product use management including temporary hold or permanent discontinuation of study product.

   The protocol specifies a number of situations in which study product use should be temporarily held, permanently discontinued and/or resumed; designated site staff may implement these holds, discontinuations, and/or resumptions in the absence of consultation with the PSRT. In other situations, however, product use management must be undertaken in consultation with the PSRT. (Protocol Section 9.3 and 9.4)

3. Respond to queries regarding adverse event (AE) assessment, reporting, and/or management.

4. Respond to investigator notification of participant withdrawal from the study

5. Respond to queries regarding study eligibility, participant evaluability, and/or re-joining of study participant's which previously withdrew consent (Protocol Section 9.8)

PSRT Composition

The following individuals comprise the MTN-028 PSRT:

- Albert Liu, Protocol Chair, San Francisco IoR
- Katie Bunge, MTN Protocol Safety Physician
- Devika Singh, MTN Protocol Safety Physician
- Ken Ho, MTN Protocol Safety Physician
- Jeanna Piper, DAIDS Medical Officer (MO)
- Jenny Tseng, SDMC Clinical Affairs Safety Associate (CASA)

Ideally, all members of the PSRT will participate in routine conference calls. At a minimum, the DAIDS Medical Officer (or designee if DAIDS MO is not available), the Protocol Chair, a MTN Safety Physician, must take part in all calls to reach quorum.

If these members are not present, the call may be deferred until the next scheduled call time unless a PSRT member requests an immediate call. MTN LOC (FHI 360) Clinical Research Managers, SDMC Project Managers, Statistical Research Associates, and Site Investigators and study coordinators may attend PSRT calls as observers and/or discussants.

PSRT Communications

A group email address (mtn028psrt@mtnstopshiv.org) will be used to facilitate communication with the PSRT. All PSRT communications will be sent to this email address.

Site consultation with the PSRT will be facilitated using the MTN-028 PSRT Query Form, which is available in the Study Implementation Materials section of the MTN-028 web page. Site staff will email completed query forms to the Protocol Safety Physicians (mtn028safetymd@mtnstopshiv.org) who will work with the PSRT to prepare a consensus response to the query, and then email the final response to the site. This process is expected to occur within three business days. When necessary, site requests for responses within one business day can usually be accommodated. All members of the PSRT are encouraged to review the information provided by the site in the query form and to contribute to the response; however, final determination rests with the Protocol Chair(s).

An emergency safety telephone number (1-412-641-8947) is also available to site staff. This telephone is carried by the Protocol Safety Physicians 24 hours a day, seven days a week. It is intended for use in emergencies only, in which immediate consultation with a Protocol Safety Physician is needed. If the Safety Physician does not answer, a voicemail should be left with the call back number. Questions that can wait for email communication should be handled using the PSRT query process described above.

To document calls made to the emergency safety telephone number, near the time of the call (either before or after) site staff will complete the site section of the MTN-028 Emergency Phone Contact form (available in the Study Implementation Materials section of the MTN-028 web page) and email the form to the Protocol Safety Physicians. Within 24 hours after the call, the responding Protocol Safety Physician will complete the remainder of the form and email the completed version to site staff, copied to the study Management Team.

Section 9. Laboratory Considerations

9.1. Overview and General Guidance

As transmission of HIV and other infectious agents can occur through contact with contaminated needles, blood, and blood products, all study staff must take appropriate precautions when collecting and handling biological specimens. Sites must have appropriate written safety procedures in place before study initiation. Guidance on universal precautions available from the US Centers for Disease Control can be found at the following website: http://www.cdc.gov/hai/.

The tests to be performed at each visit during the MTN-028 study are listed in Table 9-1. Sites are responsible to ensure that specimen volumes do not exceed what is described in the informed consent process. The total blood volumes calculated in Table 9-1 include additional blood that may be collected for any clinically indicated testing. The MTN LC may request details of collection containers and volumes for this purpose, as shown in Table 9-2.

Table 9-1: Overview of Laboratory Tests by visit for MTN-028

Sample Type	Test or Procedure	VISIT Day										
		SCR	ENR (Day 0)	Days 1,2	Day 3	Day 7	Day 14	Day 21	Day 28	Days 29,30,31	Day 35 Final Clinic	Early Termi-nation
Urine	hCG	X	X	*	*	*	X	*	X	*	*	*
	Dipstick UA	X	*	*	*	*	*	*	X	*		
	Urine culture	*	*	*	*	*	*	*	*	*		
Blood	CBC with differential and platelets	X	X						X		*	*
	Chemistries (Creatinine, AST, ALT)	X	X						X		X	X
	HIV-1 serology	X	X	*	*	*	*	*	*	*	X	X
	HBsAg	X										
	INR	X										
	Anti-HCV	X										
	Syphilis serology	X	*	*	*	*	*	*	*	*	*	*
	Plasma for Archive		X	*+	*+	*+	*+	*+	*+	*+	*+	*+
	Plasma for Blood **PK**		(hr 1, 2, 4, 6)	X	X	X	X	X	(hr 0, 1, 2, 4, 6)	X	X	X¥
Vaginal	Vaginal fluid pH	*	*	*	*	*	*	*	*	*	*	*
	KOH wet mount for candidiasis	*	*	*	*	*	*	*	*	*	*	*
	Saline wet mount for BV	*	*	*	*	*	*	*	*	*	*	*
	Vaginal NAAT GC/CT	X	*	*	*	*	*	*	*	*	*	*
	Rapid Trichomonas	X	*	*	*	*	*	*	*	*	*	*
	Vaginal Swab for **PK**		(hr 0, 1, 2, 4, 6)	X	X	X	X	X	(hr 0, 1, 2, 4, 6)	X	X	X¥
	Gram stain		X		X				X		X	X
Cervical	Collect Pap test	*										
	Cervical Tissue for PK								X			
IVR	Collect study product								X			X
Blood Volume Total (mL)	Approximate, check local laboratory requirements ♪	28	66	46	46	46	46	46	94	46	54	54

X = required; * = perform, if clinically indicated; ¥ = do not collect if vaginal ring was out for 3 or more days
♪ Maximum volume needed for study requirement, if all specimens are collected including "if clinically indicated".
+ Plasma for confirmation of viral load and HIV drug resistance testing.

Table 9-2 also shows where laboratory procedures may be performed: study site clinics or laboratories, approved commercial laboratories, and laboratories within the MTN Laboratory Center (MTN LC), including the MTN Pharmacology Core at the University of Colorado, Colorado Antiviral Pharmacology Laboratory (CAVP). Regardless of whether tests are performed in clinic or laboratory settings, study staff that performs the tests must be trained in properly associated QC procedures prior to performing the tests for study purposes (i.e. training documentation should be available for inspection at any time).

Table 9-2: Overview of Laboratory Testing Locations, Specimens, and Methods for MTN-028

Test	Testing Location	Specimen Type	Tube or Container and tube size (recommended)	Kit or Method
Urine Pregnancy Test (hCG)	In clinic	Urine	Plastic screw top cup	Beckman Coulter ICON 25
Urine Dipstick and Culture*	Local lab	Urine	Plastic screw top cup	Siemens Multistix® 10 SG or Uristix 4 or other MTN LC approved method ology
Complete Blood Count with Differential and Platelets	Local Lab	Consult Local Lab Requirements		Local methodology
Chemistries (AST, ALT, Creatinine)	Local Lab	Consult Local Lab Requirements		Local methodology
Prothrombin Time Coagulation (INR)	Local Lab	Consult Local Lab Requirements		Local methodology
Hepatitis B (HBsAg)	Local Lab	Consult Local Lab Requirements		Local methodology
HCV	Local Lab	Consult Local Lab Requirements		Local methodology
Syphilis Serology	Local Lab	Consult Local Lab Requirements		Local methodology
HIV serology	Clinic/Local Lab	Plasma, serum, or whole blood	EDTA or plain, 4-mL	FDA approved tests
Plasma for Archive or Confirmation of Viral Load and HIV Resistance Testing	Clinic/Local Lab	Plasma	EDTA 10-mL tube	MTN LC procedure MTN LC Virology
Plasma for Blood PK (MK-2048,VCV)	CAVP	Plasma	EDTA 10-mL tube	CAVP collection procedure
Vaginal pH*	In clinic	Vaginal swab	N/A	S/P pH Indicator Strips
Vaginal Saline Wet Preparation (for BV and/or KOH wet mount)*	In clinic	Vaginal swab	tube with 6 drops of saline	MTN LC procedure
Vaginal NAAT for GC/CT	Local lab	Urine or vaginal swab	Kit specific Transport tube	BD Probetec or Gen-Probe Aptima
Trichomonas Rapid Test	Local lab or in clinic	Vaginal swab (supplied with kit)	OSOM:Sterile tube with no additives	OSOM kit
Vaginal Swab for PK	CAVP	Swab	2.0-mL Cryovial	CAVP collection procedure
Vaginal Smear for Gram-stain	MTN LC	Vaginal Swab	2 Slides	MTN LC procedure
Pap Test*+	Local Lab	Consult Local Lab Requirements		Local methodology
Cervical Biopsy for PK	CAVP	Tissue	2.0 mL cryovial	MTN LC collection procedure
Used Intravaginal Ring for PK residual assessment	Merck Designated lab	Used IVR	Biohazard labeled 3"×5" amber Zippit pouch	MTN LC /Merck procedure

*Perform only if clinically indicated per local SOP.
+Perform if participant does not have a documented satisfactory Pap within 3 years prior to Enrollment.

Ideally, one method, type of test kit, and/or combination of test kits will be used for each protocol specified test throughout the duration of the study. If for any reason a new or alternative method or kit

must be used after study initiation, site laboratory staff must perform a validation study of the new method or test prior to changing methods. The MTN LC must be notified before the change and can provide further guidance on validation requirements.

Specimens that will be stored and shipped to the MTN LC or CAVP are highlighted in Table 9-3. These are the samples that will be entered into LDMS (section 9.4).

Table 9-3: Overview of Specimens for Storage and Shipment

Specimen	Processing	Ship to	Shipping schedule
Plasma for Archive (at enrollment) or for Confirmation of Viral Load and HIV Resistance (at f/u)	Prepare as many 1.5-mL aliquots as possible. If sample is collected and held at room temp, freeze ≤ -70°C within 4 hours. If refrigerated after collection, freeze ≤ -70°C within 24 hours.	MTN LC	Store frozen at site until notified by MTN LC. However, if plasma for HIV confirmation, ship immediately to MTN LC Virology Core.
Plasma for Blood PK (MK-2048,VCV)	Centrifuge and aliquot into two or more cryovials with a minimum of 1.5-mL in each. Freeze within 8 hrs of blood collection.	CAVP, MTNLC	Store frozen at site until conclusion of study or notified by MTN LC.
Vaginal Swab for PK	Record Pre- and Post-collection weight of swab. Freeze at ≤ -70°C within 2 hours of collection	CAVP	Store frozen at site until conclusion of study or notified by MTN LC.
Vaginal smear for Gram-stain	Make 2 slides. Room temp. Label with LDMS label.	MTN LC	Store one set of slides that will be batch-shipped at conclusion of the study. Store 2nd set of slides (as backup) at site until all slides from first set are confirmed as received.
Cervical Biopsy for PK	Perform Pre (without biopsy) and Post (with biopsy) weights. Flash-freeze. Store at ≤-70°C.	CAVP	Store frozen at site until conclusion of study.
Used Intravaginal Ring for PK Residual Assessment	Place IVR in amber pouch	MTN LC	2-8°C storage at site until conclusion of study.

Provided in the remainder of this section is information intended to standardize laboratory procedures across sites. Adherence to the specifications of this section is essential to ensure that primary and secondary endpoint data derived from laboratory testing will be considered acceptable to all regulatory authorities across study sites.

9.2. Specimen Labeling

All containers into which specimens are initially collected (e.g., urine collection cups, blood collection tubes) will be labeled with SCHARP-provided Participant ID (PTID) labels. Although PTIDs are pre-printed on these labels, study staff must write the specimen collection date on each label. The visit code also may be written on the label. Use an indelible ink pen (e.g., Sharpie) if information is handwritten such as the date or collection time point.

When specimens are tested at the local lab, any additional labeling required for on-site specimen management and chain of custody will be performed in accordance with site SOPs. Refer to Table 9-4 for tests that will be entered into LDMS and labeled with LDMS-generated labels.

9.3. Procedures for Specimens that cannot be evaluated

Specimen collection will be repeated (whenever possible) if samples cannot be evaluated per site SOPs. Site clinic and laboratory staff will monitor specimen collection, processing and management

as part of ongoing quality assurance (QA) procedures and take action as needed to address any issues or problems.

If additional specimens need to be collected for the same test due to either laboratory error (lost, broken tube, clerical, etc.) or clinical error, a protocol deviation form may be required. The MTN LC must be notified in the following cases:

- Any time a participant must return to the clinic for specimen collection
- When PK specimens are missed
- Insufficient blood volume is collected for the plasma archive
- Any time specimens have been mishandled, possibly compromising specimen integrity
- Any situation that may indicate a protocol deviation

If site staff has any questions regarding time windows or collection processes, call MTN LC staff as soon as possible for guidance.

9.4. Use of LDMS

The Laboratory Data and Management System (LDMS) is a program that must be used by all sites for the storage and shipping of sample types listed in Table 9-3. LDMS is supported by the Frontier Science Foundation (FSTRF). Detailed instructions for use of LDMS are provided at https://www.fstrf.org/ldms (may require a password).

All sites will be required to maintain the current version of LDMS and monitor updates relating to use of the LDMS. It is crucial to be aware of proper label formats to ensure that specimens are correctly labeled. Sites will be responsible to back up their LDMS data locally (frequency determined by site) and to export their data to FSTRF (at least weekly).

LDMS Help: Questions related to use of LDMS in MTN-028 may be directed to MTN LC or LDMS Technical (User) Support. Usual business hours for LDMS User Support are 12:00 am - 6:00 pm (ET) from Monday through Friday. Contact LDMS User Support at:

Email: ldmshelp@fstrf.org
Phone: +716-834-0900, ext 7311
Fax: +716-834-8432

All other hours and weekends, an on-call user support specialist will be available if you are locked out of your LDMS or are experiencing errors that prevent you from completing your LDMS lab work. Use the LDMS Web Pager utility to page LDMS User Support. Alternatively, you may e-mail the paging system directly at ldmspager1@fstrf.org. Please allow at least 15 minutes to get a response before sending another e-mail to the paging system.

Discrepancy Reports: Each site must export its LDMS data to Frontier Science (FSTRF) on a weekly basis. Exported data are used by the MTN Statistical and Data Management Center (SDMC) to generate a monthly specimen repository report and to reconcile data entered in LDMS with data entered on study case report forms (CRFs). Any discrepancies identified during the reconciliation are included in a monthly discrepancy report for each site. Sites are expected to resolve all discrepancies within two weeks of receipt of the report. The MTN LC is responsible for reminding sites to adhere to the two week timeframe and for following up with sites that do not resolve discrepancies within two weeks.

The MTN SDMC reviews the discrepancy reports for critical samples (e.g., plasma needed for confirmatory HIV testing) that appear to be missing and works with MTN LC and site staff to undertake appropriate corrective action. All corrective action should be documented in paper-based clinic and/or laboratory records as appropriate, and entered in the details section of LDMS. The MTN LC and SDMC will discuss and document any items that, although resolved, appear 'irresolvable' in LDMS.

9.4.1. LDMS Codes for Specimen Log In

The table 9-4 should be used as a guide when logging in MTN-028 specimens for storage or shipping. Please use the LDMS codes listed below when logging in specimens for each test listed. LDMS tracking sheets for Enrollment/Day 28 (multi PK time-point) and other visits (single PK time-point) can be found in the Study Implementation Materials section on the MTN-028 webpage.

Table 9-4 LDMS Specimen Management Guide to Logging in MTN-028 Specimens*

Sample	Primary Specimen	Primary Derivative	Aliquot Derivative	Aliquot Sub additive/ derivative	Other Specimen ID (optional)	# of Aliquots	Aliquot Volume	Units	Time or Weights
Plasma for Archive or Confirmatory Test	**BLD**	**EDT**	**PL1** (single spin); **PL2** (double spin)	**N/A**	**EPA** (enrollment); **CON** (follow-up)	2-5	1.5 mL in 2-mL cryovials	mL	--
Plasma for PK (MK-2048, VCV)	**BLD**	**EDT**	**PL1**	**N/A**	**PK**	2-5	1.5 mL in 2-mL cryovial	mL	**See 9.4.2**
Vaginal Smear for Gram Stain	**VAG**	**NON**	**SLD**	**GRS**	--	2	2 smears	Each	--
Vaginal PK Swab	**VAG**	**NON**	**SWB**	**N/A**	--	1	1 swab	mG	**See 9.4.2 and 9.4.3**
Cervical Biopsies for PK	**CVB**	**NON**	**BPS**	**N/A**	--	1	1 biopsy in 2- mL cryovial	mG	**See 9.4.2 and 9.4.3**
Used Vaginal Ring for PK residual assessment	**IVR**	**NON**	**IVR**	**N/A**	--	1	1 pouch	Each	--

*List of Codes and their definitions:

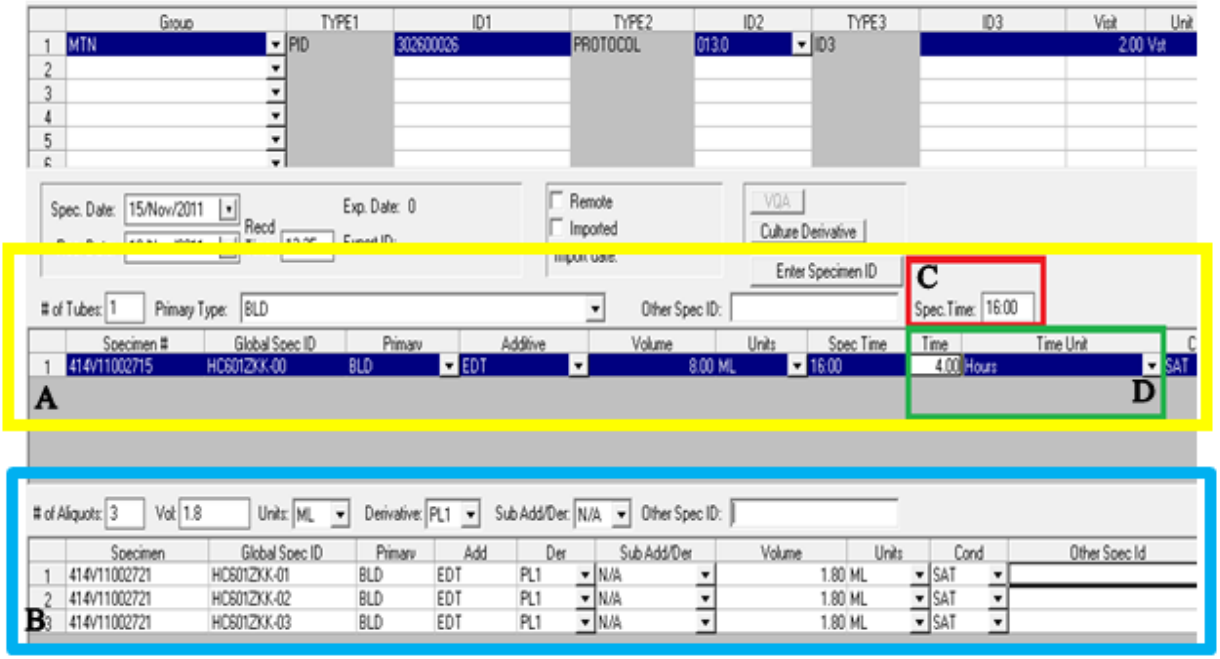
BLD: Whole Blood
VAG: Vaginal Swab
CVB: Cervical Biopsy
IVR: Used Intravaginal Ring
EDT: EDTA
NON: No Additive
PL1/2: Single or double spun plasma
SLD: Slide
SWB: Swab
BPS: Biopsy
GRS: Gram stain slide
N/A: Not Applicable

9.4.2. Logging in Time for PK Samples

In this study, there will be multi PK time-point visits, and in LDMS, in addition to time of collection, the TIME and TIME UNIT field are used to note the specific time point on your aliquot labels. In figure 9-1, the single tube of blood for PK is entered in the primary area (see yellow rectangle A), and the three aliquots of 1.8-mL plasma that are derived from the sample are entered in the lower section for the derivative (see blue rectangle B).

- The collection time, using the 24-hour clock notation, is entered in the Specimen Time area (Figure 9-1, red rectangle C). For this example, it is 16:00.
- During multiple PK time-point visits, the PK time-point information is entered in Time and Time Unit area (Figure 9-1, green rectangle D). This blood was for the 4-HR time point.

Figure 9-1: LDMS Screen for Time Entry.



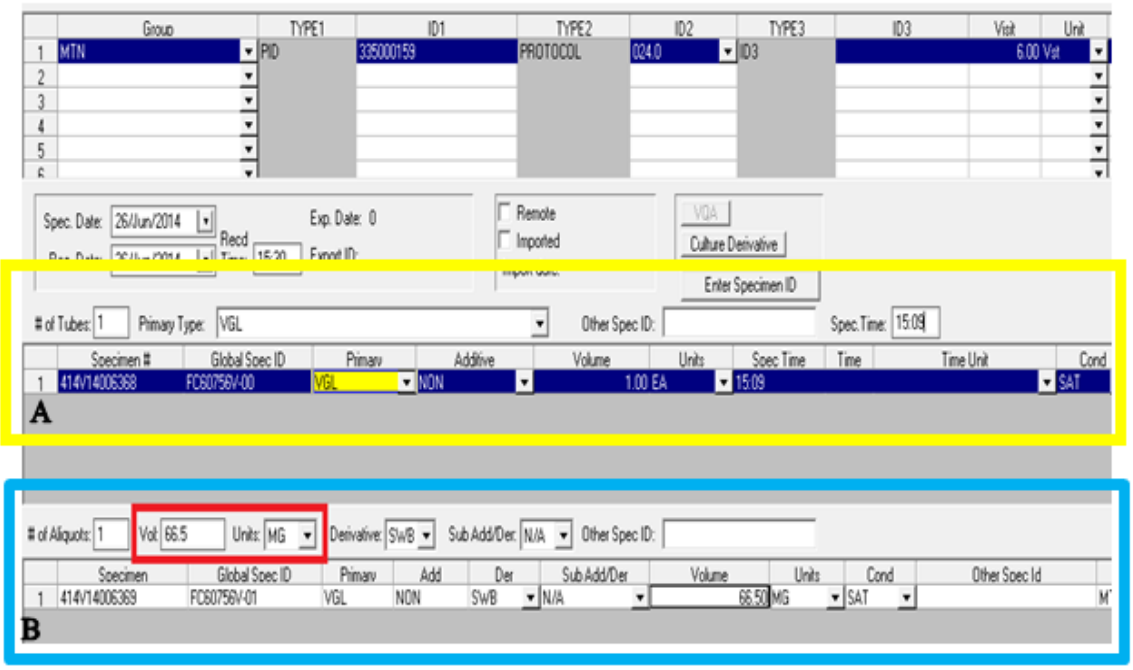
9.4.3. Entering weight measurements of vaginal swab and cervical biopsy for PK in LDMS:

In the derivative area for the primary sample, The VOLUME and UNIT field is used for displaying weight measurements with proper units. Once the net-weight is attained by subtracting the pre-weight from the post-weight, the result can be entered into LDMS as shown in figure 9-2, red rectangle.

- In the primary sample area (section A), use table 9-4 to enter correct code for the sample. Make sure to place the correct collection time under Spec Time field. Click the 'add' button to the right. This will add the sample to field. Under Units, enter EA (for each) and enter '1' for Volume (See Figure 9-2).
- To enter the actual weights, make an aliquot in Section B for the primary sample by entering a '1' in the # of Aliquots field. For Volume, enter the net-weight and select 'MG' MG (milligrams) for UNITS. Enter the correct derivative and Sub-Add/Der codes, then click the add button (See Figure 9-2).

In the example in figure 9-2: Pre-weight Swab: 3073.2 mg, Post weight Swab: 3139.7 mg, Net weight of Swab is 66.5 mg (3139.7 -3073.2 = 66.5). Enter '66.5' under VOLUME and select 'MG' for Units, 'SWB' for Derivative, and 'N/A' for Sub-Add/Der, then press add.

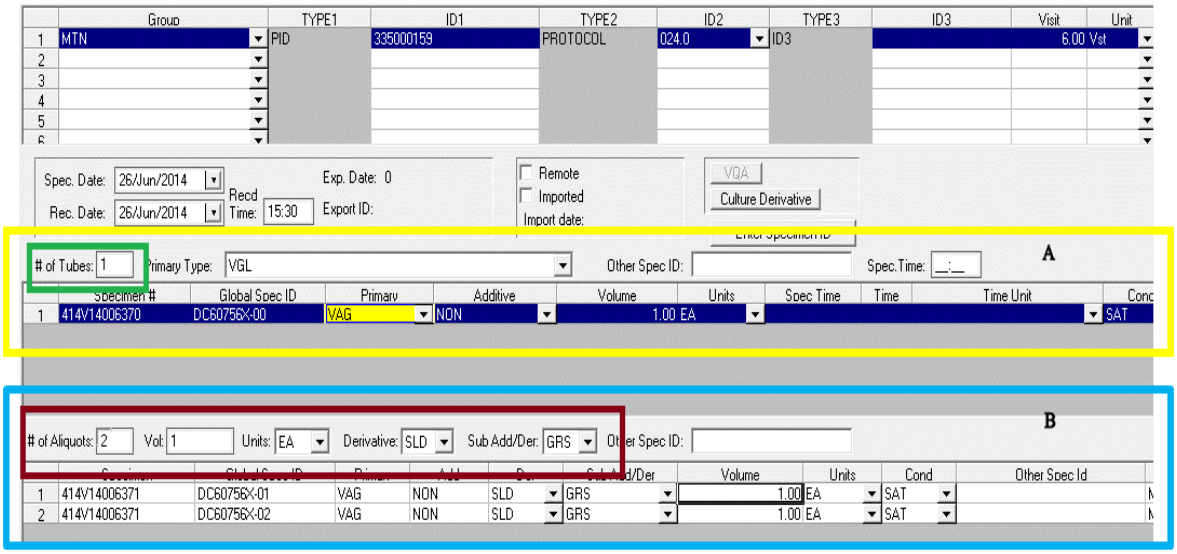
Figure 9-2: LDMS Screen for Weight Entry



9.4.4. LDMS Entry for Vaginal Smear for Gram Stain

For Vaginal Smear for Gram Stain, the one swab that was used to inoculate the two slides is the primary sample. After the primary sample information is entered, then added, the two slides are entered as aliquots. An example is shown in figure 9-3. Note that after the 2 aliquots are added, a pop-up message will warn the user that the total aliquot volume exceeds the primary volume. Ignore the message and continue.

Figure 9-3 LDMS Entry for Vaginal Smear for Gram Stain



9.5. Urine Testing for Pregnancy, Urinary Tract Infection, and Urinalysis

9.5.1. Specimen Collection

- The participant should not have urinated within one hour prior to urine collection.
- Provide the participant with a sterile, plastic, preservative-free screw-top urine collection cup labeled with a SCHARP-provided PTID label.
- Instruct the participant to collect the portion of the urine flow that is required by the test
- If the urine is to be used for culture, instruct the participant to clean the labia prior to specimen collection and to collect a midstream urine sample.
- Instruct the participant to screw the lid tightly onto the cup after collection.

9.5.2. Pregnancy Testing

Pregnancy status is a critical participant safety consideration in MTN-028. The Beckman Coulter ICON 25, Quidel QuickVue One-Step hCG urine, Quidel QuickVue Combo hCG urine/serum pregnancy, or Fisher HealthCare Sure-Vue Urine hCG test must be used at all sites. All sites must maintain an adequate inventory of the pregnancy test kits at all times. Inventory should be monitored closely and re-supply orders placed at least 8-12 weeks in advance of actual need (or longer if needed per site procurement policies and procedures). The date and time of pregnancy testing must be documented.

The pregnancy test is performed according to site SOPs and the package insert (i.e. a negative result is based on the recommended total time for test to be considered complete.) Do not perform any other urine pregnancy tests for confirmatory purposes. If the urine pregnancy test cannot adequately be interpreted because of interfering factors (e.g. excess blood or extreme cloudiness due to amorphous material), the sample can be spun down and the urine supernatant can be used. If the test continues to have interferences such as gross hemolysis making the test difficult to read, then another urine sample will need to be collected.

In the rare event in which a participant becomes pregnant, study product use will be permanently discontinued. The participant will be terminated from the study.

9.5.3. Urinary Tract Infection

Urine Dipstick and/or Culture: Perform the tests according to the package insert for the dipstick and your local SOP for culture.
For initial diagnosis and treatment of a UTI use your local standard of care (if you use a dipstick for leukocytes and nitrites record the results on the CRF “Safety Laboratory Results”). However, for confirmation of a UTI and reporting as an AE you must perform a urine culture if this is not part of your local standard of care. The culture results are not recorded on the CRF.
See also section 8.9 Clinical Considerations of the SSP for additional information.

9.5.4 Urinalysis for Renal Function

Tests for glucose and protein are required at screening and day 28 visits. Perform the test according to the package insert and your local procedure. Record the results on the CRF “Safety Laboratory Results”.

9.6. Blood Specimens for Chemistry, Hematology, HIV testing, Syphilis, Plasma Archive, MK-2048 and Vicriviroc (VCV) Blood Levels

The blood tests performed at each study visit vary depending on the time point of the visit and potentially the clinical presentation of the participant. Perform all tests according to site SOPs and package inserts.

9.6.1. Specimen Collection and Initial Processing

Label all required tubes with a SCHARP-provided PTID label at the time of collection. After collection:

- Allow serum tubes (no additive or serum separator tubes) to clot, then centrifuge per site SOPs.
- Lavender top tubes (additive = EDTA) should be gently inverted at least eight times after specimen collection to prevent clotting. If whole blood for hematology testing and plasma is to be taken from the same tube, hematological tests must be completed before the tube is centrifuged and aliquoted. If whole blood is to be used for multiple tests, ensure that the tube is well mixed before removing any specimen. EDTA tubes will be used for plasma MK-2048 and Vicriviroc PK levels, plasma archive at enrollment, and if applicable, plasma for confirmation of viral load and HIV resistance testing.
- Light blue top tubes (additive = Na Citrate) are used for coagulation determinations. These tubes should be gently inverted at least 4 times after specimen collection to prevent clotting.

Note: If locally available tube top colors do not correspond with the tube additives specified above, use appropriate tubes based on the additives, not the listed tube top colors.

9.6.2. Chemistry (Alanine transaminase, Aspartate aminotransferase, and Creatinine), Hematology (CBC with Diff and Platelets), and Coagulation

Testing will be performed per local standard of care.

- Tests performed for Chemistry
    - Liver Function:
        - Alanine transaminase (ALT),
        - Aspartate aminotransferase (AST).
    - Renal Function:
        - Creatinine
        - Creatinine Clearance Calculator, using participant's weight in conjunction with the Cockcroft-Gault formula. See EXCEL worksheet in the Study Implementation Materials section of the MTN-028 protocol on the MTN website.
- Hematology tests (Complete blood counts (CBC) with five-part differentials)
    - Hemoglobin,
    - Hematocrit,
    - Platelets,
    - White Blood Cell Count and differential
    - Red Blood Cell Count
- Coagulation Test: Prothrombin Time to include an INR.

9.6.3. HIV Testing

EDTA plasma, whole blood (fingerstick or venipuncture) and serum can be used to test for HIV using tests that have been validated at the study site. All HIV testing in laboratories must be done under Clinical Laboratory Improvement Amendment (CLIA) certification. All tests and associated QC procedures must be documented on local laboratory log sheets or other laboratory source documents.

HIV infection status will be assessed using an FDA-approved HIV immunoassay per the HIV testing algorithm (see appendix 9-1 in this section or appendix II of the MTN-028 protocol). Rapid tests, such as Oraquick, are considered immunoassays and can be used with whole blood (fingerstick or venipuncture). The first specimen drawn for immunoassay and confirmatory testing is considered Sample 1. If Sample 1 is HIV positive by the confirmatory test a second specimen (Sample 2) is drawn to confirm the first results.

Notify the MTN LC immediately if any kit inventory or quality control problems are identified, so that appropriate action can be taken.

9.6.3.1 HIV Rapid Test Result Interpretation

- If SAMPLE 1 immunoassay result is negative, the participant will be considered HIV-seronegative.
- If the SAMPLE 1 immunoassay result is positive or indeterminate, an FDA-approved confirmatory test should be performed on SAMPLE 1.
  - Go to 9.6.3.2 if SAMPLE 1 is Screening or Enrollment sample
  - Go to 9.6.3.3 if SAMPLE 1 is Follow-up Visit sample
- If there is insufficient sample to perform the confirmatory test, then additional blood must be drawn. This re-draw will still be regarded as Sample 1 per the algorithm.

9.6.3.2 HIV Confirmatory Test for Screening or Enrollment Visit

- Until enrolled, treat enrollment testing same as screening participants.
- If the confirmatory test for SAMPLE 1 is negative, indeterminate or invalid, contact the MTN Virology Core: mtnvirology@mtnstopshiv.org for guidance.
  - It is not recommended for participants with discrepant HIV testing results to continue enrollment.
- If the confirmatory test is positive for the screening visit, the participant is considered seropositive and is not eligible for enrollment.

9.6.3.3 HIV Confirmatory Test for Follow-Up Visits

- If at a follow-up visit, the confirmatory test on SAMPLE 1 is negative, indeterminate or invalid, contact the MTN Virology Core for guidance:
  - 412-383-8138
  - mtnvirology@mtnstopshiv.org.
- If the confirmatory test is positive at a follow-up visit, a second sample of blood (SAMPLE 2) will be drawn for additional confirmatory testing, HIV RNA resistance testing and plasma storage at the MTN Virology Core.
  - Draw enough whole blood to store a total of 5 mL of plasma to send to the virology core. The virology core can work with less but 5 mL is the desired amount to complete all testing.
  - ***NOTE: Draw extra blood with Sample 2, if required for local standard of care or at discretion of clinician. This blood is sent directly to a local lab following their procedures.***
- Processing of SAMPLE 2 is similar to Plasma for Archive:
  - Log into LDMS, but with special ID = CON.
  - Centrifuge at 1500xg and aliquot 1.5 mL plasma into 2-mL cryovials and freeze at <-70^{o}C.
- Alert the MTN Virology Core, 412-383-8138, about shipment.
- Package and ship 3 aliquots immediately on dry ice to:

  Dr. Urvi Parikh
  University of Pittsburgh
  3550 Terrace St.
  Scaife Hall S804
  Pittsburgh, PA 15261

- MTN Virology Core will provide test results to the site.
  - If positive, the participant is HIV positive.
  - If negative, indeterminate or invalid, the MTN Virology Core will supply guidance.

9.6.4. Syphilis Testing

RPR tests may be performed on either serum or plasma. Serum is the specimen of choice for VDRL and syphilis confirmatory tests. However, other sample types may be allowed according to the particular test's package insert. All testing and QC procedures must be performed and documented in accordance with study site SOPs.

Syphilis testing can be performed using FDA approved tests in one of two ways:

1. Perform a non-treponemal screening test, such as Rapid Plasma Reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test, followed by a confirmatory test for *Treponema pallidum*.
   - Any FDA approved *Treponema pallidum* confirmatory test can be used such as the Enzyme Immunoassay (EIA), microhemagglutinin assay for *Treponema pallidum* (MHA-TP), *Treponema pallidum* hemagglutination assay (TPHA), *Treponema pallidum* particle agglutination (TPPA), or fluorescent treponemal antibody (FTA-ABS).
   - All positive RPR or VDRL results must have a titer reported.
     - For reactive RPR or VDRL tests observed during screening, a confirmatory test is performed and appropriate clinical management action must be taken prior to enrollment in the study.
     - Enrolled participants considered positive should include repeat non-treponemal assay tests at quarterly intervals following syphilis diagnosis to evaluate treatment effectiveness.
     - If the RPR or VDRL titer does not decrease four-fold or revert to seronegative within three months after treatment, further investigation and/or treatment may be warranted.

2. Perform syphilis assessment using a specific FDA approved treponemal test (such as EIA, MHA-TP, TPHA, TPPA, or FTA-ABS) and confirming positive test results with a non-treponemal assay (RPR or VDRL).
   - If the confirmatory non-treponemal assay is reactive at screening visit, appropriate clinical management action must be taken prior to enrollment in the study.
     - If the RPR or VDRL is negative, this may indicate prior treatment, late latent disease, or a false positive test.
       - MTN LC recommends additional testing using an alternative treponemal test other than the original treponemal test used for the original assessment so the participant can be correctly evaluated. (Of note, the FTA-ABS should not be used as the alternative confirmatory test due to performance issues).
         - If the second confirmatory test is negative, the participant is not considered infected with syphilis.
         - If the second confirmatory test is positive, the participant has had prior exposure to syphilis and depending on clinical scenario may or may not require treatment.

Please consult the MTN LC with any questions related to Syphilis testing to confirm treatment effectiveness and/or interpretation of unusual test results.

Questions related to result interpretation concerning eligibility and enrollment in the study should be directed to the MTN-028 Protocol Safety Physicians (mtn023safetymd@mtnstopshiv.org).

9.6.5. Hepatitis B Surface Antigen and Hepatitis C Antibody

This testing will be done on serum or EDTA plasma per local SOPs

9.6.6. Plasma Archive

For plasma archive, use collection tubes with EDTA anticoagulant. Aliquot plasma into 2-mL cryovials, store at ≤-70˚C, and batch onsite until the MTN LC study team requests shipping and/or testing.

- LDMS will be used to label and track the specimens.
- If sample is collected and held at room temp, freeze within 4 hours. If refrigerated or placed on ice after collection, freeze within 24 hours.
- Spin blood at room temperature in a centrifuge according to one of these techniques:
    - Single spun: Spin blood at 1500×g for 10 minutes, remove plasma.
    - Double spun: Spin blood at 800×g for 10 minutes, place plasma in a tube to spin again at 800×g for 10 minutes, remove plasma.
- Prepare as many 1.5-mL aliquots as possible, at least 3-mL total volume.
- If total volume is less than 0.5 mL, redraw as soon as possible.
- If less than 1 mL of plasma is available, store that plasma and inform the MTN LC for instruction.
- If samples are hemolyzed, store the aliquots as per normal and enter comments in LDMS.
- The MTN LC will send instructions to the site when shipping and/or testing is required.

9.6.7. Blood for PK of Vicriviroc (MK-4176) and MK-2048

On single time-point days (visit days 1, 2, 3, 7, 14, 21, 29, 30, 31, & 35), The participant will self-collect the vaginal PK swab approximately within 1 hour after the blood is drawn for PK. On multiple time-point days (visit days ENR and 28), optimally the participant will self-collect the vaginal PK swab within 5 minutes after the blood PK sample is drawn. See section 9.7.5 for details.

NOTE: If it is an Early Termination visit and the vaginal ring has been out for 3 or more days, do not collect samples for vaginal fluid PK and plasma PK.

Collect blood into a labeled 10-mL EDTA Vacutainer tube using either an indwelling venous catheter or direct venipuncture.

1. Mix blood sample with the anticoagulant using gentle inversions (8 to 10 times).
2. Centrifuge the sample at approximately 1500×g for 10 minutes. The centrifugation must be completed and sample placed in the freezer within 8 hours of blood collection.
3. Use a pipette to aliquot approximately 1.5 mL of the resulting plasma into 2-mL cryovials. One of these will serve as the primary sample; the others will serve as a back-up in case the primary samples are accidentally destroyed during shipment.
4. Prepare two storage boxes and label one as “primary samples” and the other as “back-up samples”. Transfer the tubes from each participant in chronological order into the storage boxes. All samples will be tracked in LDMS.
5. Store the boxes with samples at ≤-70˚C until shipped.

SHIPPING:

- MTN LC will coordinate sample shipments throughout course of study if necessary and at its conclusion.
- All shipments will be on dry ice that will be sufficient for a 24-hour period and can be initiated Monday through Wednesday to insure that samples arrive in the lab during the work week.
- The back-up samples will be retained at the site until advised by the MTN LC or MTN-028 leadership team. One purpose of the extra aliquots is to be available in case the shipment is not received in the proper condition (e.g. thawing of samples).

9.7. Vaginal Specimens for Gram Stain, Vaginal Fluid pH, Vaginal Wet Mount, GC/CT NAAT, Trichomonas, Vaginal Fluid for PK, and IVR for Remnant Drug Content Analysis

Refer to Pelvic Exam checklist of this SSP manual for further information on the required sequence of specimen collection and diagnostic procedures to be performed during study pelvic exams.

9.7.1. Gram Stains of Vaginal Fluid

Dried vaginal fluid smears will be prepared for Gram staining and assessment for bacterial vaginosis at the MTN LC. Two slides (one designated as primary and the other as secondary) will be prepared at each required time point and both will be entered into LDMS. The primary slide will be shipped to the MTN LC and the secondary will be archived on site until written notification is received from the Statistical Center for HIV/AIDS Research & Prevention (SCHARP) that the slide may be discarded.

Instructions for slide preparation and shipping are provided below:

1. Use a pencil to write the PTID and specimen collection date on the frosted end of the slide. This is the side of the slide that the specimen is to be applied.

2. Immediately following specimen collection from the lateral vaginal wall via swab (Dacron or cotton), roll the swab across each of the slide. (Be sure to collect the specimen from opposite the vaginal wall used for the wet mount specimen collection.) Do not place the swab in saline, transport medium, or any transport container prior to slide preparation.
3. A SCHARP-provided PTID label is to be placed on the underside of the slides (on the frosted end, under the pencil markings); write the specimen collection date in indelible ink (e.g. Sharpie pen) on each label.

4. Allow the specimens to air-dry on the slides. Do not heat-fix.
5. Vaginal smears for gram stain are to be logged into LDMS (specimen type = VAG)

and label the slides with LDMS labels. Place the LDMS label on the frosted end of the slide on top of the pencil markings (same side as sample).

6. The primary slides will be positioned in a plastic slide holder and sent to the MTN LC. If there is no culture on the visit for which a gram stain is collected, then hold the gram stain slides until other samples are to be sent to the Magee-Womens Research Institute. (See shipping instructions below).
7. Store the secondary slide in the slide box location assigned in LDMS at room temperature. (This is a backup slide in case the first is lost, broken, or unreadable).

9.7.2. Vaginal pH and Wet Preps, if indicated for Bacterial Vaginosis (BV) and/or Yeast

BV will be diagnosed based on the presence of any three of the four Amsel's criteria:

- Homogenous vaginal discharge
- Vaginal pH greater than 4.5
- Positive whiff test
- At least 20% clue cells.

Wet prep assessments used to diagnose BV and candidiasis are discussed in section 9.7.2.2 and summarized in Table 9-5.

CLIA regulations require semi-annual **wet mount proficiency testing**. The MTN LC administers a web-based proficiency test approximately every six months. Wet mount slides on the MTN web pages are posted for this purpose every 6 months.

- Contact Lorna Rabe of the MTN LC (lrabe@mwri.magee.edu) to register names of clinicians who need to take the test.
- The registrants take the test and enter their answers directly on the website.
- The MTN LC sends a report of the results, including any necessary corrective action, to the Laboratory Manager.

Contact the MTN LC for additional information and guidance on performing and documenting the proficiency testing. Also contact the MTN LC when new laboratory staff is hired, so that appropriate training can take place prior to such staff performing wet mounts for study purposes.

9.7.2.1 Vaginal Fluid pH, if indicated for BV

Vaginal fluid pH will be assessed if clinically indicated for bacterial vaginosis. pH Indicator Strips (pH range 3.6 to 6.1) with brand names S/P Cardinal Health, Baker-pHIX, Whatman, or Machery-Nagel must be used at all sites.

Vaginal fluid pH swab (Dacron or cotton) may be collected in any of 2 ways depending on if a speculum is used at that particular visit:

- Obtained by the clinician during the pelvic examination
- Collected by the clinician in a non-speculum exam
  Note: a speculum is not required for pH sample collection.

Vaginal Fluid pH Procedure:

1. Swab onto the pH strip (Do not insert the pH strip into the vagina).

2. Match the resulting color of the indicator strip to the color scale provided with the strips to determine the pH value.
3. Record the pH value directly onto the appropriate case report form (CRF). It is not necessary to record pH values onto laboratory log sheets or other source documents prior to recording values onto CRFs.

Table 9-5 Summary of Wet Prep Assessments and Diagnostic Criteria		
Assessment	**Saline Prep**	**KOH Prep**
Whiff Test	Not applicable	Positive if fishy amine odor detected
Yeast	Positive if pseudohyphae and/or budding yeast are observed. Pseudohyphae and budding yeast may be obscured by epithelial cells. These cells will be lysed by KOH, thus pseudohyphae and budding yeast not observed in saline prep may be observed in KOH prep.	Positive if pseudohyphae or budding yeast are observed.
Clue Cells	Individual cells rather than clusters of cells should be examined. Positive if at least 20% clue cells observed. Cells must be completely covered with bacteria (*Gardnerella vaginalis* and/or anaerobic GNR) to be counted as clue cells.	Not applicable (clue cells are lysed by KOH)

9.7.2.2 Vaginal Fluid Wet Mount Testing, if indicated for BV and Yeast (KOH)

Wet mount procedures for this study are only performed if indicated, and consists of two different preparations: Potassium Hydroxide (KOH) and Saline. These procedures are for diagnosis of BV and candidiasis as summarized in Table 9-5.

Preparation and Examination of Wet Prep Slides

Materials:
Pencil
2 SCHARP labels, 3 if using optional tube
2 frosted end slides
Glass or plastic tube, optional
Sterile physiologic saline
10% KOH
Dacron Swab
2 cover slips
Microscope, 10x and 40X magnification

1. Use a pencil to write the PTID and specimen collection date on one side of the frosted end of two microscope slides. Affix a SCHARP-provided PTID label to the other side of the slides (on the frosted end, under the pencil markings)
2. Immediately following collection from the lateral vaginal wall via swab (Dacron or cotton), smear vaginal fluid specimens onto each slide. Alternatively, the swab may be placed in a glass or plastic tube with approximately six drops (100 µL) sterile physiologic saline to allow for non-immediate slide preparation. In this case, vaginal fluid specimens should be smeared onto the two slides upon receipt from the collecting clinician.
3. Apply one drop of 10% KOH to one slide and immediately perform whiff test for a “fishy” amine odor. Then apply cover slip.
4. Apply one drop of sterile physiologic saline to the second slide, emulsify with

the vaginal fluid specimen, and then apply cover-slip. Examine immediately at 10X magnification for epithelial cells, budding yeast, and pseudohyphae. Examine at 40X magnification to determine whether observed epithelial cells are clue cells and quantitate the cells. Clue cells are irregularly bordered squamous epithelial cells that are completely covered with bacteria (*Gardnerella vaginalis*). Clue cells must comprise at least 20 percent of the observed epithelial cells in order for the saline prep to be considered positive for clue cells.

5. Examine the KOH slide at both 10X and 40X magnification for yeast and pseudohyphae.

RESULTS:

- If wet prep slides are read in-clinic by clinical staff, results may be recorded directly on to appropriate case report forms (CRFs).
- If slides are read by lab staff (either in the local laboratory or a designated in-clinic lab area), results must be recorded on laboratory log sheets or other laboratory source documents and then transcribed onto appropriate CRF.

9.7.3. Testing for GC/CT (*Neisseria gonorrhea* and *Chlamydia trachomatis*) by NAAT

Testing for chlamydia and gonorrhea is performed at screening and when clinically indicated. Sites can choose to use the BD Probetec or Gen-Probe Aptima. If the site does not have access to these tests, they can send the samples to the MTN LC for testing. Contact the MTN LC prior to sending specimens for GC/CT testing.

- Use the Gen-Probe vaginal collection swab and transport tube
- Affix a SCHARP-provided PTID label onto the transport tube.
- Swab the lateral wall of the vagina.
- Immediately place the swab in the transport tube, break off the shaft of the swab, and cap the tube.
- Transport the specimen at ambient temperature to the local laboratory

9.7.4. Test for *Trichomonas vaginalis* using OSOM Rapid Test

Testing for *Trichomonas* is done using the OSOM Rapid *Trichomonas* test (manufactured by Sekisui Diagnostics)

- Use the rayon swab provided with the kit for collection
- Affix a SCHARP-provided PTID label to a clean glass or plastic tube with a cap.
- Collect specimen using kit-provided swab from the lateral vaginal wall (fluids also may be collected from the posterior fornix; avoid collecting specimens from the cervix).
- Immediately place the swab in the labeled tube, break off the shaft of the swab, and cap the tube.
- Testing is expected to be performed during the participant visit. However, specimens may be stored at room temperature for 24 hours or refrigerated for 36 hours before testing.

9.7.5. Vaginal Swabs for PK

PK collection times need to be recorded on the LDMS sample tracking sheet. In addition to sample collection, this section discusses acceptable 'windows' on collection time points and action to be taken if collection is outside of this.

Collection Timing and Target Times for Vaginal Swabs and Blood for PK

<u>Enrollment or Day 28, visits with multiple PK collection time-points.</u>

- When to start the timer

- At Enrollment, start timer upon ring insertion.
  - There is no blood draw at time 0, use this additional time to instruct participant on self-collection.
- On Day 28, start timer upon ring removal.
  - There is blood draw for PK at time 0.

- All serial collections are based on the starting time-point.
- When each time-point is due:
  - Blood will be drawn first,
  - Ideally, the participant will self-collect the PK swab within 5 minutes of the blood draw.
- Make sure that specimen times are accurate in case there are delays in sample collection. Correct recording will allow the interval of time to be correctly gauged.
- Missed or delayed blood draw time-point:
  - There will be no bearing on the next time point.
    - Example: Although the '1 hour' time-point draw was 15 minutes late (drawn at 75 minutes), the 2 hour PK blood would still be drawn at the 2 hour (120 minute) mark.
  - If a collection is missed entirely, notify the MTN-028 management team.

Follow-up Visits with single PK collection time point
The blood is drawn, and then the participant should collect the self-collected swab within 1 hour. The protocol states approximately within 1 hour.

In the case that the ring is removed prior to a visit:

- Vaginal swab for PK should still occur, preferably after at least 8 hours have passed from the time of re-insertion. However, if less than 8 hours, still collect the samples. In any case, comment on the LDMS tracking sheet and Ring Adherence CRF, item 4.
- This ring removal / re-insertion should be noted on LDMS tracking sheet and the Ring Adherence CRF.
- If it is an Early Termination visit and the vaginal ring has been out for 3 or more days, do not collect samples for vaginal fluid PK and plasma PK.

Procedure for Vaginal Fluid Sampling for PK assessment and weighing swab

1. Each day of collection of vaginal swab for PK, perform QC that would be required for the analytical scale to accurately weigh samples to a weight of at least 0.1 milligrams. Do not turn off balance until weighing for the day is completed.
2. Materials for each time point:
   - 2 SCHARP labels with PTID, visit number, visit date, time point.
   - 2-mL Nalgene cryovials
   - Polyester-Tipped (Dacron) Swab
   - Ziplock biohazard sample bags
   - Urine cup (without lid) or similar lightweight container, placed on middle of scale, to contain items to be weighed. (Some balances have an optional basket.)
   - A rack that will hold the cryovial
   - For clinical staff, scissors to cut swab shaft
   - Calculator
3. Handle items to be weighed with gloves.
4. Place identically-labeled SCHARP label on each the cryovial and a biohazard sample ziplock bag.
5. Perform pre-weight.

a. Zero the urine cup or similar container
b. Place the labeled 2-mL cryovial in the urine cup.
c. Place the packaged sterile Dacron swab upright in the urine cup. (Make sure it is not leaning on a part of the scale.)
d. Record this pre-weight on the LDMS Tracking Sheet.
e. Place the cryovial and the packaged Dacron swab in a biohazard sample ziplock bag with the matching label to the tube.
f. If multiple time points or multiple participants on that day, pre-weights for all time points may be obtained with careful observation of time-point labels.

6. Make sure you have the correct participant time-point and instruct the participant to wash their hands before the exam.
   a. In the exam room instruct the participant that none of the items in the bag should be thrown into the garbage – only into the ziplock bag.
   b. Prep for the participant:
      i. Have the rack ready.
      ii. Unscrew the lid of the 2-mL cryovial and place the tube in the rack, the lid in the ziplock bag.
      iii. Start the peel of the packaging of the swab. (Sometimes not a sufficient separation)
   c. The participant will peel the packaging and remove the Dacron swab to collect vaginal fluid (slow count to 10).
      i. The participant will place the swab in the tube and the swab packaging into the ziplock bag.
   d. Cutting or bending to break the swab shaft. (!!!Potential to lose swab shaft!!!)
      i. If clinical staff will cut the shaft, a suggestion, for leverage, is to not use tip of blades to cut, but make sure shaft of swab is at the pivot point of the scissors, then cut.
      ii. If clinical staff or participant will perform a repeated bend to break the shaft with dominant hand, while doing so, it may be easiest to hold the top of the tube with the forefinger and thumb of the other hand.
   e. Place the cut shaft in the ziplock bag.
   f. Screw the lid back on the cryovial and place sample in the bag with the swab packaging and the swab shaft.
7. Perform Post Weight:
   a. Zero the urine cup or similar lightweight container.
   b. Weigh the capped cryovial containing the absorbed swab tip, the swab packaging and the remainder of the swab shaft (Suggestion: Place the swab shaft into the packaging and have it upright during weighing.)
   c. Make sure that the post-weight is larger than the pre-weight.
   d. Record post-weight on the LDMS Tracking sheet.
8. Within 2 hours, place the sample tubes in the freezer at ≤-70˚C.

Shipping of PK swab samples

- LC will coordinate sample shipments throughout course of study if necessary and at its conclusion.
- The back-up samples will be retained at the site until advised by the LC or MTN-028 leadership team.
- All shipments will be on dry ice that will be sufficient for a 24 hour period and can be initiated Monday through Wednesday to insure that samples arrive in the lab during the work week.

9.7.6. Testing of Intravaginal Ring (IVR) for Remnant Content Analysis

Used rings will be analyzed for residual levels of MK-2048 and Vicriviroc, and will be collected at day 28 or early termination visit. The used rings may contain vaginal secretions and therefore treated as a biohazard. The rings will remain in the amber pouch and stored at room temperature until further notice from the MTN LC. Rings that are defective or inserted briefly and removed for various reasons may be destroyed at the site via biohazard procedures.

Important notes:

- Hour 0 Blood and Vaginal swab for PK should be collected immediately before ring removal.
- If the ring is removed by the participant prior to the clinic visit and will not be reinserted, instruct the participant to rinse and dry the ring and place it in a container that is stored at room temperature. At the clinic, the used ring is still prepared for residual drug analysis. After the used ring is taken out of the container that the participant used to return it, follow directions starting with step 1 of "Removal of ring by clinician".

Materials:

- A disposable container or a reusable container that was cleaned using 10% bleach solution for 20 minutes or sterilized.
- Tap water
- PPE: lab coat, gloves, face guard
- Paper towel or gauze
- 3"X5" amber Zippit pouch with affixed biohazard label
- SCHARP label for amber pouch

Removal of ring by clinician:

1. Wear lab coat, gloves, and protective face guards when performing this step.
2. The clinician will remove the used ring and place in a clean container with tap water.
3. Move the ring around in the water or swirl the container to remove vaginal material.
4. Take the ring out of the water and blot dry with paper towels or gauze.
5. The ring should be dry before storing in pouch.
6. Dispose of blotting materials and contaminated water according to your institution biohazard policy.

Preparation of used ring for storage on-site:

1. Site staff will place the ring into a new 3"X5" amber Zippit pouch (see figure 9-4) that was provided by LC to store the rings.
2. Label the pouch with the participant ID number and visit number.
3. Add a biohazard sticker if one is not already attached to the pouch, making sure not to cover the identifier information.
4. Store the used ring within the biohazard labeled amber pouch at 2-8°C.
5. The use of LDMS is required to log in all used rings.
6. At the end of the study, LC will contact site to coordinate shipment.

Figure 9-4: 3"×5" amber Zippit pouch

9.8. Cervical Specimens: Pap Test and Biopsy for PK

Pap smears are only required if clinically indicated or if a participant has not had a documented normal test within 12 months prior to Enrollment.

A cervical biopsy will be collected as described in the site SOP, and will be using standard cervical biopsy instruments (Kevorkian, Tischler, etc) with a bite size measuring 3 x 5 mm. Topical anesthetic will not be used, however, oral nonsteroidal anti-inflammatory drugs (NSAIDs) for pain management are allowed. Bleeding may be controlled through a combination of applied pressure, silver nitrate and/or monsel's solution.

9.8.1. Papanicolaou (Pap) Test (*only if indicated)

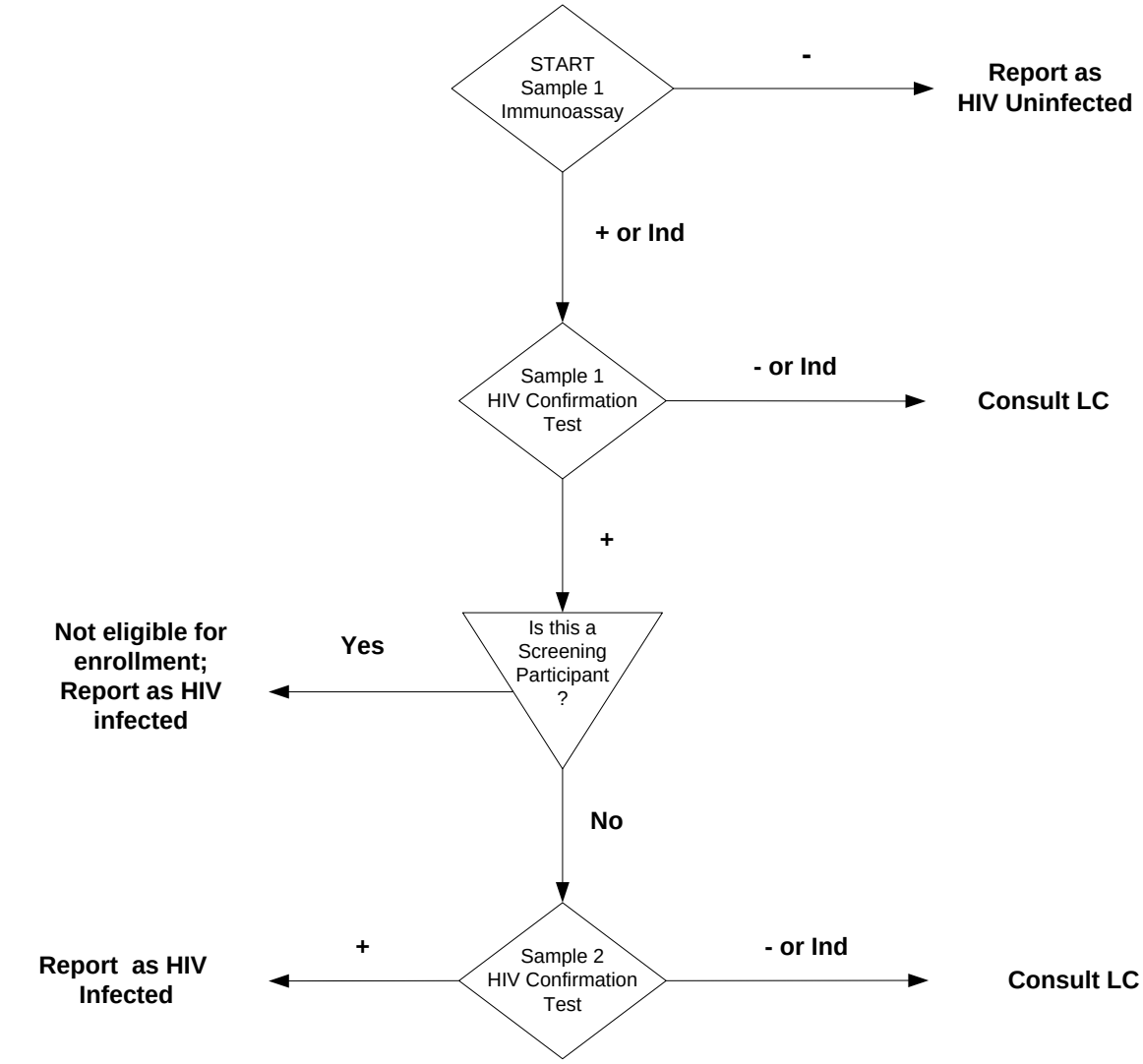
If a Pap is required, ecto- and endocervical cells will be collected after all tissues have been visually inspected, and all other required specimens have been collected. The testing will be done at the site's local laboratory. Specimen collection, testing and QC procedures must be performed and documented in accordance with study site SOPs.

9.8.2. Cervical Biopsy for PK

One biopsy will be collected for a tissue PK level at Visit day 28.

1. Label one 2 ml cryovial (Nunc or Nalgene) with a SCHARP label and the appropriate sample and study identification information.
2. Weigh the labeled cryovial using an analytical scale with a sensitivity rating of 0.1 milligrams or better. Document this pre-weight on the LDMS tracking sheet.
3. Directly transfer the biopsy to the designated pre-weighed cryovial.
4. Obtain the post-weight, which should be greater than the pre-weight, for the cryovial containing the biopsy using an analytical scale and document on the LDMS tracking sheet.
5. Calculate the net weight, which should be greater than zero.
6. Immediately freeze the cryovial containing the PK biopsy in dry ice ethanol bath (dry ice with enough ethanol to make a slushy consistency) or liquid nitrogen.
7. Document the time when the cryovial containing the biopsy is frozen on the LDMS tracking sheet.
8. Store the labeled cryovials containing the frozen biopsies at ≤-70˚C.
9. All pre and post weights are also to be logged by the processing lab onto an excel weight worksheet supplied by LC. The net-weights will be calculated by the formula in the worksheet and entered into the LDMS system.
10. LC will coordinate shipments throughout if necessary and at the end of the study. All shipments will be on dry ice and can be initiated Monday through Wednesday to insure that samples arrive in the lab during the work week.

Appendix 9-1: HIV ANTIBODY TESTING ALGORITHM



Ind: Indeterminate test results
LC: Laboratory Center

Section 10. Counseling Considerations

All counseling should be provided in a non-judgmental client-centered manner that responds to current participant needs for information, education, support, motivation, skills-building, and/or referrals. Participants' needs are likely to change over time; thus the content and focus of counseling discussions should also responsively change over time. Because of this, specific content to cover or skills to emphasize are not standardized. Rather, the process for these discussions is standardized to allow for appropriate tailoring and targeting to an individual participant's needs at a given point in time.

All counseling and referrals should be documented in participant study records. Proper documentation may be achieved through the use of counseling checklists/worksheets, and/or chart notes. To support continuity in the ongoing client-centered counseling over time, documentation of each counseling session should include sufficient information and detail to inform subsequent counseling sessions.

10.1 HIV and Risk Reduction Counseling

HIV testing is required at Screening, Enrollment, and the Day 35 Final Clinic/Early Termination Visit. HIV pre-test, post-test, and risk reduction counseling is therefore required at these visits, as well as when HIV testing is clinically indicated. All HIV counseling should be provided by trained study staff in accordance with local counseling standards. Counseling staff should also be trained on study-specific HIV testing methods and interpretation of HIV test results per the testing algorithms in protocol Appendix II. Sites are required to develop SOPs which outline site-specific procedures for HIV/Risk Reduction Counseling, Testing, and Referral.

10.1.1 HIV Pre and Post-Test Counseling

When providing pre-test and post-test counseling, participant-centered approaches should be used to assess participant knowledge of relevant information, dispel any misconceptions, ensure participant readiness for HIV testing, and ensure participant understanding of test results. A sample HIV counseling worksheet is available for use on the MTN-028 webpage under Study Implementation Materials. This worksheet provides a guide to the minimum requirements for HIV testing and counseling sessions and may be tailored for use at each study site. Counselors should provide and explain test results in a private setting per site SOPs. Counselors should assess participant understanding of results and provide clarification and further information as necessary. Regardless of status, continued risk-reduction should be emphasized.

Table 10-1
Interpretation of HIV Test Results Per Protocol Appendix II

Test Result	Counseling Message(s)
Sample 1 Immunoassay negative	HIV-uninfected; test results indicate that you are not infected with HIV.
Sample 1 Immunoassay positive or indeterminate	HIV status not clear; test results indicate that you may be infected with HIV but additional testing is needed to confirm your status. No additional blood collection is needed for this testing. Provide estimated turnaround time for results.
Sample 1 Confirmatory Test positive	**If Screening or Enrollment Visit**: HIV-infected; test results indicate that you are infected with HIV. You are not eligible for enrollment in this study. Provide counselling and referrals for HIV positive participants per site SOPs. **If during study follow-up**: HIV-infected; test results indicate that you are infected with HIV. Additional testing may be needed for study purposes and to see how your body is responding to the virus. This additional testing will be done from a new blood sample. It is common for HIV research studies to do additional testing in this situation, and unusual for this testing to show a different result. Provide counseling and estimated turnaround time for results.
Sample 1 Confirmatory Test negative or indeterminate	HIV status not clear; test results indicate that you may be infected with HIV but additional testing is needed to confirm your status. Consult the LC for specific testing and counseling guidance.
Sample 2 Confirmatory Test positive	HIV-infected. Test results have confirmed that you are HIV infected. Provide counselling and referrals for HIV positive participants per site SOPs. Counsel participant that regular study visits will discontinue at this time.
Sample 2 Confirmatory Test negative or indeterminate	HIV status not clear; test results indicate that you may be infected with HIV but additional testing is needed to confirm your status. Consult the LC for specific testing and counseling guidance.

10.1.2 Risk Reduction Counseling

Risk reduction counseling is required per protocol at the enrollment visit, and should also occur whenever HIV testing is done. More frequent counseling could be done per site SOP. Client-centered approaches should be used when assessing participant risk for HIV infection and providing risk reduction counseling. The counselor should ask open-ended questions, actively listen to participant responses, probe as needed for further information, and guide the participant in identifying her risk factors and barriers to risk reduction, as well as strategies and action plans to try to address these. Abstinence requirements for the duration of the study may also be emphasized during risk-reduction counseling.

Supported and facilitated by the counselor, the risk reduction plans identified by the participant should reflect and respond to her current risk assessment and should be practical, yet challenge the participant toward risk reduction. For participants whose risk reduction barriers are significant, risk reduction plans may need to be incremental. For participants whose risk reduction barriers change over time (e.g., due to a partner change), risk reduction plans may need to change over time. Importantly, all risk reduction plans should be agreed upon by the participant and should be documented in the participant's study records, with a copy made available to the participant if she wishes.

At each counseling session, the risk factors and risk reduction plans identified at the previous sessions should be reviewed and discussed with the participant to determine her experience since her last session, was she able to carry out her strategies and plans, and what were the outcomes. Risk reduction plans identified and agreed upon with the participant at the current session should then build on experience since the last session. Additional or alternative strategies may be identified to achieve further risk reduction if current strategies were not successful.

Risk reduction counseling sessions should also offer skills building to the participant when indicated, how to discuss sensitive issues with partners and other influential persons. HIV counseling for partners should always be offered, either as an individual session or as a couple's session.

Referrals are expected components of risk reduction plans when indicated based on participant needs. When referrals are provided, these should be fully documented in participant study records and should be actively followed up at subsequent counseling sessions to determine whether the participant sought the services to which she was referred, what the outcome of the referral was, and whether additional referrals are needed. All such follow-up should also be fully documented in participant study records.

As participants are expected to remain sexually abstinent during participation in MTN-028, and use of other vaginal products is prohibited, condoms will only be offered during HIV/Risk Reduction counseling at the Day 35 Final Clinic/Early Termination Visit.

10.2 Protocol Counseling

Per protocol, protocol requirements counseling will include adherence, product use, and contraceptive counseling. Counseling is required at Screening and Enrollment Visits, and at follow-up visits if indicated. If indicated in this case means that given the frequency of the visits, it is not necessary to go over all aspects of the counseling messages, but rather review or clarify with the participant important information relevant to their situation. Guidance about these types of counseling are described in detail in the sections that follow.

10.2.1 Contraceptive Counseling

Contraceptive counseling is required at Screening and Enrollment visits, and at other study visits if indicated. Study staff who provide contraceptive counseling should be trained to do so per local practice standards and should also be trained on MTN-028 protocol specifications related to contraception. Contraception may be provided on site or sites may opt to refer participants to non-study providers for contraception.

To be eligible for MTN-028, potential participants must report use of an effective method of contraception at enrollment and intend to use an effective method for the duration of study participation. Per protocol, effective methods include hormonal methods (except for contraceptive IVRs), intrauterine device (IUD) inserted at least 28 days prior to enrollment, engaging in sex with women exclusively, self or partner sterilization, and/or being sexually-abstinent for the past 90 days. For those participants who report sterilization, study staff must verify the sterilization per site eligibility SOPs; the site is encouraged to obtain medical records as part of their verification procedures.

All contraceptive counseling should be provided in a client-centered manner and should guide and support each participant in making the best contraceptive method choice for her. When providing information on various contraceptive methods to study participants, standard information should include how each method is taken or administered, mechanism of action, potential side effects, and level of effectiveness.

At Screening and Enrollment, contraception counseling should be provided in the context of the study eligibility criteria related to pregnancy intentions and willingness to use an effective contraceptive method. Counseling provided at these visits should therefore explain which methods are acceptable for study purposes and emphasize that women who cannot commit to use of these methods for the duration of the study should not enroll in the study (this is part of their contraceptive choice). Participants must have no intention to become pregnant within the 3 months following screening or enrollment.

During follow-up, contraceptive counseling should be offered if indicated. Issues discussed at the previous counseling session should be reviewed and discussed with the participant as needed and the counselor should determine whether the participant has any current issues, questions, problems, or concerns with her current contraceptive method. For participants with no issues or problems, counseling sessions during follow-up may be brief and supportive. For participants with issues or problems with their current method, counseling sessions during follow-up include discussion of the specific problems encountered and identify potential strategies to address these, which may include switching methods.

All sites should offer emergency contraception to study participants when applicable. The term emergency contraception refers to back-up methods for contraceptive emergencies which can be used within the first few days after unprotected intercourse to prevent unwanted pregnancy. The WHO-recommends two methods of emergency contraception: emergency contraceptive pills and copper bearing IUDs. Please see the WHO Fact Sheet (dated July 2012) for more information on emergency contraception: http://www.who.int/mediacentre/factsheets/fs244/en/.

All contraception counseling sessions should be fully documented in participant study records. For each session, sufficient information and detail should be recorded to support review and appropriate follow-up at each subsequent visit. A sample of a contraception counseling worksheet is provided on the MTN-028 Study Implementation webpage.

10.2.2 Product Use Instructions and First Product Use

During the enrollment visit, participants will be provided with detailed instructions regarding vaginal ring insertion and removal (see MTN-028 Ring Insertion Instructions available on the MTN-028 Study Implementation webpage). Staff should actively review these instructions with participants, and use visual aids and pelvic models (if available) to help explain ring insertion and removal. A copy of the illustrated instructions should be offered to each participant.

Participant Instructions for Ring Insertion: See MTN-028 Ring Insertion Instructions available on the MTN-028 website.

Participant Instructions for Ring Removal (provide verbally to participants):

1. Before removing the ring, wash and dry your hands.
2. Choose a comfortable position (can reference ring insertion instructions for illustrations of different positions).
3. Put a finger into your vagina and hook it through the ring.
4. Gently pull down and forward to remove the ring.
5. If you will be reinserting the ring, follow the ring insertion instructions, and wash your hands when you are done. If you will not be reinserting the ring, continue to steps 6-9 and contact the study clinic.
6. Place the used ring in the bag provided by clinic staff or other suitable container if the bag is not available.
7. Wash your hands.
8. Place used ring and container in a safe and private area out of reach of children or other occupants of the home.
9. Bring any used ring (in its container) with you to the clinic during your next study visit.

In addition to receiving ring insertion and removal instructions, staff should provide adherence counseling as outlined in section 10.2.3. This can be done before or after first product use.

After providing product insertion instructions and answering any questions the participant may have, study staff will ask the participant if she is ready to try inserting the vaginal ring herself. Insertion should be performed in a private space, with study staff standing by in case the participant requests guidance or technical assistance.

Difficulties in inserting the vaginal ring are expected to be rare. At the Enrollment Visit, study staff are required to confirm proper placement of the VR by a digital examination (see Section 10.2.2.1). For all other follow-up visits, this procedure should be done only if indicated (i.e. the participant is having discomfort potentially due to improper VR placement). For participants who have difficulty or who have inserted the ring incorrectly, study staff should provide further information and guidance to address the difficulty encountered. After guidance is provided, the participant should try again to insert the vaginal ring at the enrollment visit. If she is unable, study staff may insert the ring for the participant.

It is recommended that staff also confirm that the participant is able to remove and reinsert the VR. This is to encourage comfort with removal procedures, and additional practice in case the VR is removed or accidentally falls out prior to her next clinic visit.

NOTE: If ring is remove for this purpose, timing for PK purposes starts when the ring is first inserted.

After the VR is inserted, study staff should de-brief with the participant on her experience. Any issues or problems raised by the participant should be addressed by the study staff and documented in participant study documents so the information is easily available for reference at study follow-up visits.

10.2.2.1Clinician Instructions for Checking Ring Placement

At the enrollment visit, following insertion of the VR, the study clinician should check placement of the VR, regardless of who inserted it, to confirm correct placement. The following is the procedure that should be used to verify ring placement:

1. After ring placement, the participant should walk around prior to verification of correct ring placement.
2. The participant should then lie comfortably on the examination couch in supine position (on her back).
3. Upon genital inspection, the ring must not be visible on the external genitalia. If the ring is visible, the placement is not correct.
4. The ring should not press on the urethra.
5. On digital examination, the ring must be placed at least 2cm above the introitus beyond the Levator Ani muscle.
6. If, on inspection, the ring is found to be inserted incorrectly, the ring should be removed and reinserted correctly by the participant or the study clinician.

At the Enrollment visit, after correct placement is confirmed, staff should ask the participant to feel the position of her ring. This will help ensure that she understands what correct placement feels like, should she need to check this between study visits. This instruction may be repeated at any visit, as needed.

10.2.3 Study Product Adherence Counseling

Per protocol, participants will be provided product adherence counseling at their enrollment visit. At their discretion, sites may also review adherence counseling messages or product use instructions during the screening visit (e.g. as part of education on study requirements), and throughout follow-up as needed.

When discussing adherence, it is important that the topic be addressed using a neutral approach, so as to leave the participant feeling comfortable/free with discussing instances of non-adherence. Participants should be encouraged to ask questions and raise issues or problems at any time. Participants should also be encouraged to pay attention to their experiences using the ring, and to share these experiences with staff.

A MTN-028 Protocol/Product Adherence Counseling Worksheet is available for use on the MTN-028 Study Implementation Materials webpage. This worksheet provides a guide to the minimum requirements for protocol/product use counseling messages at enrollment; this

worksheet may be tailored for use. As each point is addressed, site staff should mark each message on the worksheet. Discussion points, participant questions should also be noted on the worksheet and/or in chart notes and used for future counseling sessions. These key counseling messages are also available as printed materials on the reverse side of the Ring Insertion Instructions for participants to take home. These printed materials should be IRB approved before use.

During follow-up visits, adherence counseling should be provided if indicated. At a minimum, it is recommended that staff briefly check in with participants at regular intervals (about once per week) to see how ring use is going and if they have any questions or concerns. If the participant reports ring removals or expulsions, is experiencing discomfort, and/or has any questions or concerns about ring use, these issues should be addressed in a neutral and non-judgmental way. Further guidance for the adherence counseling is provided below.

- Review documentation of previous product use adherence counseling sessions in preparation for a new counseling session.
- Emphasize the importance of open communication about ring use at the beginning of each session.
- Use open-ended questions and probes to assess the participant's experiences with ring use. For example, "What has your experience with ring use been so far?" or, "How has ring use been going for you?" If her experience was bad, ask why and when. If it was good, ask how and why.
- Work with participants to develop strategies and goals to either maintain good adherence, or to overcome adherence barriers if encountered.
- When needed, review ring use insertion instructions or key adherence messages with the participant, using the illustrated instruction sheet and any other visual aids that may be helpful to ensure participant understanding of proper product use and/or study protocol requirements.
- When needed, provide skills building to the participant, e.g., on how to discuss ring use with partners or other influential persons.

Adequate time should be taken to counsel the participant and address any questions or concerns the participant may have. Each counseling session should be fully documented per site SOPs for source documentation.

During follow-up, adherence counseling (if indicated) should occur after administration of the Ring Adherence CRFs. Sites may choose to conduct adherence counseling prior to completion of clinical/lab assessments to improve visit flow. Note that in this situation, some participants may receive adherence counseling, but may subsequently be put on product hold during the visit.

10.2.4 Biopsy Collection for PK Counseling

Participants will also undergo collection of cervical tissue (biopsies) for PK at the Day 28 visit. As part of the provision of protocol adherence counseling, study staff will explain what procedures will be performed at the visit and what to expect. The participant will be counseled and informed that in order to collect cervical biopsies, a clinician will use an instrument called a speculum. Once the speculum is inserted, the clinician will take one or two small tissue samples from the participant's cervix, each about the size of a grain of rice. These samples will be used to see how much of the study drug is in her tissue.

Participants should be counseled to abstain from inserting anything in the vagina, including engaging in vaginal intercourse, as she may be at increased risk for STIs and HIV acquisition, if exposed. Participants should also be counseled that they may experience some pressure or discomfort in her genital area during the pelvic examination and sample collection. During the collection of biopsies, the participant may feel slight to moderate pain (similar to the feeling of being pinched) which usually resolves within a few hours following tissue collection. The participant should be informed that she may have spotting (small amounts of bleeding) for 1 – 2 days following the biopsies and that there is a small risk of the biopsy area becoming infected or having bleeding that is heavier than spotting. The participant should be instructed to contact the study clinic immediately if she experiences heavy bleeding, more than a usual menstrual period, a foul odor or a heavier vaginal discharge (more than usual).

10.2.5 Protocol Adherence Counseling

As safety is of the utmost importance, site staff will counsel participants to refrain from engaging in certain practices and/or using prohibited medications during the course of study participation which could potentially increase the possibility of adverse events due to agents other than the study ring and product. Note that protocol adherence counseling may be reviewed and documented as part of the study product adherence counseling session at enrollment (specifically, refer to the "AVOID" section of the adherence counseling messages worksheet). If sites wish to conduct protocol and product adherence counseling separately, worksheets/tools may be modified to suit this approach (e.g. if different staff members will be assigned these responsibilities).

10.2.5.1 Prohibited Practices and Medications

Participants will be counseled to avoid the following prohibited practices and medications during participation in the study:

- Receptive intercourse (vaginal, anal, or oral intercourse, finger stimulation and the use of sex toys) should be avoided for duration of study and for 5 days preceding Enrollment, i.e., participants should be sexually abstinent.
- Tampons should not be used during the first week of study participation (starting at the enrollment visit) and for 24 hours prior to each clinic visit following enrollment.
- Non-study vaginal products and other devices should be avoided. This includes, but is not limited to: spermicides, female condoms, diaphragms, contraceptive intravaginal rings, vaginal medications (with the exception of single dose fluconazole (diflucan) for the treatment of vaginal fungal infections), menstrual cups, cervical caps, douches, lubricants, and sex toys (e.g., vibrators, dildos, etc.).
- Participation in other research studies involving drugs, medical devices, or vaginal products for the duration of study participation
- Use of female-to-male transition medications (i.e. cross gender hormonal therapy) during the study is prohibited.
- Avoid using certain CYP3A inhibitors and CYP3A inducers (see SSP Section 7)

Site staff should counsel study participants to refrain from using CYP3A inhibitors and inducers. These medications are not recommended because VCV (MK-4176) is a CYP3A substrate. Co-administration with CYP3A inhibitors and inducers may increase and/or decrease the concentration of either drug within the blood and/or vagina. Participants are asked to refrain from using CYP3A inhibitors and CYP3A inducers however allowances will be made to treat symptomatic Candida vaginitis. Several types of CYP3A inhibitors and/or inducers that are PROHIBITED during study participation are listed in section 7 of this manual.

Section 11. Data Collection

The purpose of this document is to provide site staff with the information they need to successfully complete and submit MTN-028 case report forms. For questions about this section or about general data collection policies, procedures, or materials, please contact the SCHARP Project Manager for the study as listed below.

The SDMC (Statistical and Data Management Center) for this study is SCHARP (the Statistical Center for HIV/AIDS Research and Prevention). SCHARP is located in Seattle, USA, and is in the US Pacific Time (PT) time zone. The DataFax database will be housed at DF/Net Research. The SCHARP MTN-028 team members, along with their job role and e-mail address, are listed below.

MTN-028 Statistical and Data Management Center (SDMC) Staff

Job Role	Name	Email Address
Protocol Statistician	Jingyang Zhang	Jzhang2@fhcrc.org
Statistical Research Associate	Jason Pan	zpan@fhcrc.org
Project Manager	Melissa Peda	mapeda@scharp.org
Operations Programmer	Drew Edwards	drew@scharp.org
Database Manager	Dena Seabrook	dena@dfnetresearch.com
Lab Programmer	Katie Snapinn	ksnapinn@scharp.org
Clinical Affairs Safety Associate	Ning Jiang	njiang2@scharp.org

11.1 DataFax Overview

DataFax is the data management system used by DF/Net Research to receive and manage data collected at study sites. The site faxes an electronic image of each case report form (CRF) to DataFax, and the original hard copy CRF is retained by the site.

11.1.1 CRF Transmission and Troubleshooting

Case report forms can be transmitted to DF/Net Research in one of two ways: faxed using a fax machine connected to a land phone line (fax to phone number 1-866-807-8681); or faxed using a fax machine connected to the internet (fax to e-mail < mtn@dfnetresearch.com >).

DF/Net Research's DataFax support group is available to consult with the site to determine the best method for data transmission. The DataFax support group can be contacted via e-mail at <support@datafax.com>. This group should also be contacted anytime the site has technical questions or problems with their fax equipment.

11.1.2 Data Entry/Quality Control

Once a CRF image is received by DF/Net, the following occurs:

- DataFax identifies the study to which each CRF belongs using the barcode at the top of the form. It reads and enters the data into the study database and stores each CRF on a computer disk.
- Next, each CRF is reviewed by at least two staff members at DF/Net. Problems such as missing or potentially incorrect data are identified and marked with Quality Control notes (QCs).
- QCs are compiled into QC reports that are sent via e-mail to the study site on a regular basis. Sites are asked to correct or clarify any problems identified on the QC reports and refax the corrected CRFs to DF/Net.
- When the refaxed pages are received, DF/Net Research staff review the corrected pages and resolve the QCs.

If a change is made to a CRF but the updated page is not refaxed to DF/Net Research DataFax, the change will **not** be entered and the study database will continue to contain incomplete or incorrect data. Additionally, if the change was prompted by a QC, the QC will continue to appear on subsequent QC reports until the modified CRF is received at DF/Net Research. Therefore, it is very important that the site refax updated CRF pages to DF/Net Research DataFax **any time** a change is made to a CRF, regardless of whether or not the change was made in response to a QC report.

11.1.3 iDataFax View-only Access

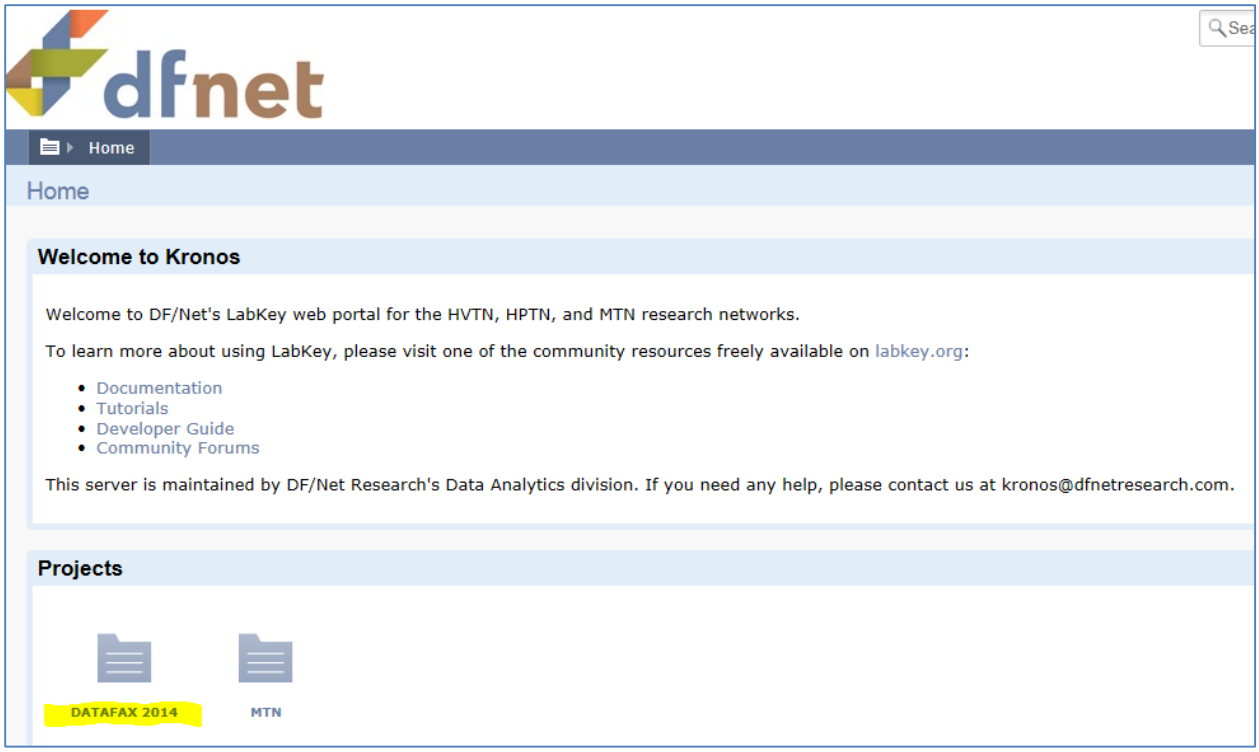
Each site will be able to access and view its own MTN-028 CRF data via iDataFax view-only access. With view-only access, sites can view their faxed CRF images and data, view their QCs and clinical queries, identify missing CRF pages or visits, and export their data. This will allow the user to review and resolve QCs even before they can be included on a QC report. Being able to see the CRF image and what is in the database can also help the user to better understand what needs to be modified or reported on the paper CRF to resolve the QC or query.

NOTE: View-only access means that the user can view what's in iDataFax, but cannot enter or modify data, or respond to QCs or clinical queries. In addition, sites will not be able to view or access other sites' data.

To obtain view-only access to its study data, each site must first download the iDataFax software by logging into the DF/Net Research Kronos web site: https://kronos.dfnetresearch.com.

Each Site Coordinator will be set up with a Kronos and iDataFax user account prior to study start. As each new user account is set up, the user will receive a "Welcome to the Kronos Web Site new user registration" e-mail, from the e-mail address kronos@dfnetresearch.com, with instructions on logging into the Kronos system for the first time and setting up a new user password. To obtain new user accounts for additional site staff members, please contact the SCHARP Project Manager.

Once a site staff member logs into the Kronos site, s/he may access and download the iDataFax software by clicking on the "DATAFAX 2014" project folder (see screenshot below).



The folder contains links for downloading the iDataFax software, as well as an iDataFax User Manual with detailed instructions on downloading, logging into, and using iDataFax (see screenshot below).

For technical assistance with logging into and navigating the Kronos site, please contact the SCHARP Project Manager and the team at kronos@dfnetresearch.com.

For questions or technical assistance with iDataFax, please contact the SCHARP Project Manager and the team at support@dfnetresearch.com.

11.2 DataFax Form Completion

11.2.1 General Guidelines

Based on the use of fax technology and Good Clinical Practices (GCPs), the following guidelines should be used for completing DataFax CRFs:

- Use a black or dark blue medium ballpoint pen. Do not use any other type of writing tool. Use only one color per form. That is, do not begin completing a form using a blue pen and then switch to a black pen during the same form completion session.
- Press firmly when recording data or writing comments.
- Print all data and comments legibly by hand. Entries that cannot be read will result in QC notes.
- Do not type data onto CRFs. Do not use cursive/script handwriting, as it can be difficult to read.
- Write numbers as large as possible while staying within the boundaries of the boxes.
- Record data on the front of CRFs only. DataFax cannot read the back of CRFs.
- Do not record data or make marks in the 0.5-inch/1.5-cm margins at the top, bottom, or sides of the CRF.
- If the lines provided for written responses are not long enough, continue in another blank area of the form (within the page margins).
- Mark only one answer except when given the instruction "Mark all that apply."
- A response is required for every item unless instructed otherwise by a skip pattern.
- **Never** obscure, mark over, or punch holes through the barcode at the top of each CRF. DataFax requires the barcode to identify the CRF.
- **Never** use correction fluid ("white-out") or correction tape on CRFs.
- Remove any paper clips, staples, or other attachments before faxing CRFs.
- The site staff person who initially completes the form **must** record his/her initials **and** the date in the space provided in the bottom right-hand corner of each CRF page.
- Fax forms as soon as possible after they have been completed and reviewed. Ideally, completed forms will be faxed to DF/Net within 1–2 days of completing the visit, though up to 5 days is allowed.

11.2.2 How to Mark Response Boxes

Many items on DataFax CRFs have a box or series of boxes for recording a response. Mark the box clearly with an **X**. Do not fill in the box with shading or mark it with a slash or other character.

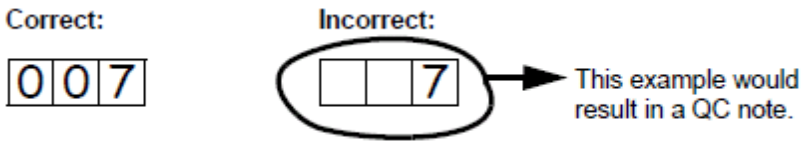
Mark only one response box for each item unless the "Mark all that apply" instruction is present.

11.2.3 How to Record Numbers

Some questions on DataFax CRFs include boxes for recording a numeric response. DataFax can only read the numbers in these boxes if they are recorded clearly. The following instructions should be followed when recording numeric responses:

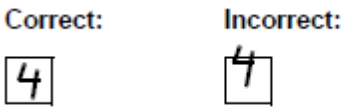
- Right justify **all** numbers and fill in any blank leading boxes with zeroes. If boxes are left blank, a QC note will be applied asking for the boxes to be filled in.

  The following example shows how a value of 7 is recorded when three response boxes are provided:



- Write the number(s) as large as possible while staying within the boundaries of the box; try not to stray outside the boundaries of the box.

  In the following example, the 4 could be misinterpreted as a 7 or a 1 because DataFax can only read what is *inside* the box:



- Write the number(s) simply, with few loops.

  The following example shows the format in which numbers will be most easily read by DataFax. Also included are some commonly used formats that may be difficult for DataFax to identify.

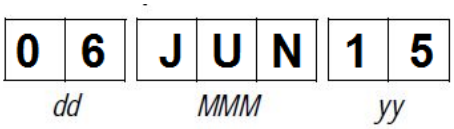
11.2.4 How to Record Dates

Dates are recorded using the "dd MMM yy" format, where "dd" represents the two-digit day, "MMM" represents the three-letter abbreviation of the month (in capital letters), and "yy" represents the last two digits of the year.

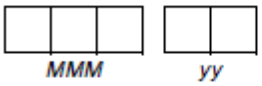
The month field must be filled in with the three-letter abbreviation *in English* for the date to be read in DataFax. Abbreviations are shown in the table below.

Month	Abbreviation	Month	Abbreviation
January	**JAN**	July	**JUL**
February	**FEB**	August	**AUG**
March	**MAR**	September	**SEP**
April	**APR**	October	**OCT**
May	**MAY**	November	**NOV**
June	**JUN**	December	**DEC**

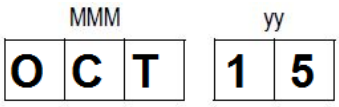
For example, June 6, 2015 is recorded as:



Sometimes, only a month and a year are required (e.g., diagnosis date for a pre-existing condition), in which case the response boxes will look like this:

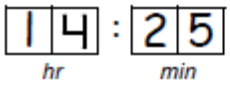


A diagnosis date of October, 2015 would be recorded as follows:



11.2.5 How to Record Time

Time is recorded on DataFax CRFs using the 24-hour clock (00:00-23:59), in which hours are designated from 0–23. For example, in the 24-hour clock 2:25 p.m. translates to 14:25 (2 p.m. = 14), which would be recorded as follows:



Midnight is recorded as 00:00, not 24:00.

The following chart shows equivalencies between the 12- and 24-hour clocks:

12-hour clock (a.m.)	24-hour clock
Midnight	00:00
1:00 a.m.	01:00
2:00 a.m.	02:00
3:00 a.m.	03:00
4:00 a.m.	04:00
5:00 a.m.	05:00

12-hour clock (p.m.)	24-hour clock
Noon	12:00
1:00 p.m.	13:00
2:00 p.m.	14:00
3:00 p.m.	15:00
4:00 p.m.	16:00
5:00 p.m.	17:00

6:00 a.m.	06:00	6:00 p.m.	18:00
7:00 a.m.	07:00	7:00 p.m.	19:00
8:00 a.m.	08:00	8:00 p.m.	20:00
9:00 a.m.	09:00	9:00 p.m.	21:00
10:00 a.m.	10:00	10:00 p.m.	22:00
11:00 a.m.	11:00	11:00 p.m.	23:00

11.2.6 Data Corrections and Additions

Sometimes, data on a DataFax CRF may need to be changed, clarified, or amended. There are many reasons why data may need to be changed, such as in response to a QC report or as a result of site review of the CRF before faxing.

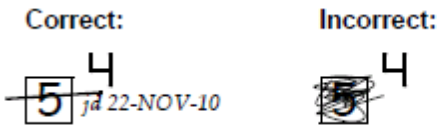
It is important to make these changes to the original CRF—***never*** copy data onto a new form. After making the change, the CRF *must* be re-faxed to DF/Net Research DataFax.

Note: If a correction or addition is made to one page of a multiple-page CRF, only refax the page that was changed. Initial and date all changes or additions.

Note: Never write over an entry once it is recorded. Use the standards outlined in the following paragraphs when changing, clarifying, or amending data.

Whenever an entry on a DataFax CRF is changed, do the following:

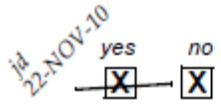
- draw a single horizontal line through the incorrect entry (do not obscure the entry or make it un-readable with multiple cross-outs),
- place the correct or clarified answer near the box, and
- initial and date the correction as shown below:



If an **X** is marked in the wrong response box, correct it by doing the following:

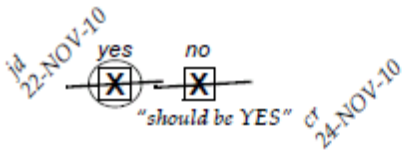
- draw a single horizontal line through the incorrectly marked box,
- mark the correct box, and

- initial and date the correction as shown below:



If the correct answer has previously been crossed out, do the following:

- circle the correct item,
- write an explanation in the white space near the item, and
- initial and date all corrections as shown below:

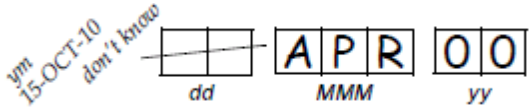


The standards above must ***always*** be followed whenever a CRF is changed, clarified, or amended, even if the change is made ***before*** the CRF is faxed to DF/Net Research for the first time.

11.2.7 How to Handle Missing and Unknown Data

If the answer to an item is not known, is not available, or if the participant refuses to answer, draw a single horizontal line through the blank boxes and initial and date the item. It is helpful to write "don't know," "refuses to answer," "UNK" (unknown), "N/A" (not applicable), or "REF" (refused) near the blank boxes.

For example, when recording a date, if the exact day is not known, draw a single horizontal line through the "dd" boxes and write "don't know" next to the response boxes, as shown below:



A skip pattern is the **only** valid reason to leave a response blank. Initials and date are required for any data item that is refused, missing, unknown, or not applicable, regardless of whether it is marked as such during the initial form completion, or as an update to the form.

11.2.8 Non-DataFax Forms

Non-DataFax forms are case report forms that are used for data documentation purposes, but are not faxed to DF/Net Research. These forms are created to ensure consistent and accurate data documentation across study sites for data that is not needed in the study database. Non-DataFax form is easily identifiable because there is no DataFax barcode along the top of the CRF. In place of the barcode, the following text appears: "NOT A DATAFAX FORM. DO NOT FAX TO DATAFAX." Non-DataFax forms are completed using the general guidelines presented above, and completed forms are stored just as DataFax forms in participant files/binders.

11.2.9 Faxing DataFax Forms

Each CRF with a bar code at the top is a DataFax form, and is faxed to DataFax once completed and reviewed as described in the site's MTN Data Management SOP. Sites are encouraged to develop a system that identifies each time a form page is faxed so that re-faxing of unchanged forms can be avoided. A date stamp used on the back of the form page may be used for this purpose as long as the date stamp does not obscure data recorded on the front of the form page.

11.2.10 Form Storage

Specifications for form storage are described in the site's MTN Data Management SOP. It is recommended that for each participant, study CRFs be stored in a hard-cover notebook, with a tabbed section for CRFs completed at each study visit.

It is suggested that log forms (such as the Concomitant Medications Log, Adverse Experience Log, Clinical Product Hold/Discontinuation Log, Social Impact Log, and Protocol Deviations Log) be kept in their own tabbed sections within the participant study notebook. This makes page numbering and updating of these forms easier than if these forms are stored by visit within the participant's study notebook.

11.2.11 MTN Data Management SOP

As a condition for study activation, each study site must have an SOP for MTN Data Management. This SOP should be reviewed and followed in combination with the information contained in the study protocol, this SSP Manual, and the site's Clinical Quality Management Plan (CQMP).

The MTN Data Management SOP contains information on and outlines site staff responsibilities for several data topics, including:

- Participant ID (PTID) assignment
- Participant study file organization
- Participant confidentiality
- Site data quality control (QC) processes
- Timing of DataFax form data transmission
- Data QC processes
- Data storage

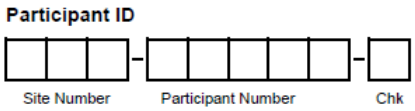
11.3 Study-specific Data Collection

11.3.1 Participant ID numbers (PTIDs)

DataFax uses a unique participant identification number (PTID) to identify each study participant in the database. Prior to study start, SCHARP provides each site with a list of PTIDs to be used for the study in the form of a study-specific MTN PTID Name-Linkage Log. The site assigns one PTID to each participant screened for the study. The PTIDs are assigned in sequential order as participants present for the screening visit. The site should ensure that each PTID is assigned only once. Once a participant has received a PTID that same PTID is maintained for that participant for the duration of her study participation.

PTID boxes are located near the upper left corner of each CRF page.

The PTIDs used for this study are nine digits and formatted as "XXX-YYYYY-Z." The PTID consists of three parts: the DataFax site number (XXX), the participant number (YYYYY), and a numerical check digit (Z). The check digit (Z) is a number generated by SCHARP with the participant number, and helps ensure that the correct PTID is recorded. Below is an example of the PTID structure used in MTN-028.



11.3.2 Study Visit Timing

Screening and Enrollment

The initial screening visit is defined as the day the participant provided written informed consent to be screened and enrolled for the study. The initial Screening Visit (that is, the date the informed consent form was signed for screening and enrollment) may take place up to 45 days prior to the Enrollment Visit. The date the participant is enrolled/randomized is Study Day 0 for the participant.

Screening Attempts (Re-screens)

Refer to Section 4: Study Procedures of this manual for guidance related to repeat screening attempts (re-screens) by a participant.

If a participant re-screens, all screening procedures and CRFs must be repeated with the exception of PTID assignment and Eligibility Criteria CRF completion (see paragraph below). Once a PTID is assigned to a participant that PTID is used for the re-screen procedures and forms completed for that participant (do not assign a new PTID).

If a participant re-screens and enrolls in the study, only case report forms from the successful screening and enrollment visits are faxed to DF/Net. Note that in this case, the Eligibility Criteria CRF completed during the failed screening attempt should be updated and re-faxed with CRFs from the participant's successful screening and enrollment visits (do not complete a new Eligibility Criteria CRF for the successful screening attempt).

Follow-Up Visits

For each required follow-up study visit, the visit type, visit code, target visit day, and visit window are listed in Table 11-1. Target days and windows are listed in days, with the day of enrollment/randomization as study day 0.

Target Days and Visit Windows

Whenever possible, visits should be completed on the target day or within the target window.

SCHARP will provide sites with a spreadsheet tool that may be used to generate individual participant follow-up visit calendars based upon the participant's enrollment date and menstrual

cycle. The spreadsheet requires that the participant's Enrollment date be entered. Once the enrollment date is entered, the target days and visit windows for follow-up visits through Day 28 will appear. The remaining study visit target days and visit windows will depend on the actual date of each participant's Day 28 visit. There are no visit windows around Days 1, 2, 29 and 30 as these are daily visits. The calendar can be printed, added to the participant's study notebook and updated as needed.

Split Visits

For MTN-028, Enrollment Visits may not be split. Whenever possible, all required follow-up visit evaluations should be completed on the same day. In those cases where this is not possible, the participant may come back and complete the remaining evaluations on another day, as long as that day is within the allowable visit window. For example, a participant comes in on Day 35 to complete the Final Clinic Visit and completes all of the required evaluations, but has to leave prior to completing a blood draw for safety labs. She comes back the next day on Day 36 and completes the remaining required procedures. This is allowed, and is referred to as a "split" visit; as the participant completed all required visit evaluations on two separate days, both days being in the visit window.

Note that for split visits, only one Follow-up Visit Summary CRF is completed, and all CRFs completed for the visit are assigned the same visit code. The "Visit Date" on the Follow-up Visit Summary CRF is the date of the first part of the split visit. See Section 11.3.3 for more information on assigning visit codes to split visits.

Table 11-1: Visit Timing Requirements

MTN-028 study visit schedule

Visit code	Visit type	target day	Visit Window
1.0	Screening Visit	</- 45 days	n/a
2.0	Enrollment	0	+45 days after Scr.
3.0	Day 1	1	Same as target day
4.0	Day 2	2	Same as target day
5.0	Day 3	3	Days 3-5
6.0	Day 7	7	Days 6-8
7.0	Day 14	14	Days 13-15
8.0	Day 21	21	Days 20-22
9.0	Day 28	28	Days 27-29
10.0	Day 29	1 day after visit 9.0	Same as target day
11.0	Day 30	2 days after visit 9.0	Same as target day
12.0	Day 31	3 days after visit 9.0	+2 after target day
13.0	Day 35/Final Clinic Visit	7 days after visit 9.0	+/- 1 day around target day

Missed Visits

In those cases where a participant is not able to complete any part of a required follow-up visit within the visit window, the visit is considered "missed". For example, an enrolled participant does not report to the clinic for her Day 2 Visit. Per table 11-1, this visit has been missed. The missed visit is documented in the study database by completion of a Missed Visit CRF that is faxed to DF/Net.

Interim Visits

An interim visit occurs when there is a contact with the participant, but required follow-up visit procedures are not done because the required follow-up visit has already been completed. An interim visit may also occur via a phone contact if the participant reports a new AE that requires reporting on an AE-1 CRF, or the participant is instructed by study staff to hold or permanently discontinue study product use.

All interim contacts with the participant should be documented in a chart note. Additionally, if the interim contact results in at least one newly-completed DataFax CRF, the interim contact is assigned an interim visit code (visit code ending in something other than ".0"). All phone contacts that meet interim visit criteria per paragraph above are also assigned interim visit codes. See section 11.3.3 for information on how to assign visit codes to interim visits.

Note that for MTN-028, there is no Interim Visit CRF. Instead, a Follow-up Visit Summary CRF is completed for interim visits/contacts as needed. Item 6 of the Follow-up Visit Summary CRF will document whether the visit is a required (regular) visit or an interim visit.

The following is an example of an interim visits:

> A participant completes her Day 7 visit as scheduled. On Day 10 post-enrollment, the participant reports to the clinic unexpectedly to report a new AE.

Why is this an interim visit? The required visit procedures for the Day 7 visit have been completed already, and a new AE is reported. An interim visit code is assigned as new CRFs will be completed (Follow-up Visit Summary, AE Log, possibly others).

Early Termination Visits

An early termination visit can occur at any point during the study after participant randomization. If an early termination visit is conducted, the Day 35/scheduled Final Clinic Visit procedures should be completed, providing participant willingness. The visit code of the early termination visit will depend on where the participant is at in her visit schedule at the time of early termination.

11.3.3 Visit Codes and Page Numbers

The MTN-028 non-log CRFs will include boxes in the upper right corner for a visit code. DataFax uses the visit code to identify the visit at which a CRF is completed. When visit code boxes are

present, site staff is responsible for recording the appropriate visit code. The table below lists the visit codes assigned to each required follow-up visit.

Table 11-2: Visit Code Assignments for Required Follow-up Visits

Visit #	Visit	Visit Code
1	Screening Visit	01.0
2	Enrollment Visit	02.0
3	Day 1	03.0
4	Day 2	04.0
5	Day 3	05.0
6	Day 7	06.0
7	Day 14	07.0
8	Day 21	08.0
9	Day 28	09.0
10	Day 29	10.0
11	Day 30	11.0
12	Day 31	12.0
13	Day 35/Final Clinic Visit	13.0

Visit Codes for Split Visits

See Section 11.3.2 for a definition of split visits. When split visits occur, the CRFs completed for the visit are all assigned the same visit code (ending in ".0"), even though the dates will differ between some of the CRFs.

Visit Codes for Interim Visits

For interim visits, interim visit codes are assigned using the following guidelines:

- In the two boxes to the left of the decimal point, record the two-digit visit code for the most recently required visit, *even if the visit was missed and/or if the participant is within the next visit's window.*
- For the box to the right of the decimal point:
  - #.1 = the first interim visit after the most recently-required follow-up visit,
  - #.2 = the second interim visit after the most recently-required follow-up visit,
  - #.3 = the third interim visit after the most recently-required follow-up visit, and so on.

Example #1: A participant completes her Day 31 visit (visit code = 12.0) on the target day. She returns to the site one day later to report a new symptom. This interim Visit is assigned an interim visit code of 12.1:

Visit code for this Interim Visit

Page numbers

Other CRFs, such as log forms (e.g., Adverse Experience Log or Concomitant Medications Log), may include boxes in the upper right corner for page numbers, as shown below:

Assign page numbers in sequential order, starting with 01 (or 001, for Adverse Experience Log CRFs). Assign numbers in sequential order (for example, the second Concomitant Medications Log page would be assigned page number 02, the third page would be assigned 03, and so on.

11.3.4 Staff Initials/Date

Most forms include a line in the lower-right corner for a staff member's initials and the date on which the form was completed. When more than one staff member records data on a CRF, the site should designate the staff member who has primary responsibility for the form. This individual completes the staff initials/date field. The individual not identified in the staff initials/date field writes his/her initials and date next to each data element for which he/she is responsible.

11.3.5 Form Supply

Sites are responsible for creating their own supplies of MTN-028 case report forms. Sites should print CRFs from pdf files provided by SCHARP (available on the MTN-028 Atlas web page). CRF pdf files will include visit packets pdfs (containing all of the CRFs required to be completed for the visit) as well as a pdf file containing all of the CRFs created for the study.

Site are encourage to test and make sure the CRFs they have produced can be read into DataFax by using a test fax pdf provided by DF/Net Research. A test fax should be done each time new printing, photocopying, or faxing equipment is installed or modified, and also when paper used for CRFs changes.

11.3.6 Case Report Form Completion Schedule

The provided forms for this study include DataFax forms (forms that are completed and faxed to DF/Net Research DataFax) and non-DataFax forms (forms that are completed but not faxed to DF/Net Research DataFax).

Some DF/Net Research -provided forms are required to be completed at each visit, while other forms are required only at one visit or only when specifically indicated. The following table (Table 11-3) lists the DataFax and non-DataFax forms that are required to be completed at each study visit.

Table 11.3: Schedule of Forms – CRFs Required to be Completed at Each Visit

Visit 1 (Screening Visit): Visit Code 1.0	
DataFax forms	**Non-DataFax forms**
Concomitant Medications Log Demographics Eligibility Criteria Pelvic Exam Pre-existing Conditions Physical Exam Safety Laboratory Results	Pelvic Exam Diagrams
Visit 2 (Enrollment Visit): Visit Code 2.0	
DataFax forms	**Non-DataFax forms**
Enrollment Physical Exam Pelvic Exam Pharmacokinetics Specimens – Enrollment Safety Laboratory Results Specimen Storage	Pelvic Exam Diagrams
Visit Day 1, 2, 3, 7, 21: Visit Codes 3.0 – 8.0	
DataFax Forms	**Non-DataFax forms**
Follow-up Visit Summary Physical Exam Pelvic Exam Pelvic Exam Ring Assessment Pharmacokinetics Specimens – Days 1, 2, 3, 7, 14, 21, 29, 30, 31, 35 Ring Adherence <u>At Visit 5.0/Day 3 only:</u> Specimen Storage	Pelvic Exam Diagrams
Visit Day 28: Visit Code 9.0	
DataFax forms	**Non-DataFax forms**
Follow-up Visit Summary Pelvic Exam Pelvic Exam Ring Assessment Physical Exam Pharmacokinetics Specimens– Day 28 Ring Adherence Ring Collection and Insertion Specimen Storage Safety Laboratory Results	Pelvic Exam Diagrams
Visit Days 29, 30, & 31: Visit Code 10.0-12.0	
DataFax forms	**Non-DataFax forms**

Follow-up Visit Summary Pelvic Exam Physical Exam Pharmacokinetics Specimens – Days 1, 2, 3, 7, 14, 21, 29, 30, 31, 35	Pelvic Exam Diagrams
Visit Day 35: Visit Code 13.0	
DataFax forms	**Non-DataFax forms**
Follow-up Visit Summary HIV Results Pelvic Exam Physical Exam Pharmacokinetics Specimens - Days 1, 2, 3, 7, 14, 21, 29, 30, 31, 35 Safety Laboratory Results Specimen Storage Termination	Pelvic Exam Diagrams

11.3.7 Completing Interviewer-administered Forms

In order to standardize interviewer-administered data collection from site to site and to maximize quality, it is critical that participant interviews be conducted with a non-biased, non-judgmental approach. Study staff should help a participant feel comfortable sharing personal information and opinions while asking the study questions in a consistent manner from participant to participant.

11.3.8 Site Review (Quality Control) of DataFax Forms

As described in the site's MTN Data Management SOP (and referenced in the site's Clinical Quality Management Plan, CQMP), each site must perform two Quality Control (QC) review steps prior to faxing DataFax forms to DF/Net Research. While DataFax CRFs are being reviewed, it is important that they are stored and tracked systematically.

11.4 Form-specific Completion Instructions

Detailed form completion instructions for each form are provided on the back of each form page. Some items on forms are straightforward and do not require specific instructions. Therefore, you will not see all form items listed in the form-specific completion instructions, but rather, only those items needing detailed explanation.

Below are additional instructions for some of the CRFs used in this study. These instructions do not appear on the back of the form page due to lack of space.

Enrollment (ENR) CRF – Randomization date and time (Item 5)

- The date and time of a participant's randomization should be completed using the FSTRF randomization confirmation email. The randomization time within this confirmation email is provided in Eastern Standard Time (EST). When completing item 5 on the Enrollment CRF, convert the time of randomization according to the site's local standard time zone.

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Adverse Experience Log (AE)

- Do not wait until the AE resolves before faxing the form page to DF/Net.
- Always make changes, corrections, and updates to the originally-completed form page (do not complete a new form). Once an AE Log form page has been started and faxed to DF/Net Research, the data from that page should never be transcribed onto another AE Log form page.
- Note that AE Log page numbers do not need to be assigned in any special order with regard to AE onset date or date reported to site. For example, if it is discovered that for a participant, page 001 and 003 were assigned, but not 002, simply assign page # 002 to the next AE Log form you complete. It does not matter if the AE's onset date or date reported to site on page 002 is later than these dates reported on AE Log page 003 (a QC will not be generated).
- For item 1, note that planned procedures or surgeries are not AEs. For example, a tonsillectomy is not an AE; rather, it is a treatment that will be collected in item 8. Any adverse experiences associated with the planned procedure or surgery, are AEs.
- Provide a rationale or alternative etiology in the Comments section for all reported AE regardless of relationship to study product. Ensure that any relevant information provided in the Comments section is also provided in item 1 (the text description of the AE). This will help avoid MedDRA coding queries during the study. For example, if a participant reports vaginal discharge and the AE is deemed not related to study product due to an infectious etiology, provide relevant descriptors (either the diagnosis or that the vaginal discharge is due to infection) in item 1.

Pharmacokinetics Specimens - Enrollment (PKS-1)

- In item 1, record the start and stop dates of the participant's last last menstrual period. If the participant is unable to recall the complete date of last menstrual period, obtain participant's best estimate. At a minimum, the month and year are required. Only record dates of menstrual period bleeding (including expected monthly bleeding on oral contraceptive pills). If a participant has not had a menses in the past 30 days, mark 'none'. If the participant is currently on her menses, mark 'ongoing'. In these cases, this item does not need to be updated with a stop date once known at a later visit.

Pharmacokinetics Specimens – Day 28 (PKS-1) and Pharmacokinetics Specimens – Days 1, 2, 3, 7, 14, 21, 29, 30, 31, 35 (PKD-1)

- In item 1, record the start and stop dates of the last vaginal bleeding that the participant experienced. This includes menstrual period bleeding, withdrawal bleeding, and expected breakthrough bleeding experienced while the participant is on Depo, Mirena, or other continuous contraceptive method where a women does not experience a monthly menstrual period. If a participant has not had any vaginal bleeding in the past 30 days, mark 'none'. If the participant is currently bleeding at the time of the study visit, mark 'ongoing'. This item does not need to be updated with a stop date once known at a later visit.

- If silver nitrate/monsels solution is used to stop bleeding during the collection of cervical biopsies, this should be noted in the comments section of the PKS to better inform PK analyses of the vaginal swabs collected on Day 28. Document this medication on the concomitant medications log CRF.

Concomitant Medications Log (CM-1)

- When recording injections (e.g., Hepatitis B vaccine, Depo-Provera), record each injection as its own separate entry. The "Date Started" and "Date Stopped" dates should be the same date. Mark the "once" box for "Frequency" and the appropriate box for "Route" (e.g., "IM", or "Other" for subcutaneous injections).
- Recreational drugs should not be reported as concomitant medications for this protocol.

Clinical Product Hold/Discontinuations log (PH-1)

- If "no – hold continuing at the Day 28 visit" is marked in Item 4, record the date that the Day 28 (visit 9.0) visit was completed. If the Day 28 visit is missed, record the target date of the Day 28 visit, per the participant's visit schedule. If the reason for the hold later meets criteria for permanent discontinuation between the participant's Day 28 visit and her date of termination, update the response in Item 4 to "no – permanently discontinued" and record the date the reason first met criteria for permanent discontinuation.
- If "no – permanently discontinued" is marked in Item 4, record the date that the reason in Item 2 met criteria for permanent discontinuation. This date could fall anytime between the participant's enrollment visit up through her Termination date.

Pelvic Exam Ring Assessment (PER)

- When completing the PER CRF at the Day 28 visit, mark 'yes' in item 2 if the vaginal ring was present at the start of the exam, as you will remove and collect the vaginal ring at this visit. The hour and minute boxes in item 2a should be lined through, initialed, and dated to indicate that this item is not applicable. Item 3 should be marked "not reinserted". For item 3a, record "Day 28 – end of product use" as the reason that the ring was not reinserted.

11.5 Case Report Forms

The MTN-028 CRFs are posted on the ATLAS webpage for downloading and printing. The current version of the MTN-028 case report forms (not for actual data collection purposes use) can be found on the MTN-028 SSP web page on the MTN website (www.mtnstopshiv.org).

Section 12. Data Communiqués

For MTN-028, SCHARP will use "Data Communiqués" to document and communicate data decisions and procedures that are made or revised during the study. By using Data Communiqués, SCHARP avoids having to re-distribute a revised version of the Data Collection section of this SSP every time a form completion clarification or revision is made.

Data Communiqués are considered official study documentation. As such, each time a Data Communiqué is sent (via email), please circulate it among relevant staff for their review, print the Data Communiqué, and place it in this section of each MTN 028 SSP binder in your possession. Consider each Data Communiqué an official part of the SSP.

Each Data Communiqué sent will consist of three sections: a Reminders section, used to remind sites of specific data collection or forms completion procedures; a Clarification section, used to clarify data collection or form completion procedures; and an Updates section, used to communicate when an updated version of a form is being issued or to notify the sites that an updated version of the forms instructions is about to be distributed (for example).

Note that a "Data Communiqué" does not request specific actions or corrections to a particular participant's data - it is just a listing of general items to keep in mind when performing data collection for the study.

MTN-028 Data Communiqué #1

2 September 2015

This is official study documentation for MTN-028. Please circulate it among relevant staff for their review, print it, and place it in your MTN-028 SSP Manual in the Data Communiqués section. This document is considered part of the MTN-028 SSP manual.

REMINDERS

None.

CLARIFICATIONS

Documenting Abnormal and Normal Findings due to Observed Blood and the Healing Biopsy Site

Observation of any unexpected genital blood or bleeding is considered an abnormal finding. For example, a biopsy site that is considered to be healing abnormally or if bleeding associated with the procedure exceeds that which is expected, per clinical judgment of the IoR or designee, this would be considered an abnormal finding. Also, this should be documented as a reportable AE. "Abnormal findings" can be marked on the Pelvic Exam CRF as well as its associated findings. An Adverse Experience Log CRF should also be completed.

However, any genital blood or bleeding that is expected, per clinical judgment of the IoR or designee, is not considered an abnormal finding. In addition, any finding that is considered normal, per clinical judgment of the IoR or designee, is not reported as an abnormal finding. For example, a biopsy site that is consistent with normal healing, per clinical judgment of the IoR or designee, would not be reported as an abnormal finding. Thus, this is not a reportable adverse event (AE). "No abnormal findings" can be marked on the Pelvic Exam CRF. If there is any expected non-menstrual bleeding associated with the biopsies during or after the pelvic exam procedure, the findings can be documented on the non-DataFax Pelvic Exam Diagrams as source documentation and chart notes as needed.

See Section 8.7.2 of the SSP for further clarification.

UPDATES

None.

Section 13. Study Reporting Plan

MTN-028 Statistical and Data Management Center (SDMC) and DF/Net Research Staff:

Job Role	Name	Email Address
Protocol Statistician	Jingyang Zhang	Jzhang2@fhcrc.org
Statistical Research Associate	Jason Pan	zpan@fhcrc.org
Project Manager	Melissa Peda	mapeda@scharp.org
Operations Programmer	Drew Edwards	drew@scharp.org
Database Manager	Dena Seabrook	dena@dfnetresearch.com
Lab Programmer	Katie Snapinn	ksnapinn@scharp.org
Clinical Affairs Safety Associate	Ning Jiang	njiang2@scharp.org

13.1 Purpose of Reporting Plan

The purpose of this reporting plan is to describe the reports that will be generated for MTN-028.

The specific purposes of this plan are:

- To identify the purpose and content of each report;
- To identify those responsible for the preparation and distribution of each report;
- To identify who should review the reports so that corrective action (if necessary) is taken;

This reporting plan was prepared by the MTN-028 SDMC Project Manager in collaboration with other MTN-028 SDMC staff.

13.2 Study Reports

Table 13-1 lists the reports the SDMC will produce and distribute via email. Table 13-2 lists the

reports the SDMC will produce and make available via the MTN-028 Atlas web page:

https://atlas.scharp.org/cpas/project/MTN/028/begin.view?

Following the tables is a description of each report that includes the purpose and components of the report.

Table 13-1: MTN-028 SDMC Reports Distributed via Email

Report Title	Distribution Frequency	Email Distribution List
Data Quality Control (QC)	Biweekly	• Site Staff as designated by site • SDMC Project Managers
Clinical Queries	As needed (as queries are identified)	• Site Staff as designated by site • SDMC Project Managers
Unresolved Adverse Experiences (AEs)	Monthly	• Site Staff as designated by site • SDMC Project Managers
Unresolved Product Holds	Monthly	• Site Staff as designated by site • SDMC Project Managers
Unresolved Social Harms	Monthly	• Site Staff as designated by site • SDMC Project Managers
LDMS Specimen Monitoring	Monthly	• Site LDMS Laboratory Staff • Network Lab Representative • SDMC Project Managers

Table 13-2: MTN-028 SDMC Reports Posted on Atlas

Report Title	Update Frequency	Atlas Viewing Area
Screen Out	Daily	Unsecure
Enrollment	Daily	Unsecure
Retention	Daily	Unsecure
Procedure Completion	Daily	Unsecure
Missed Visit	Daily	Unsecure
Data Management Quality	Monthly	Unsecure
Data Summary	Monthly	Unsecure
Protocol Deviations - Listing	Daily	Secure
Protocol Deviations – Summary	Monthly	Secure
PSRT (Safety)	One week prior to each scheduled PSRT call	Secure

AE Listings	Daily	Secure
SMC	Every 4-6 months	Secure

1. Data Quality Control (QC Report)

Purpose: To identify missing and inconsistent data
Components: Quality control notes; overdue visit reminders, missing page reminders

2. Clinical Queries

Purpose: To identify inconsistencies/questions identified in safety or clinical data
Components: Queries containing clinically-based questions about safety and clinical data

3. Unresolved Adverse Experiences (AEs)

Purpose: To identify those AEs that have been continuing for 21 or more days (per the AE Log CRF) so that AE status updates are made as needed
Components: Listing of AEs that have had a "continuing" status for 21 or more days

4. Unresolved Product Holds

Purpose: To identify those clinical product holds that have been continuing for 21 or more days (per the PH Log CRF) so that product status updates are made as needed
Components: Listing of product holds that have been ongoing for 21 or more days

5. **Unresolved Social Harms**
Purpose: To identify social harms that have been ongoing for 21 or more days (per the Social Impact Log) so that status updates are made as needed
Components: Listing of Social Harms that have been ongoing for 21 or more days

6. **LDMS Specimen Monitoring**

Purpose: To identify stored specimens whose information in LDMS does not match corresponding information collected per the CRFs
Components: Listing of those specimens whose LDMS information does not match the information recorded on CRFs or are listed on CRFs as not having been collected; listing of specimens designated as "collected" per CRF but missing from LDMS; listing of specimens in LDMS from PTIDs who did not enroll; listing of specimens in LDMS with unexpected or missing specimen information

7. Screen Out

Purpose: To summarize the number of participants screened for the study, the number enrolled,

and the reasons participants were not enrolled
Components: Number screened, number enrolled, number screened out per reason listed on the Eligibility Criteria CRF

8. **Enrollment**

Purpose: To report on participant accrual as reflected by data received and data entered at the SDMC
Components: By site, activation date, date of first and last enrollments, duration of accrual, enrollment target, total number screened, total number enrolled, screening to enrollment ratio, average number of enrollments per week, percentage of site target enrolled

9. **Retention**

Purpose: To report on participant retention as reflected by data received and data entered at the SDMC
Components: By site and by visit, the number of participants expected and not expected for the visit. For expected visits, the number and percentage of visits completed not completed will be listed. For the expected visits listed as not completed, the number and percentage of missed visits, and Early Terminations will be provided

10. **Procedure Completion**

Purpose: To provide visit adherence information on completion of required study procedures during follow-up
Components: By site, listing of number and percentage of completed required follow-up visit procedures. Listed procedures may include specimen storage, laboratory assay testing, and pelvic exam completion. This does not include visits that are missed

11. **Missed Visit Report**

Purpose: To provide a summary of the total and by site number of missed visits
Components: Site-specific cumulative listing of missed visits cumulative and within the past month. A visit is considered missed if a Missed Visit CRF has been completed for that visit and the visit window has closed.

12. Data Management Quality Report

Purpose: To provide information on site performance with regard to key data management and quality metrics
Components: By site, for cumulative and previous month time periods, the total number of CRF pages received, total number of QCs created, QC rate per 100 CRF records, % QCs resolved (cumulative report only), % CRFs received within 5 days, and mean days to fax in AE Log CRFs

13. Data Summary Reports

Purpose: To provide summary information on site performance regarding data management quality, enrollment, retention, and selected procedure completion
Components: Cumulative enrollment and retention data, cumulative procedure completion data for selected study procedures, and cumulative and monthly data management quality data

14. Protocol Deviations Listing

Purpose: To provide MTN Regulatory with a listing of all protocol deviations reported for the study
Components: Each of the fields/data items as listed on the Protocol Deviations Log

15. Protocol Deviations Summary Table

Purpose: To provide MTN Regulatory with a summary table of cumulative protocol deviations.
Components: Cumulative protocols deviations by type of protocol deviation and by site

16. AE Listings

Purpose: To provide the MTN-028 Safety Physicians with a cumulative listing of all adverse events in order to monitor participant safety.
Components: Cumulative listing of all adverse events reported to the SDMC per the AE-1 log CRF.

17. PSRT (Safety) Reports

Purpose: To help the Protocol Safety Review Team monitor participant safety as reflected by adverse experiences and clinical product hold reported to the SDMC
Components: Cumulative AE, product hold data reported to the SDMC

18. Study Monitoring Committee (SMC) Reports

Purpose: To provide information on study conduct and ability to answer study objectives to key Protocol Team members and Site Investigators
Components: Summary by site and overall of baseline characteristics, data management quality,

protocol deviations, accrual, retention, completion of primary and main secondary endpoint assessments, study or lab issues, and, in closed report, safety data by arm of the study, and other components as requested by the SMC