MTN-023/IPM 030 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	2.1	23 February 2016	Updated per Protocol Version 2.0; Letter of Amendment #01
2	Documentation Requirements	2.0	25 February 2015	Updated per Protocol Version 2.0
3	Participant Accrual and Retention	2.0	25 February 2015	Updated per Protocol Version 2.0
4	Informed Consent	2.1	2 September 2015	Procedure for consenting an illiterate parent was added to section 4.1
5	Study Procedures	2.3	23 February 2016	Section 5.8.1 was updated per Protocol Version 2.0; Letter of Amendment #01
6	Study Product Considerations For Non-Pharmacy Staff	2.1	7 April 2015	Added section 6.10; study product complaints
7	Clinical Considerations	2.0	2 September 2015	Section 7.6.4 was updated to specify location of PK vaginal swab collection
8	Adverse Event Reporting and Safety Monitoring	2.0	25 February 2015	Updated per Protocol Version 2.0
9	Counseling Considerations	2.0	25 February 2015	Updated per Protocol Version 2.0
10	Laboratory Considerations	2.1	7 April 2015	Updated instructions for Sample 2 plasma storage and shipment, if seroconversion occurs during follow-up
11	Data Collection	2.2	1 February 2016	Updated SDMC staff listing; Updated requirements for datafax transmission
12	Data Communiqués	2.0	25 February 2015	Updated per Protocol Version 2.0
13	Study Reporting Plan	2.1	1 February 2016	Updated SDMC staff listing; Clarified components for missed visit report
14	Behavioral Considerations	2.2	23 February 2016	Updated per Protocol Version 2.0; Letter of Amendment #01

Section 1. Introduction

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This section specifies the sources of procedural information available to MTN 023/IPM 030 study staff, the responsibilities of MTN 023/IPM 030 Investigators of Record (IoR), and the process by which the study site is approved to begin implementation of MTN 023/IPM 030. Also included is information on required submissions to Institutional Review Boards and/or Ethics Committees (IRBs/ECs).

1.1 Protocol Specifications

The table below documents the history of the MTN 023/IPM 030 protocol, along with Clarification Memos, Letter of Amendments, and Full Amendments. These documents 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 023/IPM 030 Protocol, Version 1.0	23 October 2013
Protocol Version 1.0, Letter of Amendment #01	15 April 2014
Protocol Version 1.0, Clarification Memo #01	19 May 2014
MTN 023/IPM 030 Protocol, Version 2.0	14 January 2015
Protocol Version 2.0, Letter of Amendment #01	16 February 2016

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 ethics committee/institutional review board of the given site. 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.

Further information on the content and required handling of protocol clarification memos, letters of amendment, and full amendments is available in Section 10.2 of the MTN Manual of Operational Procedures (http://www.mtnstopshiv.org/node/187).

1.2 Sources of Procedural Information

All study procedures must be conducted in accordance with the MTN 023/IPM 030 protocol and this manual. The purpose of this manual is to supplement the protocol, not to replace or substitute for it. In the event that this manual is inconsistent with the protocol, the specifications of the protocol take precedence. Please alert the MTN 023/IPM 030 Management Team of any such inconsistencies.

Electronic versions of this manual, the MTN 023/IPM 030 protocol, and all other study implementation tools are available on the MTN 023/IPM 030 website:

http://www.mtnstopshiv.org/studies/5223

Note that all study documents can be searched electronically for key words and phrases using the "find" feature (CTRL+F). Sites are encouraged to become familiar with electronic searching to make specific guidance easier to locate in the study documents.

Please contact the MTN 023/IPM 030 Management Team using the following alias list for general questions on protocol implementation or study procedures, including clinical, lab, product, and/or CRF procedures:

mtn023mgmt@mtnstopshiv.org

Current contact details for all MTN 023/IPM 030 colleagues and collaborators, as well as study alias lists, can be found in the MTN Directory at:

http://www.mtnstopshiv.org/people/directory

1.3 Investigator Responsibilities

MTN 023/IPM 030 must be conducted in accordance with the United States (US) Code of Federal Regulations and the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (GCP). Copies of these regulations and guidelines are referenced in the MTN Manual of Operations (MOP).

The Division of AIDS (DAIDS) policies Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials are useful for interpreting and operationalizing the applicable regulations and guidelines in accordance with DAIDS expectations. These policies are posted on the MTN website under Resources and Links: http://www.mtnstopshiv.org/node/4537.

MTN 023/IPM 030 must also be conducted 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. The site must file copies of all such regulations, policies, and guidelines in their MTN 023/IPM 030 essential document files (see also Section 2.1).

The IoR must sign both a protocol signature page and an FDA Form 1572 to formally indicate his/her agreement to conduct MTN 023/IPM 030 in accordance with the study protocol, applicable US regulations, and MTN/ATN policies. A copy of the protocol signature page can be found in the protocol. The site will keep copies of the protocol signature page and 1572 on site with their essential documents (See SSP Section 2.1).

The obligations and responsibilities assumed by the IoR when signing the FDA Form 1572 are listed on the form itself, also outlined in 3.4.3 of the MTN MOP. ATN sites should submit updates on the 1572 to Westat Regulatory. MTN sites should submit updates to the DAIDS PRO, as well as to MTN Regulatory Department (mtnregulatory@mtnstopshiv.org) with a short summary of any updates that were made. The IoR may delegate his/her obligations and responsibilities for conducting MTN 023/IPM 030 to other study staff members; however, 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 on the site's Delegation of Authority log throughout study implementation.

1.3.1 Sub-Investigators Listed on the FDA Form 1572

Per the DAIDS Protocol Registration Procedures Manual all study staff at a CRS that are responsible for making a direct and significant contribution to the data must be listed as a sub-investigator on the FDA Form 1572. This includes site personnel who have more than minimal involvement with the conduct of the research (performing study evaluations or procedures or providing intervention) or more than minimal study conduct-related contact with study participants or confidential study data, records, or specimens. Individuals who will sign study medication prescriptions and physicians who submit SAE/EAEs to DAIDS must be listed on the Form FDA 1572. The DAIDS Protocol Registration Procedures Manual can be accessed via the DAIDS RSC website at the following: http://rsc.tech-res.com/protocolregistration/.

1.4 Study Activation Process

Prior to undertaking any study procedures, the study site must obtain approval to conduct MTN 023/IPM 030 from all required regulatory authorities and IRBs/ECs.

- MTN sites must complete Protocol Registration procedures with the DAIDS Regulatory Support Center.
- ATN sites must complete Protocol Registration procedures through Westat. Westat will confirm this process by registering the ATN sites in the DAIDS PRO system.

Study Activation procedures will be completed in conjunction with DAIDS or Westat and with the MTN LOC, MTN SDMC, and MTN LC. Detailed information on the requirements of these pre-implementation steps will be summarized in the Activation Checklist.

The MTN LOC will issue a Site-Specific Study Activation Notice for all sites when all study activation requirements have been met. No protocol-specified study procedures may be undertaken prior to issuance of the Site-Specific Study Activation Notice.

1.5 IRB/EC Submissions

Figures 1-1 and 1-2 list IRB/EC submission and approval requirements pertinent to MTN 023/IPM 030. Figure 1-1 lists requirements that must be met prior to study initiation. Figure 1-2 lists requirements that must be met during and following 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 must 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. Procedures for IRB/EC communication must be documented in site-specific SOPs. 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 must also be submitted to the MTN LOC and Westat.

Figure 1-1: IRB/EC Submissions Required Prior to Initiation of MTN 023/IPM 030

Documents to be submitted to IRB/EC	Written Approval Required*
MTN 023/IPM 030 Current Protocol Version	Yes
Informed consent forms: • Informed Assent & Parent/Guardian Permission Form (Screening, Enrollment, and Long -Term Storage) • *If not within the enrollment consent:* Consent for Storage and Future Testing of Specimens	Yes
Investigator of Record current CV	No
Dapivirine Vaginal Ring Investigator's Brochure	If required by the IRB/EC
Participant pre-screening, recruitment plans and materials (prior to use)	Yes
Other written information for study participants (prior to use)	Yes
Other documentation required/requested by the IRB/EC such as SOPs, CRFs, and interview questionnaires.	If required by IRB/EC

*Denotes approvals required by US regulations and GCP guidelines.

Figure 1-2: IRB/EC Submissions Required During and Following Conduct of MTN 023/IPM 030

Document to be submitted to IRB/EC	Written Approval Required*
Study status reports/updates (at least annually)	Yes
Protocol clarification memos (submission encouraged but not required by DAIDS)	If required by the IRB/EC
Protocol amendments (including full amendments (to a new protocol version) and letters of amendment)	Yes
Amended informed consent forms (including forms that are amended due to protocol amendments as well as forms that are amended for site-specific reasons, e.g., to update participant incentive information or to update site contact information)	Yes
Dapivirine Vaginal Ring Investigator's Brochure updates	If required by the IRB/EC
New information that may affect adversely the safety of study participants or the conduct of the study (e.g., IND Safety Reports)§	If required by the IRB/EC
Reports of adverse events, serious adverse events, and/or events meeting criteria for expedited reporting to DAIDS (per IRB/EC requirements)	If required by the IRB/EC
Protocol departures/deviations/violations (per IRB/EC requirements and/or as directed by DAIDS)	If required by the IRB/EC
Investigator of Record current CV (if Investigator of Record changes during study)	No
Updated/additional participant recruitment plans and materials (prior to use)	Yes
Updated/additional written information for study participants (prior to use)	Yes
Other documentation required/requested by the IRB/EC	If required by IRB/EC
Final study report/closure report	If required by the IRB/EC

*Denotes approvals required by US regulations and GCP guidelines.
§Safety information will be distributed by the DAIDS RSC or the MTN LOC. All distributions will include instructions related to IRB/EC submission of the safety information.

Section 2. Documentation Requirements

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Study staff members are responsible for the proper collection, management, storage, quality control, and quality assurance of all study-related documentation. This section contains information on the essential documents that each study site must maintain throughout the study. It also contains information related to establishing adequate and accurate participant research records for MTN-023/IPM 030.

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* and/or the ATN *Manual Of General Operations (MOGO)* 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 on the MTN-023/IPM 030 webpage. The suggested filing structure assumes that participant research records will be stored separately from the other essential documents. Section 2.2 below provides information on the required contents of these records. Study sites are not required to adopt this filing structure but are encouraged to consider it when developing their filing approach for the study. Further clarifications of the suggested filing structure are as follows:

- Essential documents may be stored in files and/or in binders, which may be subdivided, consolidated, and/or re-organized.
- It is recommended that a contents sheet be maintained and inserted as the first page(s) of each file/binder. Within each file/binder, it is recommended that documents be filed in ascending date order (most recent documents in front).

- Certain documents related to the investigational study products will be stored in site pharmacies. A listing of essential documents to be maintained in the pharmacies is provided in Section 2.3.
- To facilitate routine inspection by study monitors, certain laboratory-related essential documents should be stored in the main study essential documents files/binders. Other lab-related essential documents (e.g., lab standard operating procedures [SOPs]) may be filed in site laboratories.
- The MTN-023/IPM 030 PTID-Name Linkage Log and Randomization Tracking Record must be maintained in hard copy throughout the duration of the trial. The suggested filing structure assumes that these logs will be stored in the study clinic or data management area throughout the screening and accrual process and not necessarily with the other essential documents 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

MTN-023/IPM 030 study sites must maintain adequate and accurate participant research records containing all information pertinent to each study participant. See protocol section 13.6 for further information regarding all participant information, which should be stored in locked file cabinets with access limited to authorized study staff.

2.2.1 Concept of Source Data and Source Documentation

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

The term **source data** refers to all information in original records and certified copies of original records related to clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the trial (including all screening, 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* and/or the ATN *MOGO*. The DAIDS policy specifies both requirements and recommendations. Study sites must comply with all requirements and are encouraged, but not required, to comply with all recommendations.

2.2.2 Required Source Documentation

For MTN-023/IPM 030, participant research records should consist of the following source documents:

- Chart notes

- Documentation that the participant provided written informed assent/consent to screen for and participate in the study prior to the conduct of any screening or study procedures, respectively
- Documentation that the participant met the study's eligibility criteria
- Randomization tracking records and prescriptions documenting participant's random assignment
- A record of the participant's use of the investigational study product
- Pharmacy investigational product dispensing and chain of custody records (maintained in the study site pharmacy), as well as 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)
- 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 recommended 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 is provided below. Detailed information on proper completion, maintenance, and storage of participant randomization and product dispensing documentation is provided in Sections 3, 5, and 6 of this manual, and the MTN-023/IPM 030 Pharmacist Study Product Management Procedures Manual. Detailed information on proper completion of CRFs is provided in Section 11 of this manual.

2.2.2.1 Chart Notes:

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

- Visit date at which a contact takes place or at which a particular procedure takes place
- Visit type (scheduled, interim, etc.)
- Purpose of the visit and location of the contact if other than the research clinic
- General status of the participant at the time of the visit

Chart notes should also be used to document the following:

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

- Other pertinent data about the participant that are not recorded on other source documents
- Reason(s) why protocol-specified procedures were not performed
- Contact attempts to follow up on participants who missed a scheduled study visit

2.2.2.2 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 10 for more information on source documentation requirements for the lab.

2.2.2.3 Case Report Forms (CRFs):

See Section 11 of this manual for further details regarding the use of case report forms (CRFs) with the DataFax data management system. 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 is not able to record data directly onto forms designated as source documents, the following procedures should be undertaken:

- Record the data onto an alternative source document
- File the alternative source document 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

2.2.3 Protocol Deviations

MTN and ATN sites will follow the DAIDS requirements for Protocol Deviations. DAIDS requires that all protocol deviations be documented in participant records, along with efforts made to correct and prevent similar deviations in the future. The MTN Manual of Operational Procedures should be referenced for complete guidance on protocol deviations.

For MTN-023/IPM 030 the Protocol Deviation Log CRF will be used to document each protocol deviation with few exceptions. Missed visits are considered protocol deviations per the MTN policy; however these will *not* be captured on the Protocol Deviation Log CRF. The Missed Visit CRF will capture this information instead. Protocol deviations related to study product adherence or failure to return the used ring to the clinic will be captured via the Ring Adherence CRF and Ring Collection/Insertion CRF, respectively. Like all CRFs, completed Protocol Deviation Log CRFs are faxed to the SDMC and will be filed in the participant's study binder.

Corrective and preventive action plans are required components of protocol deviation documentation. It is important to ensure that chart notes or other source documentation include any associated counseling that was done to address the protocol deviation (i.e. counseling on the importance of retention for missed visit deviations, study product non-adherence or failure to bring the used study product to the clinic visit). Note that the actions documented are not required to be completed in order to report the deviation to SCHARP. The Protocol Deviation Log page should be transmitted to SCHARP once the CRF is completed, even if all of the actions/plans are still in-progress.

Protocol deviations should be reported within 7 days of site awareness. If there is a question as to whether a deviation has occurred, or how it should be documented, the MTN Regulatory

Department and the study Management Team should be contacted at mtnregulatory@mtnstopshiv.org and mtn023mgmt@mtnstopshiv.org. Once the potential protocol deviation has been confirmed, the site will be contacted with this confirmation and the 7-day reporting requirement will begin. Once the CRF is faxed, the MTN Regulatory Department will follow up with the site if any clarifications or additional information on the CRF is needed.

It is recommended that a complete list of all PDs occurring at the site 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, the MTN recommends that this be done at the time of IRB renewal submission, annually or semi-annually per local requirements. These listings may be provided by the MTN Regulatory Department to the sites upon request.

Note that 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.

2.2.4 Document Organization and Participant Confidentiality

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

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

All documents contained in participant case history records must bear a participant identifier, which generally will consist of either the participant identification number (PTID) or the participant name. The PTID should be used whenever possible to maximize participant confidentiality. Any documents transferred or transmitted to a non-study site location — including DataFax forms— must be identified by PTID only. Care should also be taken to only refer to participants by PTID in email communication when people outside of the site are included.

Note: Regardless of whether the identifier on a particular document 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.

All on-site databases and ACASI questionnaire data must be secured with password protected access systems. Any lists, appointment books, or other documents that link PTIDs to other participant identifiers should be stored securely (locked cabinet/drawer if hard copy; password protected if electronic). 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 Study Product Accountability, Chain of Custody, and Dispensing Documentation in the Pharmacy

Pharmacy staff will document the receipt and dispensing of each vaginal ring and the quarantine or storage of each unused vaginal ring. Separate accountability records must be maintained for product, per instructions provided in the MTN-023/IPM 030 Pharmacist Study Product Management Procedures Manual available from the MTN Pharmacist.

Pharmacy staff also will maintain in the study pharmacies a Participant-Specific Pharmacy Dispensing Record for all enrolled study participants, per instructions in the MTN-023/IPM 030 Pharmacist Study Product Management Procedures Manual. Study clinic staff will contribute to the documentation of product dispensation and chain of custody as described in Sections 3 and 6 of this manual.

The specifications related to document security and participant confidentiality described in Section 2.2.4 also apply to records maintained in the study pharmacies. All records must be stored securely in the pharmacies with access limited to authorized study pharmacy staff only.

To preserve the blinding of participants' random assignments, neither study clinic staff nor study participants will be provided access to product-related documentation maintained in the study pharmacies. The following essential documents should be maintained in study site pharmacies:

- Current MTN-023/IPM 030 Protocol
- Investigator's Brochure for Dapivirine Vaginal Ring: current version and any updates
- Current FDA Form 1572
- Current list of authorized prescribers and staff authorized to sign Study Product Request Slips (names and signatures)
- Pharmacy Establishment Plan (DAIDS PAB approved or MTN Pharmacist approved)
- MTN-023/IPM 030 Pharmacist Study Product Management Procedures Manual and applicable SOPs for investigational study product management and Chain of Custody
- MTN-023/IPM 030 product shipping and receipt documentation, product storage temperature logs, and investigational product accountability records
- MTN-023/IPM 030 participant-specific records (including prescriptions and ring request slips, randomization tracking record, participant-specific dispensing record, record of receipt of participant study product and documentation of unused product returns)
- MTN-023/IPM 030 monitoring visit reports
- MTN-023/IPM 030 communications with site clinic staff, communications with the MTN Pharmacist, IPM Clinical Supply Coordinator and/or product distributor
- MTN-023/IPM 030 communications with the MTN LOC and/or the MTN SDMC or other 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, with access limited to authorized study pharmacy staff only, until the study is unblinded. DAIDS and NICHD 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 or NICHD.

Section Appendix 2-1: Source Documentation of Study Procedures

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

Evaluation/Procedure	Source Document(s)
ADMINISTRATIVE AND REGULATORY	
Obtain informed assent and consent	**Signed and Dated Informed Consent form** **Informed Consent Coversheet** (or chart note) **Informed Consent Comprehension Checklist**
Assign a unique Participant Identification (PTID) number	**MTN-023/IPM 030 PTID-Name Linkage Log**
Assess and/or confirm eligibility	**Eligibility Criteria CRF (item 1)** **Screening Behavioral Worksheet** **Enrollment Behavioral Worksheet** **Eligibility Checklist**
Collect/review/update locator information	Site locator document (collect/update) Visit checklist
Randomization	**MTN-023/IPM 030 Randomization Tracking Record,** **MTN-023/IPM 030 Prescription**
Provide reimbursement	Visit checklist, site-specific reimbursement log, and/or chart note
Schedule next visit	Visit checklist and/or chart note
BEHAVIORAL	
Protocol adherence counseling	Chart note, site-specific counseling worksheet or Protocol Adherence Counseling Worksheet
Product adherence counseling	Chart note, site-specific counseling worksheet or Ring Use Adherence Worksheet
HIV/STI risk reduction counseling	Chart note, site-specific counseling worksheet or HIV/STI Risk Reduction and Male Condom Counseling Worksheet
HIV pre- and post-test counseling	Chart note, site-specific counseling worksheet or HIV Pre/Post Test Counseling Worksheet
Behavioral assessment includes sexual activity, condom use, and intravaginal practices	**ACASI Baseline and Follow-up Questionnaires** Completed interviewer-administered CRFs: **Vaginal Practices** ACASI completion documented on: **Enrollment and Follow-up ACASI Tracking CRFs**
Male condom counseling	Male Condom Counseling Worksheet and/or chart note
Product adherence assessment	**Ring Adherence CRF**
Social harms assessment	Chart Note
CLINICAL	

Medical and menstrual history	**Baseline Menstrual History CRF** Pre-existing Conditions CRF (all baseline conditions including clinical evaluations will be summarized here) Adverse Experience Log CRF (all follow-up conditions including abnormal findings from clinical evaluations will be documented on this CRF) **MTN-023/IPM 030 Baseline Medical History Questions** and Chart Notes
Concomitant medications	**Concomitant Medications Log CRF**
Physical examination	**Physical Exam CRF**
Pelvic exam	**Pelvic Exam Diagrams** **Pelvic Exam CRF**
Disclose available test results	Chart note and/or visit checklist
Contraceptive counseling	Chart note and/or site-specific counseling worksheet
Record/update AEs	**Adverse Experience Log CRF** Chart note
Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings	Chart notes, prescription and/or referral documentation
LABORATORY	
hCG	Site-specific lab requisition form Site testing log/results report
Dipstick UA/Urine culture (if indicated)	Site-specific lab requisition form Lab result report
Urine NAAT or Gen-Probe Aptima for GC/CT	Site-specific lab requisition form Lab result report
HIV-1 Serology	Site-specific lab requisition form Site testing log/results report Lab result report HIV Results CRF
CBC with platelets	Site-specific lab requisition form Lab result report Safety Laboratory Results CRF
Serum Chemistries	Site-specific lab requisition form Lab results report Safety Laboratory Results CRF
Syphilis serology	Site-specific lab requisition form Site testing log/results report Lab result report
Plasma archive	Enrollment CRF or LDMS Specimen Tracking Sheet

Rapid test or Gen-Probe Aptima test for Trichomonas	Site-specific lab requisition form/ Lab result report Site testing log/results report
Herpes lesion testing (if clinically indicated)	Site-specific lab requisition form/ Lab result report Site testing log/results report
Vaginal fluid (for pH)	Site testing log/results report, chart note, visit checklist or STI Test Results CRF
KOH wet mount for candidiasis (if clinically indicated)	Site testing log/results report/ Lab result report
Saline wet mount for BV (if clinically indicated)	Site-specific lab requisition form/ Lab result report Site testing log/results report
Blood (for PK)	Pharmacokinetics CRF or site-specific lab requisition or LDMS Specimen Tracking Sheet
Vaginal quantitative culture	Specimen Storage CRF or site-specific lab requisition or LDMS Specimen Tracking Sheet
Gram stain collection	Specimen Storage CRF or site-specific lab requisition or LDMS Specimen Tracking Sheet
Pap smear interpretation	Site testing log/results report/ Lab result report
Vaginal fluid (for PK)	Pharmacokinetics CRF or site-specific lab requisition or LDMS Specimen Tracking Sheet
CVL for biomarkers	Specimen Storage CRF or site-specific lab requisition or LDMS Specimen Tracking Sheet
Vaginal swab for biomarkers	Specimen Storage CRF or site-specific lab requisition or LDMS Specimen Tracking Sheet
STUDY PRODUCT/ SUPPLIES	
Provision of study specified condoms	Site-specific counseling worksheets or visit checklist
Provision of study VR instructions	Chart notes or Visit checklist or site-specific counseling worksheet
Provision of one study VR for insertion with amber zip bag	**Ring Collection/Insertion CRF (Follow-up)** Clinic Study Product Accountability Log Chart Note and/or Visit Checklist
Participant or clinician/designee to remove used study VR	**Ring Collection/Insertion CRF** Chart note or Visit checklist
Exam(s) by clinician to check VR placement	Chart note or Visit checklist
Collection of used study VR	**Ring Collection/Insertion CRF** Clinic Study Product Accountability Log
OTHER	
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
Participant Demographics	**Demographics CRF**
Staff-initiated Study Product Holds and Permanent Discontinuations	**Clinical Product Hold/Discontinuation Log CRF** and/or chart notes

Section Appendix 2-2: CRFs Used as Source Documents

Form Name	Acronym	Comments
Adverse Experience Log	AE-1	Form may be source for all items.
Baseline Menstrual History	BMH-1	Form may be source for all items.
Clinical Product Hold Discontinuation Log	PH-1	Form may be source for items 1, 3, and 4. Depending on the hold reason, item 2 source may be a lab report/ testing log, Concomitant Medications Log, AE Log, Follow-up Medical History Log, or chart notes.
Concomitant Medications	CM-1	Form may be source for all items.
Demographics	DEM-1	Form will be source for all items as participant responses are recorded directly onto the form.
Eligibility Criteria	ECI-1	Form may be source for item 1. Eligibility Checklist and/or Screening and Enrollment Log may be source for all other items.
Enrollment	ENR-1	The applicable informed consent form is source for items 1-4. This form or Lab requisition (*sites to specify*) will be source for item 5.The MTN 023/IPM 030 Envelope Tracking Record is source for items 6-7. This form or the Enrollment Visit checklist is source for items 8 and 9 (site to choose). This form or the chart notes are source for items 10-10a.
Follow-up ACASI Tracking	FCT-1	Form may be source for all items. *Visit checklists may also be source – site to choose.*
Follow-up Visit Summary	FVS-1	All items should be completed based on source data recorded on other source documents.
HIV Confirmatory Results	HCR-1	Local laboratory report(s) are source for items 1-2. Form or chart notes may be source for item 3.
Laboratory Results	LR-1	Local laboratory result reports are source for all lab values. Form may be source for all non-lab value items (i.e. severity grade, etc.).
Missed Visit	MV-1	Form may be source for all items.
Participant Receipt	PRC-1	Items 1 and 2 may be source; applicable informed consent forms should be source for items 3-6.
Participant Transfer	PT-1	Form may be source for items 1, 2, and 4. Participant study records (visit checklist, CRFs, or chart notes) are source for item 3.
Pelvic Exam	PE-1	Pelvic Exam Diagrams is source for items 2, 2a,and 2b. Form may be source for items 1, 3, and 4.
Pharmacokinetics	PK-1	Form or Lab requisition (*sites to specify*) will be source for all items.

Form Name	Acronym	Comments
Physical Exam	PX-1	Form may be source for all items
Pre-Existing Conditions	PRE-1	Baseline Medical History Questions Sheet, Baseline Menstrual History form, and other study documents are source for all items. Note to site – if you are using something different than the Baseline Medical History Question sheet provided, specify what will be source.
Pregnancy Outcome	PO-1, PO-2	Form may be source for all items if medical records are not available (and data are based on participant self-report). If medical records are obtained, then they will be source for as many items as possible.
Pregnancy Report and History	PR-1	Form will be source for all items.
Protocol Deviation Log	PDL-1	Form will be source for all items.
Ring Adherence	RA-1	Form will be source for all items.
Ring Collection and Insertion	PRD-1	Form may be source for all items except item 3. Pharmacy dispensing records should be source for item 3.
Specimen Storage	SS-1	Form or Lab requisition (*sites to specify*) will be source for all items.
STI Test Results	STI-1	All laboratory value items should be completed based on laboratory source documents.
Termination	TM-1	All items are based on source data recorded on other documents.
Vaginal Practices	VP-1	Form will be source for all items.
Vaginal Ring Storage	VRS-1	Form or Lab requisition (*sites to specify*) will be source for all items.
Version 2.0 Re-Consent	RC-1	The applicable informed consent form is source for all items.

Section Appendix 2-3: Non-DataFax Forms Used as Source Documents

Form Name	Comments
Baseline Medical History Questions Sheet	Form may be source for all items.
Enrollment Behavioral Eligibility	Form is source for all items as participant responses are recorded directly onto the form.
Follow-up Medical History Log	Form may be source for all items.
MTN 023/IPM 030 LDMS Specimen Tracking Sheet	Form may be source for all items.
Pelvic Exam Diagrams	Form will be source for all items.
Screening Behavioral Eligibility	Form is source for all items as participant responses are recorded directly onto the form.

Section 3. Participant Accrual and Retention

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This section provides information on requirements and procedures for recruiting participants in MTN-023/IPM 030. Information on required screening and enrollment procedures are included in Section 5 of this manual. This section also presents information related to definitions, requirements, and procedures for participant retention.

3.1 Pre-Screening Procedures

It is encouraged that sites implement pre-screening procedures for MTN-023/IPM 030 as part of their outreach and recruitment strategy. Like all outreach and recruitment strategies, pre-screening approaches and materials used during the pre-screening process must be IRB approved.

During pre-screening, staff may explain MTN-023/IPM 030 to potential study participants and ascertain elements of presumptive eligibility, to be confirmed at an on-site screening visit. The information obtained during pre-screening activities cannot be considered for eligibility determination. No information collected from participants may be used for publication purposes unless written informed consent is provided from potential participants.

Note: SCHARP-provided PTIDs should not be assigned until after participants provide informed assent/consent at the screening visit.

It is recommended that pre-screening cover behavioral and basic demographic eligibility criteria, such as (but not limited to):

- Age
- Willingness to comply with other protocol requirements, such as:
  - Study visit schedule for 25 weeks and associated HIV testing
  - Use of study products
  - Non-participation in other research studies
  - Assessment of known allergies

Participants found to be presumptively eligible may also be provided the study informed assent/consent or other IRB approved IC materials for review prior to their screening visit as part of the pre-screening procedures.

3.2 Participant Accrual

3.2.1 Study Accrual Plan and Site-Specific Accrual Targets

Approximately 96 born females, 15 - 17 years old (inclusive) will be recruited across six US sites; participants may be enrolled up until their 18th birthday. The accrual target for each site is approximately 16 participants. The study-wide accrual period is 12 months. Each site-specific accrual period may vary as this period is considered to begin on the first day of participant enrollment at each site.

A site's total accrual target may change in the event that enrollment slots need to be transferred from one site to another, as authorized by the study leadership.

For each site, accrual will begin after all applicable approvals are obtained and a Site-Specific Study Activation Notice is issued by the MTN Leadership and Operations Center (LOC) at FHI 360.

Screening and enrollment data will be captured on case report forms (CRFs) and submitted to the 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.

3.2.2 Accrual Tips and Reminders:

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 be tracked over time. 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.

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

3.2.3 Participant Accrual SOP

Site staff members 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

- Methods for tracking actual accrual versus accrual targets
- Recruitment methods and venues
- Methods for identifying the recruitment source of participants who present to the site for screening
- Methods for timely evaluation of the utility of recruitment methods and venues
- Pre-screening procedures
- 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

3.3.1 Retention Definitions

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-023/IPM 030, 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. Importantly, retention shortfalls can be made up by ensuring that participants return for their next scheduled visit after missing a visit.

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.

3.3.2 Retention Requirements

Each study site will target retention of at least 95% of enrolled study participants for each scheduled follow up visit. 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. To avoid these problems, and thereby avoid bias in the study results, high participant retention rates must be maintained throughout the study.

3.3.3 Retention SOPs

Site staff members 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
- Procedures for completing and updating participant locator information
- Site-specific definition of “adequate” locator information (for purposes of determining participant eligibility)
- Visit reminder methods and timeframes
- Methods and timeframes for identifying when a visit has been missed
- Planned retention methods (including what outreach/locator efforts are taken within 24 hours, 1-3 days, 1 week, or 2 weeks after a missed visit)
- Methods for timely evaluation of the utility of 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)

3.3.4 Obtaining and Updating Locator Information

Successful retention begins with collection of locator information from each study participant. All study participants will be asked to provide locator information during the study screening process, and to continually review/update this information during follow-up. 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 retention SOP.

Each study site is encouraged to develop an exhaustive locator form to maximize contact effectiveness and participant retention.

Potential locator items include:

- Participant's full name, alias, and/or nickname; government-issued identification number; home address; home phone number; mobile phone number; work address; work phone number; fax number; or e-mail address; daytime and nighttime locations, meeting places and hangouts.
- Name, address, telephone number, and/or other contact information for stable community contacts (i.e., participant family members and friends) who typically know the whereabouts of the participant.

Note: Although contact information for a participant's current primary partner will likely be useful, contact information for other contacts also should be collected, since the participant’s relationship with this partner could change during the course of the study.

During the informed assent/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.

3.3.5 Retention Tips

Some general strategies for maximizing participant retention are as follows:

- 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.
- Keep locator information up-to-date and maintain thorough documentation of all efforts to contact the participant. Keep all this information in an organized manner, so that different staff members can easily review the information and contribute to re-contact efforts when necessary. Make use of all information collected on the participant's locator form. Even if a locator source is not useful/successful on one occasion, try it again later.
- Schedule all follow-up visits at the participant's Enrollment Visit. Thereafter, at each follow-up visit, confirm the scheduling of the next visit and give the participant an appointment card with the scheduled visit date and time noted.
- Prepare a calendar of scheduled visits for each enrolled participant, based on 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.
- For participants who demonstrate a pattern of late or missed appointments, schedule follow-up visits for the beginning of the allowable visit window (i.e., up to one week before the actual target date) to allow maximum time for re-contact and re-scheduling if needed.
- 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.
- Make use of all available contact methods (e.g. phone, mail, home visits, street outreach, newspapers, e-mail/internet). Also make use of other available locator information sources, such as phone and postal directories and other public registries.
- Dedicate adequate staff time and effort to retention efforts.
- Work with community members to identify the most applicable contact and retention strategies for the local study population, including the type and amount of participant incentives.
- Keep participants and community members up-to-date on study progress to foster a sense of partnership and ownership of the study (through the use of participant newsletters, for example).
- 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.

- 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.
- 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.

3.3.6 Participants Who Voluntarily Discontinue Study Participation

If a participant wishes to discontinue participation in the study, her wishes must be respected. Participants should be advised that she is always welcome to come back if she wishes. Refer to SSP section 5.8.6 (Voluntary Withdrawal of Study Participation) for procedures to be followed for all participants who prematurely discontinue study participation.

Section 4. Informed Assent and Consent

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This section provides information on informed assent and consent procedures for MTN 023/IPM 030. MTN 023/IPM 030 involves two types of informed assent/consent:

- Informed Assent & Parent/Guardian Permission Form for Screening, Enrollment, and Long-term Storage [for participants not of legal age to provide Informed Consent and their parent/guardians]
- Informed Consent for Screening, Enrollment and Long-term Storage [for participants that reach legal age to provide Informed Consent based on state regulations while enrolled in the study; or for emancipated minors]

This section contains general information and instructions applicable to providing informed assent/consent and parent/guardian permission required for MTN 023/IPM 030. In addition, detailed guidance is provided for the standardized approach to the informed assent/consent process that must be followed at all sites. For the purpose of this document, ICF will refer to the informed assent/consent and parent/guardian form.

4.1 Overview of Informed Consent Requirements and Procedures

Informed consent is a process by which an individual voluntarily expresses her willingness to participate in research, after having been informed of all aspects of the research that are relevant to her decision. It is not merely a form or a signature, but a process, involving information exchange, comprehension, voluntariness, and documentation. Please also 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.

Prior to Screening Visit Procedures:

- Written informed assent will be obtained from each study participant
- Informed consent will be obtained from parents/guardians (as applicable, per site IRB requirements)
    - If a site is required by its IRB to obtain signatures from both parents/guardians, only one is needed if the other parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. Details on the availability of the 2nd parent/guardian should be documented in chart notes.

    - If two parents/guardians provide informed consent this can be done separately or together and they can sign the same form or different forms. The site process for this should be detailed in the site IC SOP and in accordance with IRB requirements.
- For emancipated minors, written informed consent may be obtained from the participant herself, and not from her parent/guardian; however sites should follow local IRB policies

For MTN 023/IPM 030, the ICF for screening, enrollment and long term specimen storage is obtained at one time point at Screening. For participants or their parent/guardian who do not provide assent or permission to screen and enroll, 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. The Screening and Enrollment visits will occur on separate days due to the need to wait for screening laboratory results and confirmation of study eligibility at the Enrollment visit. Informed assent/consent is an ongoing process that continues throughout the study follow-up period through open dialog between study staff and the participant.

Participant informed assent/consent for future storage and testing of blood specimens and vaginal and cervical fluids is optional. The participant or her guardian(s) may choose to not have the specimens stored for future research testing and the participant may still enroll/remain in the study. For participants or guardians who do not consent to specimen storage and possible future research testing, specimens collected and stored on-site per protocol will be retained until the study is completed and all protocol-specified testing has been done. Thereafter, any remaining specimens collected from these participants will be destroyed.

For this study, participants are randomized to the in-depth interview (IDI) and therefore consent for their possible participation is imbedded within the main consent. No additional signatures are needed for this component of the study.

US regulations (45 CFR 46) 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 by delegation of all study staff involved in the informed consent process, to deliver all required information to potential study participants and their guardians.

It also is the responsibility of the IoR and designated study staff to:

- Deliver all required information in a manner that is understandable to potential study participants and their parents/guardians
- Assure that informed assent/consent is obtained in a setting free of coercion and undue influence
- Confirm that the participant and her guardian comprehend the information
- Document the process

Per protocol, potential participants must be literate in English as an eligibility criterion for MTN 023/IPM 030. However, if a parent/guardian of the participant is illiterate, then an impartial witness should be present for the parental permission process.

4.2 Informed Consent/Assent SOP

As a condition of study activation, each study site must establish an SOP for obtaining informed assent from potential participants and permission from the parent/guardian of potential participants. It is recommended that the SOP contain the following elements (listed below):

- Procedures for determining participant identity and age

- Procedures for determining participant literacy
- Procedures for providing all information required for informed assent/consent to the participant and her parent/guardian
- Procedures for determining participant/guardian comprehension of the required information
- Procedures to ensure that ICF is obtained in a setting free of coercion and undue influence
- Procedures for documenting the informed assent/consent and parent/guardian permission process
- Procedures for obtaining permission from second parent, if applicable, understanding and determining reasonable availability of second parent including the procedures for determining if the second parent is reasonably available to provide permission
- Procedures to re-consent participants once they turn the age of 18 (or legal age for providing informed consent per state regulations). Sites may also obtain input from their IRB on whether their original signature form is sufficient
- Storage locations for blank ICFs
- Storage locations for completed ICFs
- Procedures (e.g., color-coding) to ensure that the different study ICFs forms are easily distinguished and used appropriately, if applicable
- Procedures for implementing a change in the version of the ICFs used
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

At each site, the informed assent/consent process will be conducted according to site SOPs. The consent process may be conducted with the participant and her guardian/s together or separately, per participant request and site procedures. Additional details related to key steps in the process are provided in the remainder of this section.

4.3 Site Specific Informed Assent/Consent and Parent/Guardian Permission Forms

A sample ICF is provided in the MTN 023/IPM 030 study protocol. Sites are responsible for adapting the sample as needed for local use. Local adaptation may include reformatting the ICF in accordance with local IRB/EC requirements. Unless waived by the IRB, the adapted ICF must still contain the eight required elements of informed consent as defined in 44 CFR 46.116. It is recommended that all ICF forms are reviewed and approved by MTN LOC (FHI 360) and/or Westat prior to IRB/EC submission. After IRB/EC approval, the ICF must be submitted to the DAIDS Protocol Registration Office (DAIDS PRO) for MTN sites or Westat for ATN sites prior to its initial use.

Each site is responsible for preparing bulk supplies of the approved ICF and for only using the currently approved version of the ICF 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 ICFs are easily distinguished and used appropriately. A system for tracking version control and approvals of the ICF is also recommended. Upon receiving final IRB/EC and any other applicable regulatory approval(s) for an amendment to the ICF, MTN sites should implement the ICF immediately and submit the updated version to DAIDS PRO per the timelines outlined in the protocol registration manual. ATN sites should implement and submit the amended ICF per the ATN Manual of General Operations (MOGO).

4.4 Informed Consent Support Materials

Use of visual aids is 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 will be provided to each site to use as visual aids. In addition to the visual aids decided upon at each 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 each site to consider using are as follows:

- Calendar
- Male condoms
- Sample vaginal ring and packaging
- Urine specimen cup
- Blood collection tubes
- 4 L jug (to demonstrate the total blood volume in the human body)
- Vaginal and/or pelvic model or illustrations
- Speculum
- Randomization explanation visual aids (e.g., sack or box containing two items of different colors)
- Placebo explanation visual aids (e.g., sugar with and without vitamin A, hair gels with and without straightener, food flavoring sauces in sweet and non-sweet versions). Visual aids to explain placebos should look identical to each other.

When using vaginal and pelvic models, remember that participants may not be familiar with such models. Introduce the models in a sensitive manner and use information, rapport, and humor to help make the participant feel comfortable with the models. If using a pelvic model to demonstrate ring placement, it may be necessary to first orient the participant to the model and the anatomical parts shown. Point out that the vaginal opening starts at the outside edge of the plastic model. Be sure that all staff members that may use the model are able to explain what each part is and, if demonstrating ring use, are able to insert and remove the ring with ease using the model.

Regardless of use of the vaginal and pelvic models, study staff who take part in informed consent discussions should be prepared to demonstrate the various insertion positions and "mime" the insertion of the ring.

4.5 Comprehension Assessment

Study staff are responsible for determining whether each potential participant and their parents/guardians understand all information provided to them to ensure they are able to make an informed decision about study participation. This assessment of IC comprehension may be administered separately for the participant and her guardians. The participant and her parents/guardians must not be asked to agree to take part in the study, or sign the ICF, until they fully understand the study.

Study staff should ask some questions that indicate if the participant and guardians understand significant points of the study. If the participant and guardians do not mention one or more of the main points, study staff should follow-up with another open-ended question to elicit a response about that point. Sample tools to assist with this assessment are available on the MTN-023/IPM 030 website under Study Implementation Materials. The sample IC assessment "open ended questions" tool may be administered to both the participant and her guardian. The "true/false" assessment tools have been separated for participant understanding and parent/guardian understanding. Instructions to administer the assessment should be included in the site SOP for obtaining informed consent. The comprehension assessment must be administered to each potential participant and her parent/guardian(s) individually after they have completed the informed assent/consent discussions with site staff as described above but before they are asked to sign the ICF.

4.5.1 Administration of Comprehension Assessment Tool

A comprehension assessment tool should be administered to each potential participant and guardians after they have completed the informed consent discussions described above and before they are asked to sign the ICF. It is expected that study staff administering the ICF and assessment will be sufficiently knowledgeable about MTN 023/IPM 030 to make good judgments about potential participants' comprehension of the required information. The comprehension assessment tool should not be presented to participants as a "test," but rather as a way of assuring that study staff have fulfilled their responsibility to provide all information needed for the participant to make an informed decision about enrolling in the study. If any misinformation is reported back, study staff should explain the correct information before proceeding to another question.

The comprehension assessment tool is considered a study source document that should be completed, handled, and retained in the participant's study chart like any other source document. After administering the assessment tool, study staff should carefully review the assessment to verify that all required points have been satisfactorily addressed by the participant and guardian(s), 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 before proceeding with study procedures 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; 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 ICF.

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 assessment tool should ensure his/her signature is recorded in the space provided. All comprehension assessment tools utilized should be submitted to local IRB/ECs for approval prior to use. Detailed information for how comprehension will be assessed must be specified in the site SOP for obtaining informed consent.

4.6 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 ICF 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 her name using an initial for her first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

In addition to completing signature requirements as described above, the participant and her guardian(s) must indicate on the form whether she agrees to storage and future testing of biological specimens. The participant may decline and still enroll in MTN 023/IPM 030.

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 023/IPM 030 webpage under Study Implementation Materials. Sites choosing to use a coversheet (one for the participant and one for each guardian) should list the coversheet as a source document in their SOPs for source documentation 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 "Version number/date of informed consent form used during informed consent process/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.

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 ICF. If a participant opts not to receive a copy, document this in source documents (for example, 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.

4.7 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 initial assessment. 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 informed consent process that are, and are not, optimally effective for study participants. This discussion should be noted in the participant's chart note for that visit date.

Section 5. Study Procedures

Table of Contents

This section provides information on requirements for screening, enrollment and follow-up visits in MTN-023/IPM 030. Additional procedure-specific details can be found in the following locations:

- Visit Checklists (available on Study Implementation Materials webpage)
- Section 6 for product-related guidance
- Section 7 for clinical considerations
- Section 9 for counseling considerations
- Section 11 for data management

5.1 Visit Considerations

Because of the nature of study procedures required to be performed during MTN-023/IPM 030, Screening, Enrollment, and Follow Up visits are expected to be completed at the study clinic only. However, per IRB regulations, sites may choose to consent either the participant or guardian/parent at an off-site location for convenience.

5.2 Eligibility Determination 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 SOP that describes how study staff will fulfill this responsibility. Minimally the SOP 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/designee should contact the MTN-023/IPM 030 Management Team.

5.3 Visit Checklists:

Visit checklists are convenient tools designed to guide site staff in proper study procedures and may serve as source documentation if completed appropriately. These checklists alone may not be sufficient for documenting all procedures, but can be used to indicate that the procedure was completed. Visit checklist templates are available on the MTN-023/IPM 030 website under Study Implementation Materials.

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

- Enter the participant identification number (PTID) and visit date in the top section of each checklist. If checklists are multiple pages, enter the PTID and visit date on each page.
- The “Procedures” column indicates when the item is required per-protocol. Complete staff initials next to procedures completed.
- Enter your initials only beside the procedures that you perform. Do not enter your initials beside procedures performed by other staff members. If other staff members are not available to initial checklist items themselves, make a note on the checklist documenting who completed the procedure, enter initials and date the entry , e.g., “done by {name} on dd/mmm/yy” or “done by nurse on dd/mmm/yy.”
- 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 templates is a suggested ordering. In consultation with the MTN LOC (FHI 360), site staff members 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/assent and parental/guardian permission 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, administration of the Vaginal Practices CRFs, and collection of blood for plasma archive.
    - Note: The Baseline Audio Computer Assisted Self-Interview (ACASI) Questionnaire may be completed after randomization but prior to insertion of the study ring
- Pelvic exam procedures must be performed in the sequence shown on the pelvic exam checklist.
- If at all possible, behavioral assessment forms and ACASI questionnaires should be administered prior to the delivery of HIV and adherence counseling.
- It is recommended that procedures for determining eligibility for continued product use be conducted early in the visit to ensure that these procedures are conducted in the event that the participant needs to abruptly leave the clinic or is short of time.
- Vaginal Rings (VRs) should be removed immediately upon identification of conditions that require a hold or discontinuation. At visits with pelvic exams, timing of VR removal should be coordinated with the pelvic exam itself. At these follow-up visits, clinicians should not remove the current VR until the pelvic exam. Provision of a new VR for insertion should occur after the exam. At visits without pelvic exams, timing of VR removal may occur when it best fits into the clinic flow.

5.4 Screening and Enrollment Timeframe

All protocol-specified screening and enrollment procedures must take place within 56 calendar days of when the potential participant provides written parental/guardian and participant informed consent/assent. If participant and parent assent/consent occurs on different days, the screening window will begin with the first provision of consent. If all screening and enrollment procedures are not completed within 56 days of obtaining written informed consent, the participant will be considered ineligible for study participation. Participants may only re-screen once for MTN-023/IPM 030.

5.5 Screening and Enrollment Logs

Study sites are required to document screening and enrollment activity on screening and/or enrollment logs. Screening and enrollment logs should be updated in real time and completed once a participant provides informed consent for screening and when enrolled/randomized into the study. Participants who are approached, but do not provide informed consent should not be included on this log.

5.6 Screening Visit

The term “screening” refers to all procedures performed to determine whether a potential participant is eligible to take part in the MTN-023/IPM 030 study. The study eligibility criteria are listed in protocol Sections 5.2 and 5.3. Required screening procedures are listed in protocol Section 7.2.

5.6.1 Screening Visit Procedures:

Sites will be provided with an Eligibility Checklist to document participant eligibility for study participation. The Eligibility Checklist and Behavioral Eligibility Checklist provide further operational guidance on the timing of each assessment and suggested source documentation for each eligibility criterion. This document is available on the MTN-023/IPM 030 Study Implementation Materials webpage.

Screening procedures are specified in protocol section 7.2 (Table 5) and are reflected in the Screening Visit Checklist, which is available on the MTN-023/IPM 030 Study Implementation Materials webpage.

- Informed consent/assent and parental/guardian permission must be obtained prior to conducting any study procedures. After consenting, participants will be assigned a PTID and undergo a series of behavioral assessments, clinical evaluations, and laboratory tests.
- Locator information will be collected initially during the screening visit, and updated at subsequent visits throughout the study. Staff should confirm adequate locator information is provided prior to enrollment/randomization.
- Some eligibility criteria, which are based on self-report will be evaluated by administration of the Screening Behavioral Eligibility and Enrollment Behavioral Eligibility worksheets. It is suggested that staff administer these questionnaires early in the 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). These worksheets are available on the MTN-023/IPM 030 Study Implementation Materials webpage.

  Note: Eligible participants must have a history of sexual intercourse, at least one episode in their lifetime. For MTN-023/IPM 030, sexual intercourse is defined as penile-vaginal intercourse.

Clinical screening visit procedures are further detailed in Section 7 of this manual. In brief, clinical procedures include:

- Collection of medical and menstrual history including assessing concomitant medications, onset and progression of puberty, use of effective method of contraception, conducting a physical exam and a pelvic exam, and specimen collection.

Note: The study's protocol Section 5.2 (Inclusion criteria) specifies that a participant is required to report using an effective method for at least 30 days prior to enrollment. If a potential participant is currently using the contraceptive ring and agrees to switch to a protocol-allowed contraceptive method during screening; the site is not required to wait 30 days from initiation of the *new* method. The language in this section of the protocol, excluding use of the contraceptive ring is intended to exclude its use while in the study. The site may schedule enrollment given her history of using a reliable hormonal method.

- Evaluation of the use of prohibited medications such as PrEP, PEP and non-therapeutic injection drug use, assessing STI/RTI/UTIs, genital signs/symptoms, and overall general health.
- Undergoing HIV testing and urine pregnancy testing.
- Provision of all available test results and treatment or referrals for UTI/RTI/STIs.
- Provision of risk reduction, male condom, contraception, and HIV pre-and post-test counseling. Further considerations related to counseling requirements are detailed in Section 9 of this manual.

Details regarding laboratory tests and sample collection at screening are provided in Section 10 of this manual. In summary:

- Participants will undergo testing for STIs (Gonorrhea, Chlamydia, Syphilis, Trichomonas, and HIV), liver and kidney function (serum chemistries: AST, ALT and Creatinine), and a complete blood count with platelets.
- If indicated, participants may be tested for bacterial vaginosis, vaginal candidiasis, or herpes simplex virus (per local standard of care).

Designated staff will document the status of eligibility criteria assessed at screening, as applicable, by checking each set of "yes/no" checkboxes upon assessment and initialing and dating on the “Screening Visit” column of the MTN-023/IPM 030 Eligibility Checklist.

Between Screening and Enrollment, appropriately delegated site staff should review available lab results and other eligibility criteria and update the “Screening Visit” column of the MTN-023/IPM 030 Eligibility Checklist. No screening CRFs should be faxed to SCHARP until a participant is enrolled. Should a participant be ineligible for enrollment, the Eligibility Criteria CRF should be completed and faxed, and the screening file should be retained on site per the site’s Data Management SOP. Refer to section 5.6.2 below for further information on the appropriate documentation, which should be included in the participant chart for those who screen-fail.

If the participant meets eligibility criteria at the end of the screening visit, she should be scheduled for her enrollment visit, making sure the enrollment visit takes place within the allowable 56-day time frame. Participants should be provided with study informational material, clinic contact information, and instructions to contact the clinic with any questions as needed prior to her scheduled enrollment visit.

5.6.2 Assignment of Participant ID Numbers

The MTN SDMC (SCHARP) will provide each study site with a listing of participant identification numbers (PTIDs) for use in MTN-023/IPM 030. The PTIDs will be provided in the form of a hard-copy MTN-023/IPM 030 PTID-Name Linkage Log (see Figure 5-1). Information regarding the storage and completion of the PTID-Name Linkage Log can be found in the site’s Data Management SOP. Additional information on the structure and use of PTIDs can be found in the Data Collection section of this manual (Section 11). PTIDs will be assigned to all potential participants who provide informed consent/assent, regardless of whether they enroll in the study.

Figure 5-1: Sample Site-Specific PTID-Name Linkage Log (PTID List)

	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			

5.6.3 Participants Found to be Ineligible (Screen Failures)

Screening should be discontinued if the participant is determined to be ineligible. If a participant screens out due to a clinical condition requiring follow-up, appropriate referrals should be provided. 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 informed consent/assent and parental/guardian permission form
- 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 SCHARP
- 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. Once ineligibility status is determined, the MTN-023/IPM 030 Eligibility Checklist may be stopped and the remaining items may be left blank. Site staff should document in chart notes why items on the checklist were left blank.

5.7 Enrollment Visit

Participants will be considered enrolled in MTN-023/IPM 030 once they have been assigned an MTN-023/IPM 030 Randomization Envelope. Further information on methods and materials for random assignment is provided in Section 5.7.2.

5.7.1 Enrollment Visit Procedures

Study enrollment procedures are specified in protocol section 7.3 and reflected in the Enrollment Visit Checklist, which is available on the MTN-023/IPM 030 Study Implementation Materials webpage. Additional details regarding enrollment procedures are outlined below.

The following procedures should be completed as part of eligibility determination prior to randomization on the day of enrollment. The IoR or designated staff will confirm and document the criteria indicated on the "Enrollment Visit" column of the MTN-023/IPM 030 Eligibility Checklist prior to proceeding with randomization/enrollment per site SOPs.

Before randomization, the participant should undergo the following procedures:

- Confirm the informed consent/assent and parental/guardian permission form is signed and dated and the participant remains willing and able to participate in the study
- Confirm 56-day screening window has not been exceeded
- Update and re-confirm adequacy of locator information
- Confirm behavioral eligibility criteria through administration of the Enrollment Behavioral Eligibility worksheet and completion of the Eligibility Checklist
- Review/update medical/medication/menstrual history since screening visit. Re-evaluate use of prohibited medications, STI/RTI/UTIs, genital signs/symptoms and overall general health
- Perform pregnancy testing, HIV testing, and plasma archive (Note for sites not conducting finger stick HIV rapids: to reduce participant burden, sites 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, including provision of condoms.
- Provide contraceptive counseling
- Conduct a physical exam
- Conduct pelvic exam procedures in the sequence shown on the pelvic exam checklist
- Participants should receive all available test results and treatment or referrals for UTI/RTI/STIs

- Complete the following behavioral assessments: Vaginal Practices CRFs, and Baseline ACASI (Note: Baseline ACASI may be conducted after randomization but must occur prior to insertion of study ring)
- Protocol adherence and vaginal ring (VR) adherence counseling
    - NOTE: this may also be conducted after randomization, but it could be helpful to provide the participant with more information about the ring prior to her final decision to enroll in the study

Designated staff will document the status of eligibility criteria assessed at Enrollment, as applicable, by checking each set of "yes/no" checkboxes upon assessment and initialing and dating on the “Enrollment Visit” column of the MTN-023/IPM 030 Eligibility Checklist. A staff member and the IoR/designee must review and sign/date the MTN-023/IPM 030 Eligibility Checklist to document the participant’s eligibility status is confirmed prior to enrollment/randomization. The Eligibility Criteria CRF must also be completed for all screened participants once the participant's eligibility/enrollment status is determined. If the participant is confirmed to be eligible based on procedures listed above, the IoR or designee should complete final sign-off of eligibility on the Eligibility Criteria CRF, have this verified by a second staff member who will also sign-off on the Eligibility Criteria CRF.

After randomization, participants will undergo the following procedures:

- Provision of VR instructions and one VR for self-insertion
- Digital (bimanual) exam to check for correct VR placement
- Reimbursement
- Schedule next visit

To ensure an accurate assessment of baseline conditions is documented and eligibility is confirmed on the day of randomization, the enrollment visit should not be conducted as a split visit. If for some reason the participant cannot complete the Enrollment visit in a single day, (e.g. participant has to leave early due to an emergency) follow the guidance below:

- If she has not been randomized, reschedule the participant for the Enrollment visit within the 56-day window. No CRFs from an incomplete Enrollment visit should be sent to SCHARP.
- If she has been randomized, the visit is considered her Enrollment visit regardless of whether all procedures post-randomization were completed. Document any procedures not done. If the participant did not receive a study ring at the Enrollment Visit, she should be scheduled to come in as soon as possible after Enrollment to receive her first study ring and associated procedures (first product use, digital (bimanual) exam etc.).

No missed Enrollment visit procedures should be made up prior to the 2-Week visit with the exception of ring provision (described above) and the collection of plasma archive. Ring provision should only be done if all eligibility requirements continue to be met. If blood for plasma archive was missed during the Enrollment visit, the site should make every attempt to bring the participant back as soon as possible to collect and archive this specimen as part of an interim visit. Contact SCHARP with any CRF completion questions if this situation occurs.

5.7.2 Random Assignment/Prescription Assignment

Participants will be randomly assigned 3:1 to one of the two study arms.

The SDMC will generate and maintain the study randomization scheme and associated materials. Randomization Envelopes will be shipped from the SDMC to each study clinic. Envelopes are stored in the clinic and must be assigned in sequential order to each participant who has been confirmed as eligible and willing to take part in the study. Only one envelope may be assigned to each participant; once an envelope is assigned to a participant, it may not be re-assigned to any

other participant. All envelopes are sealed with security tape to ensure envelopes are not tampered with or opened prior to assignment to a participant. Sites should complete all randomization procedures as specified in the MTN-023/IPM 030 Randomization SOP.

Envelope assignment will be documented on the Randomization Envelope Tracking Record. The act of assigning a Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once the Randomization Envelope is assigned, the participant is considered 'enrolled' in the study. Once assigned, the prescription should be completed as outlined in Section 6 of this manual and provided to the pharmacy.

5.8 Follow-up Visits

After enrollment, each participant will be scheduled to complete seven clinic visits and two follow-up phone calls. The clinic visits will occur at approximately 2-Weeks, 4-Weeks, 8-Weeks, 12-Weeks, 16-Weeks, 20-weeks, and 24-Weeks following the enrollment visit. The phone calls will occur one week following the Enrollment Visit and one week following the 24-Week Final Clinic Visit/Early Termination Visit. The total duration of their participation will be about 25 weeks.

5.8.1 Follow-up Visit Procedures

Required follow-up clinic visit procedures are listed in protocol sections 7.4 and 7.5 and Appendix I. Several additional clarifications of the procedural specifications are provided in the remainder of this section. Further operational guidance on completing protocol-specific procedures during follow-up visits is incorporated into the visit checklists, which are available on the MTN-023/IPM 030 Study Implementation Materials. More information on components of follow-up visits can be found in the following locations within this manual:

- Section 6: Product Use Instructions and Study Product Dispensing Instructions
- Section 7: Clinical Considerations
- Section 10: Laboratory Procedures
- Section 11: Data Management and CRF completion
- Section 14: Behavioral Assessment Instructions (including ACASI, SMS, and IDI). As per Protocol Version 2.0, Letter of Amendment #01, dated 16 February 2016, all IDIs and SMS activities related to the secondary and exploratory endpoints of acceptability and adherence were discontinued in February 2016.

5.8.2 Pharmacokinetic (PK) Procedures

PK blood draws are collected at the 2-Week, 4-Week, 12-Week Study Visits, and the 24-Week Final Clinic Visit/Early Termination Visit. Vaginal fluid for PK is collected at the 2-Week, 4-Week, 12-Week Study Visits, and the 24-Week Final Clinic/Early Termination Visit. Blood and vaginal fluid PK Samples should be collected on the same day and within approximately one hour of each other.

5.8.3 Types of Follow-up Visits

Throughout study follow-up, the following types of visits will be conducted:

- **Scheduled visits** are those study visits required per protocol.
- **Scheduled phone calls** are those phone calls required per protocol.
- **Interim visits** are those visits that take place between scheduled visits. There are a number of reasons why interim visits may take place including, but not limited to:
    - For product-related reasons, e.g., a participant may need a replacement vaginal ring or want to discuss problems with adherence to ring use.
    - In response to AEs, SAEs, or social harms.
    - For interim STI counseling and testing in response to STI symptoms, or interim HIV counseling and testing in response to presumed exposure to HIV.

- All scheduled and interim visits will be documented in participants' study records and on applicable CRFs. Site staff should also refer to Section 11 for details about visit scheduling, visit windows, and visit codes for scheduled and interim visits.

5.8.3.1 1-Week and 25-Week Follow-Up Phone Calls

The two required phone calls to study participants which are scheduled at 1-Week and 25-Week/Study Termination serve the purpose of inquiring about AE's and any updates to concomitant medications. More details are provided in protocol Section 7.4.5. Sites should include how they will reimburse participants for these phone calls in their site-specific informed consent form. Call attempts should be documented per site SOP or on the Phone Call visit checklist, which is available on the MTN-023/IPM 030 Study Implementation Materials webpage. Note: sites may conduct the required visit procedures for the 1-week and 25-week phone calls via phone call or an in-person clinic visit. For example, if a participant returns to the clinic for AE follow-up after the 24-week visit, that visit may take the place of the phone call and be considered the termination visit (provided the visit takes place within the 25-week phone call window). Sites should contact the MTN-023/IPM 030 Management Team for additional guidance, as needed.

5.8.3.2 Split Visit Procedures

All procedures specified by the protocol to be performed at a particular follow-up visit ideally will be completed on a single day. In the event that all required procedures cannot be completed on a single day (e.g. a participant must leave the study site before all required procedures are performed), the remaining procedures may be completed on subsequent day(s) within the visit window. When this happens, it is referred to as a "split visit" (required visit procedures are split across more than one day within the visit window). Split visits are permitted for any type of follow-up visit in MTN-023/IPM 030. For more information on visit codes for split visits, see SSP Section 11.

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

- AE assessment and reporting (verbal report of symptoms is acceptable; if symptoms indicate that further evaluation is necessary, this must be conducted prior to dispensing study product)
- Pregnancy test
- Collection of used or unused vaginal ring, if available or applicable
- Adherence counseling/vaginal ring use instructions, as needed

Note that while a visit may be split, individual procedures should not be split. For example, ACASI completion or collection of the PK blood draw and PK vaginal swab should occur on the same day and not be split across days.

5.8.4 Missed Visits

If no procedures of a scheduled visit are conducted within the visit window, a Missed Visit CRF should be completed and faxed to SCHARP as soon as the visit window ends. If feasible, and the participant is willing, schedule the participant to return to the clinic for an interim visit. At the interim visit, conduct the missed visit procedures and complete the applicable CRFs using the interim visit code. The site must also document this occurrence on a protocol deviation CRF, using the reason code for a "visit completed outside of window". The site should also clearly document in chart notes that the site staff attempted to schedule the visit per protocol, but the participant was unable to make the appointment. Section 11 gives detailed information regarding the completion of the Missed Visit form and interim visit codes.

5.8.5 Follow-up Procedures for Participants Who Discontinue Study Product

Section 7.5 of the protocol provides information on the procedures for participants who discontinue study product. Participants that discontinue study product will be encouraged to remain in the study, if they are willing, until their scheduled end-date.

5.8.5.1 Participants Who Become Infected with HIV-1

Study product use must be held immediately for participants with a positive EIA result, or an indeterminate result. Clinic staff should inform the pharmacist of the product hold in writing, using a Study Product Request Slip, and should complete and fax a Clinical Product Hold/Discontinuation Log form to the MTN SDMC.

Participants who seroconvert during study follow-up will discontinue the following study procedures:

- HIV testing
- Provision of study product and associated procedures
- Product Use Adherence assessments*
- Pelvic exams, unless required for AE follow-up
- PK specimen collection (blood and pelvic samples)*
- Provision of counseling (HIV pre/post-test, product use adherence)
- HIV/STI risk reduction counseling will be modified to address primary and secondary prevention for infected women.

*Perform at the first visit where study product is discontinued, but omit at subsequent visits.

Participants who are confirmed HIV positive during follow-up will undergo the following additional procedures:

- CD4 testing
- HIV RNA testing
- HIV drug-resistance testing
- Consent to notify the participant's medical care provider of the participant's involvement in MTN-023/IPM 030
- Referral to available resources in the area for HIV testing, treatment, and support. Refer to protocol sections 7.5.1, 9.3 and 9.7.

5.8.5.2 Participants Who Become Pregnant

All study participants are required to be using an effective method of contraception according to Protocol Section 5.2. Study staff will provide contraceptive counseling to enrolled participants throughout the duration of study participation and will facilitate access to contraceptive services through direct service delivery. Study staff also will provide participants with condoms and counseling on use of condoms ideally during every sex act during study participation.

Pregnancy testing is performed at all study visits and may be performed as indicated at interim visits. In addition, participants are encouraged to report all signs or symptoms of pregnancy to study staff. If a participant becomes pregnant during follow-up, the following should occur:

- Counsel participant regarding possible risks to the fetus according to the study product's Investigator's Brochure.
- Refer the participant to local health care services. The referral should be documented in chart notes.
- A Pregnancy Report and History form must be completed to document the pregnancy and relevant history.

- A Pregnancy Outcome CRF also must be completed to document the outcome of the pregnancy. Whenever possible, pregnancy outcomes should be collected from medical records or other written documentation from a licensed health care practitioner. When medical records cannot be obtained, however, outcomes may be based on participant report.

Participants will be permanently discontinued from VR use and will be instructed to return the study VR. The participant will be offered the option to continue follow-up visits per her original study schedule until her originally scheduled study exit date. For those who choose to remain in follow-up, protocol-specified procedures will continue except the following:

- hCG testing*
- Samples for PK*
- Provision of contraceptive counseling
- Provision of study product and associated procedures
- Provision of product adherence counseling
- Pelvic exams, unless required for AE follow-up
- Product Use Adherence assessments*
- Consent to notify the participant's medical care provider of the participant's involvement in MTN-023/IPM 030

*Perform at the first visit where study product is discontinued, but omit at subsequent visits.

Participants who are pregnant at the 24-Week Final Clinic/Termination Visit will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Outcomes meeting criteria for EAE reporting also are reported on EAE forms.

5.8.5.3 Modified Procedures for Visits When Product Is Not Dispensed (Participant is on a Clinical Hold/Discontinuation or Refuses to Accept Study Product)

This section applies to situations where study product will not be dispensed to the participant, either because the participant has been placed on a clinical product hold/discontinuation by study staff, or she refuses to accept/use study product.

A "clinical" hold or discontinuation is one which is initiated by study staff. Clinical product holds/permanent discontinuations require documentation on a Clinical Product Hold/Discontinuation Log CRF.

Note: Instances where a participant declines or refuses study product should not be documented as product holds/discontinuations on a Clinical Product Hold/Discontinuation CRF.

For those who choose to remain in follow-up, protocol-specified procedures will continue except the following:

- Samples for PK*
- Provision of study product and associated procedures
- Provision of product adherence counseling
- Product Use Adherence assessments*
- Pelvic exams, unless required for AE follow-up

*Perform at the first visit where study product is discontinued, but omit at subsequent visits.

Completion of these procedures will resume if/when study product use is restarted.

Participants who have voluntarily chosen to not use study product but are willing to continue in follow-up should be approached at all remaining visits about restarting VR use. This should be documented in chart notes.

5.8.6 Voluntary Withdrawal/Early Termination

As stated in the informed consent form, a participant or her guardian may choose to withdraw consent from the study and terminate their study participation for any reason at any time. If a participant/guardian wishes to discontinue participation in the study, their wishes must be respected.

If the participant decides to withdraw from the study, staff should complete the following:

- Ask participant if she is willing to complete one last visit, which would count as her termination visit. If the participant is willing, site staff should conduct all required early termination procedures at this final visit. Early termination procedures will be done per Section 7.4 of the protocol (24-Week Final Clinic Visit/Early Termination Visit) and will be documented via completion of all required CRFs for this visit including completion of the in-depth interview, if randomized
- Site staff should complete the Termination CRF and mark item 2c “participant refused further participation”
- 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

At the time when the participant states that she wishes to discontinue participation, study staff must document, in participants’ study records, the participant’s stated wishes in detail. The following information should be obtained if possible:

- Why the participant wishes to leave the study.
- Whether the participant is willing to have any further contact with study staff in the future and, if so, for what purpose, at what frequency, and through what methods. For example, a participant who is not currently able to complete study visits may be willing to have study staff check in with her in several months’ time to see if her circumstances may have changed. In this case, study staff must document the timing and type of contact that the participant agreed to (e.g., in person, telephone, delivery/mail), as well as the participant’s preferences for the location of the contact (e.g., at her home, at a family member’s home, at her workplace).
- If the participant has any pending laboratory test results, whether and how she is willing to be contacted for purposes of receiving her results.
- Whether and how the participant wishes to be contacted for purposes of learning the results of the study or unblinding (when available).

5.8.7 24-Week Final Clinic Visit/Early Termination

Procedural requirements for conducting the 24-Week Final Clinic/Early Termination visit is specified in protocol section 7.4; further procedural guidance is incorporated in the 24-Week Final Clinic/Early Termination visit checklist which is available on the MTN-023/IPM 030 Study Implementation Materials webpage. Provided in the remainder of this section is additional information related to key aspects of final clinic/early termination visits.

5.8.7.1 Participant Locator Information

Accurate participant locator information will be needed for post-study contact with study participants. As such, locator information should be actively reviewed and updated at all study exit visits and all participants should be counseled to contact the study site should their locator information change after study exit.

5.8.7.2 AE Management and Documentation

More information about the clinical management of AE's is discussed in Sections 7 and 8 of this manual. All AE Log forms completed for each participant should be reviewed at the study exit visit and updated as needed. For AEs that are ongoing at the 25-Week Follow-up Phone Call, the status/outcome of the AE should be updated to "continuing at end of study participation" and the AE Log form should be re-faxed to MTN SDMC DataFax. Information related to following up AEs after participant termination can be found in Section 8 of this manual.

5.8.7.3 Referral to Non-Study Service Providers

After the 25-Week Follow Up Phone call, participants will no longer have routine access to services provided through the study, such as routine health care and HIV counseling and testing. Participants should be counseled about this —ideally before and during their study exit visits — and provided information on where they can access such services after study exit. It is strongly recommended that all study sites develop written referral sheets that can be given to participants at their study exit visits.

5.8.8 Post-Study Contact

- It is expected that all participants will be re-contacted by study staff after study completion, when study results will be available for dissemination.
- To facilitate post-study contact with participants, locator information should be updated at the study exit visit, and participants should be counseled to contact the study site should their locator information change after study exit. In addition, participant preferences for methods to be used for contacting them when 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. In addition, for ease of retrieving information on participant permissions, it is recommended that study staff maintain future study contact permission logs.

Section 6. Study Product Considerations for Non-Pharmacy Staff

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This section provides information and instructions for non-pharmacy staff related responsibilities regarding blinding, transport, receiving the MTN-023/IPM 030 vaginal ring from pharmacy and delivery of the vaginal ring to study participants. Record keeping requirements for non-pharmacy staff also are provided. Associated instructions for pharmacy staff are provided in the MTN-023/IPM 030 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 9 of this manual for product use instructions and guidance on study product adherence counseling.

6.1 Responsibilities and Obligations with Regard to Blinding

MTN-023/IPM 030 Investigators of Record (IoRs), and by delegation all MTN-023/IPM 030 study staff members are responsible for maintaining the integrity of the study's blinded design. The identity of the specific study product (Dapivirine Vaginal Ring (VR) or Placebo VR) to which each participant is randomly assigned is double-blinded, 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.

Study documentation maintained by clinic staff members — who are responsible for ascertaining primary and secondary study endpoints —will identify the randomization envelope number to which each participant has been assigned. Study documentation maintained by pharmacy staff — who are excluded from ascertaining primary and secondary study endpoints —will include blinded coded information indicating the specific sublot code for the vaginal ring to which participants have been assigned.

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 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 her study product, the IoR may hold or 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.

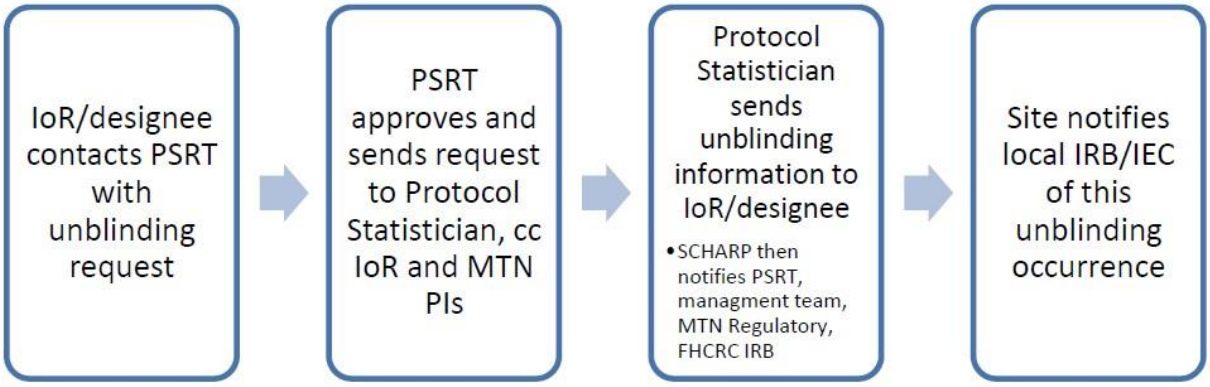
6.1.1 Emergency Unblinding Process

During the trial, an IoR/designee may request that a participant's study 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) (412-641-8947 or mtn023psrt@mtnstopshiv.org).
2. If the PSRT rules that unblinding is required, the PSRT will send the unblinding request to the Protocol Statistician (Jingyang Zhang), 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 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 6-1. Flow Chart of Emergency Unblinding Process



6.2 Randomization Assignment

The MTN Statistical Data Management Center (SDMC) will generate and maintain the study randomization scheme and associated materials, which consist of the following:

- MTN-023/IPM 030 Randomization Envelopes

- MTN-023/IPM 030 Randomization Envelope Tracking Record (Appendix 6-1)
- MTN-023/IPM 030 Prescription (Appendix 6-2)
- MTN-023/IPM 030 Vaginal Ring Request Slip (Appendix 6-3)
- MTN-023/IPM 030 Randomization Number Tracking Record for Pharmacy
- MTN-023/IPM 030 Participant-Specific Pharmacy Dispensing Records

Randomization Envelopes will be shipped from the MTN SDMC to each study clinic. They will be stored in the clinic and assigned in sequential order (via increasing envelope number) to participants who have been confirmed as eligible and have provided written informed consent to take part in the study. Envelopes must be assigned in sequential order, and only one envelope may be assigned to each participant. Once an envelope is assigned to a participant, it may not be re-assigned to any other participant. All envelopes are sealed with security tape that, when opened reveals the word “OPENED” or “SECURITY TAPE” in the residue of the tape.

Envelope assignment to eligible participants will be documented on the Randomization Envelope Tracking Record (Appendix 6-1) that will accompany each envelope shipment to each site. The act of assigning a Randomization Envelope to a participant is considered the effective act of randomization and enrollment into the study. Once a Randomization Envelope is assigned, the participant is considered enrolled in the study.

Each Randomization Envelope will contain a prescription (Appendix 6-2). Prescriptions will be produced as two-part no carbon required (NCR) forms preprinted with the CRS name, CRS ID, CRS Location, Randomization Number, and randomization status for the in-depth interview. After recording the PTID 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. The Randomization Envelope and the yellow copy will be retained in the participant’s study notebook in the clinic. Only one prescription may be assigned to each participant. Once a prescription is assigned to a participant, it may not be re-assigned to any other participant. A prescription must be signed by an authorized prescriber as designated on FDA Form 1572.
If pharmacy staff identify possible errors on the original prescription, they will return the 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 by the authorized prescriber. 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 original prescriptions.

6.3 Dispensing Study Product

Each participant is assigned to either 25 mg dapivirine vaginal ring or a placebo vaginal ring based on the randomization number pre-printed on the prescription (see Appendix 6-2).

Each vaginal ring will be dispensed in its original sealed pouch. The pharmacist/designee will also dispense an amber or white participant vaginal ring return bag. The pharmacist/designee will complete the PTID and date the bag was dispensed, and clinic staff will complete a contact name and phone number on the label of the return bag. Clinic staff must be sure to provide the participant with the correct vaginal ring and the return bag. Clinic staff should instruct the participant that the ring should be rinsed and dried and placed in the bag if the used ring 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 reinserting the ring. Participants may request a new bag at clinic visits as needed if the bag is used or misplaced.

6.3.1 Chain of Custody

For MTN-023/IPM 030, the vaginal rings and return bag will only be dispensed from the pharmacy directly to a clinic staff member who will then deliver the participant-specific study product to the participant. If staffing issues make it impossible for a clinic staff member to pick up the ring from the pharmacy, a designated transport staff member (runner or courier) may pick up the vaginal ring and bag, and then transfer the study product to a designated clinic staff member who will then provide the participant the study product. The MTN-023/IPM 030 Chain of Custody (Pharmacy) SOP provides documentation regarding who receives the vaginal ring from the pharmacist. 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. The 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.

6.3.2 Initial Vaginal Ring Dispensing - Prescription Overview

All prescriptions will have the assignment “MTN-023/IPM 030 Vaginal Ring (25 mg dapivirine or placebo)”, as all participants will be randomized to vaginal ring. The randomization number pre-printed on the prescription (which is the same as the randomization envelope number) will indicate to the pharmacy which MTN-023/IPM 030 Participant-Specific Pharmacy Dispensing Record should be used to instruct the pharmacy staff as to which ring sub-lot should be dispensed to the participant. Note that only one vaginal ring may be dispensed at each visit.

The in-clinic procedures are listed below.

6.3.2.1 In Clinic (procedures C1-C5):

C1. Obtain the next sequentially-numbered Randomization Envelope which contains a MTN-023/IPM 030 prescription. Assign the Randomization Envelope to the participant by documenting the PTID, date assigned, time assigned, and the designated clinic staff initials on the MTN-023/IPM 030 Randomization Envelope Tracking Record in the row corresponding to the assigned Randomization Envelope Number. 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.

6.3.2.2 In Pharmacy (procedures P1-P3):

P1. Upon receiving the completed MTN-023/IPM 030 Prescription (at enrollment), the pharmacist will review the document for completion and accuracy. 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. Receipt of the MTN-023/IPM 030 Prescription will be documented on the Randomization Number Tracking Record for Pharmacy. The PTID, pharmacy staff initials, and date the prescription is received must be recorded for the corresponding Randomization Number.

P3. Following review of the signed MTN-023/IPM 030 Prescription pharmacy staff will dispense the study product for participants per instructions in the MTN-023/IPM 030 Pharmacy Study Product Management Procedures Manual and in accordance with the site pharmacy Chain of Custody SOP.

6.4 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-023/IPM 030 sites. A sample Participant-Specific Clinic Study Product Accountability Log is available on the MTN-023/IPM 030 website under Study Implementation Materials. This log includes tracking the date it is distributed to the study participant, the date of ring 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.

6.4.1 Documentation of Ring Provision and Ring Collection

6.4.1.1 Clinic Participant-Specific Vaginal Ring Accountability Record

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-023/IPM 030 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 at least daily and indicated in the Source Document SOP whether any of the data points will collect source data.

6.4.1.2 Ring Collection and Insertion CRF

Site staff must document all vaginal ring 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 rings on the CRF and clinic log, clinic staff should proceed to follow the directions outlined in SSP Section 10.9 (Testing of Intravaginal Ring (IVR)). The placement of the used ring in the biohazard bag (supplied by Laboratory Center) 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. Clinic staff and pharmacy staff will complete the Pharmacy Record of Returns.

6.4.1.3 Clinic Study Product Destruction Log

In the rare event that a ring must be destroyed, this log (also available on the MTN-023/IPM 030 website under Study Implementation Materials) should be completed to document the

destruction of the specific biohazard waste container/bin. 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 container for destruction.

6.5 Duration of Use of Each Vaginal Ring

Participants should be counseled to refrain from removing the ring until the next scheduled visit (approximately 28 days) unless instructed otherwise by the study clinic. The ring should be replaced after 28 days. If this is not possible, every effort should be made to replace the ring within the next 7 days. Sites must consider this when developing visit scheduling and tracking systems.

If the next scheduled visit is greater than 35 days from the current visit, the participant should be counseled to use the ring as usual and the ring will be replaced when she comes in for her next scheduled visit. IoR discretion must be used regarding ring use depending on the length of time until this next visit. If the ring is used >35 days, attempts should be made to contact the participant and retrieve the study product as soon as possible.

6.6 Vaginal Ring Re-supply During Follow-up

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 sections 8 and 9 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).
- Pregnancy test: participant must have a documented negative pregnancy test prior to dispensing product
- Collection of used vaginal ring (and unused, if applicable), if available.
- Adherence Counseling/Vaginal Ring Use Instructions, as needed.

The above listing of procedures is also required in the event that a participant returns to the clinic for an interim visit to resupply study product. The MTN-023/IPM 030 Vaginal Ring Request Slip, which will be produced as two-part NCR forms, (see Appendix 6-3) will be used by clinic staff to communicate that a new vaginal ring should be resupplied to a participant, either for a scheduled study visit or for an interim visit. The slip is also used to communicate clinic staff decisions to temporarily hold, permanently discontinue, or resume (after a hold) vaginal ring 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.

Bulk supplies of the slips will be provided to the clinic staff by SCHARP. Sites will identify the individual responsible for receiving the slips and for contacting the SCHARP Project Manager should additional slips be needed during the study. Instructions for completion of the MTN-023/IPM 030 Vaginal Ring Request Slips are printed on the slips themselves. Additional guidance for clinic staff is as follows:

- Record the CRS name, 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 each month to document the continued refusal. If the participant agrees to start receiving product again, mark the RE-SUPPLY box to indicate she is restarting product.
- At the scheduled 24-Week/Final Clinic Visit, 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-023/IPM 030 Vaginal 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 a ring is dispensed, clinic staff will document on the Ring Collection/Insertion CRF the needed details regarding the dispensation of the vaginal ring.

6.6.1 Vaginal Ring Hold and Resumption

Protocol Section 9 (Clinical Management) and SSP Section 7 (Clinical Considerations) specify the circumstances under which use of study product may be 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-023/IPM 030 Vaginal 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 SCHARP. 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-023/IPM 030 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, rinse the ring with clean water, pat dry with a paper towel and place it in the study-provided return bag until further instructions are available.
- Follow-up as clinically appropriate per protocol, SSP and/or site SOPs.
- The participant should not resume vaginal ring use until it is determined safe by the IoR/designee. Vaginal ring use may be resumed by asking the participant to come to the clinic for a new vaginal ring.

A vaginal ring should not be removed for a hold and later reinserted for reuse.

Once an MTN-023/IPM 030 Vaginal Ring Request Slip is completed and a "HOLD" is marked, regardless of the reason or duration, no further vaginal 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-023/IPM 030 Vaginal Ring Request Slip marked RESUME. The Product Hold/Discontinuation Log CRF documenting the hold should be updated and re-faxed to SCHARP when the participant resumes study product.

6.6.2 Permanent Discontinuation

If it is determined by the site clinician that vaginal ring use will be permanently discontinued, site staff will complete an MTN-023/IPM 030 Vaginal Ring Request Slip marked PERMANENT DISCONTINUATION. No further Vaginal Ring Request Slips need to be completed after this visit. A Product Hold/Discontinuation Log CRF must also be completed and faxed to SCHARP. If the participant opts to remain in follow-up, follow guidance per SSP Section 5 (Study procedures) regarding visit procedures for participants who have discontinued use of study product.

6.7 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.

Figure 6-2 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.

Figure 6-2. Requirements for Retrieval of Study Product Due to Temporary Hold or Permanent Discontinuation

	Retrieve Study Product
Permanent discontinuation or temporary hold due to potential HIV	Within 24 hours
Permanent discontinuation for any	Within 5 working days
Temporary hold for reasons with expected duration of at least 7	Within 7 working days

For all product holds requiring product retrieval, if the vaginal ring is not retrieved within the time frame listed in Figure 6-2, the PSRT must be informed.

In addition to the above, all vaginal rings should be retrieved from all participants at their 24-Week/Final Clinic Visit. If the participant does not bring her vaginal ring to this visit, study staff must arrange to retrieve the vaginal ring within 2 working days. If the vaginal ring is not retrieved within this timeframe, the PSRT must be informed. The retrieved vaginal ring must be documented by clinic staff on the Ring Collection and Insertion CRF.

6.8 Study Product Considerations During Split Visits

In cases where follow-up visit procedures are split across more than one day, every effort should be made to complete pregnancy testing and all other safety evaluations required for product

dispensation (as listed in Section 6.6 of this manual), and product dispensation on the first day of the split visit. If safety testing cannot be performed, the IoR or designee should determine if a new ring should be provided to the participant at that visit.

6.9 Study Product Considerations During Missed or Late Visits

In the event of a missed or late visit, staff members should immediately assess the amount of time that has passed since the participant was last dispensed a vaginal ring. The IoR or designee should determine the next steps to follow, and consult the PSRT as needed.

6.10 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 concern 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 IPM. If the complaint/issue is concerning an unused IVR, then the unused IVR should be held 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 6-1: MTN-023/IPM 030 Randomization Envelope Tracking Record

CRS	<pre-fill>	CRS ID:	<pre-
CRS	<pre-fill>		

Instructions: Complete one row each time a randomization envelope is assigned to an MTN-023/IPM 030 study participant. All entries must be made in blue or black ink. Corrections may be made by drawing a line through incorrect entries, entering correct information, and initialing and dating the correction.

Randomization	Envelope Assigned to	Date Assigned	Time Assigned (hh:mm)	Clinic Staff Initials
101				
102				
103				
104				
105				
106				
107				
108				
109				
110				
111				
112				
113				
114				
115				
116				
117				
118				
119				
120				

Appendix 6-2: MTN-023/IPM 030 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:	**Pre-fill**	**CRS ID:**	**Pre-fill**
CRS Location:	**Pre-fill**	**Randomization #:**	**Pre-fill**
Participant selected to complete the in-depth interview at Week 12?	**Pre-fill**		

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did the participant provide written informed consent for enrollment into MTN-023/IPM 030? . . . . . Yes ☐ No ☐

Clinic Staff Initials _____

MTN-023/IPM 030 Vaginal Ring (25 mg dapivirine or placebo)

Sig: Insert one ring into the vagina.

Quantity: One vaginal ring. May be refilled as needed per request by designated clinic staff on MTN-023/IPM 030 Vaginal 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: _____

☐☐–☐☐☐–☐☐
dd MMM yy

Appendix 6-3: MTN-023/IPM 030 Vaginal Ring Request Slip

CRS Name:

Participant ID: ☐☐☐–☐☐☐☐☐☐–☐

Randomization Number: ☐☐☐

Clinic Staff Instructions: Mark whether this is a study vaginal 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 vaginal ring.

☐ **HOLD** → **Reason**: _____

Pharmacy: Do not dispense further vaginal rings to the participant until another MTN-023/IPM 030 Vaginal Ring Request Slip marked "RESUME" is received.

☐ **RESUME** → **Pharmacy:** Dispense 1 vaginal ring.

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

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

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

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

Clinic Staff Name (please print): _____

Clinic Staff Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd MMM yy

Section 7. Clinical Considerations

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This section presents information on the clinical procedures performed in MTN 023/IPM 030. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 8. Information on performing laboratory procedures is described in Section 10. Instructions for completing data collection forms associated with clinical procedures are provided in Section 11.

The Schedule of Study Visits and Evaluations in Appendix I of the protocol indicates when specific clinical and laboratory assessments are to take place. While the protocol dictates the schedule for data capture, the Investigator of Record or designee should perform the symptom-directed examination at his/her discretion during any visit if s/he determines it to be clinically necessary,

particularly if there are any on-going medical or mental health conditions that require closer follow-up. The participant's research record should include documentation of these procedures. Throughout this section the term 'clinician' will refer to a study doctor or a nurse in settings where nursing training, scope of practice, and delegation, permit nurses to perform clinician activities under doctor supervision.

7.1 Baseline Medical Conditions (Pre-existing Conditions) and Medications

7.1.1 Pre-existing Conditions Collection at the Screening Visit

In order to establish each participant's medical status at Enrollment (and also assess medical eligibility), pre-existing conditions will be captured starting at the Screening Visit. The purpose of having pre-existing conditions documented is to ensure that abnormalities that are present at baseline and later observed during follow-up are not documented as adverse events (see Section 8 for more information).

7.1.2 Participant-Reported Conditions

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 her past medical conditions as well as any conditions she is currently experiencing at the time of the Screening and Enrollment visits. To best do this, it is recommended that sites use the MTN-023/IPM 030 Baseline Medical History Questions sheet and Baseline Menstrual History CRF. Complete an entry on the Pre-existing Conditions CRF for any abnormal bleeding patterns (e.g., amenorrhea, menorrhagia, metrorrhagia) or menstrual symptoms which contribute to a medical condition (e.g. dysmenorrhea, pre-menstrual syndrome).

When collecting medical information from the participant, ask probing questions in order to obtain the most complete and accurate information possible. This is especially important with regard to severity and frequency of pre-existing conditions. 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.

Chronic conditions should be marked as "ongoing" at enrollment. 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.

The Pre-existing Conditions CRF (PRE-1) can be updated with new or corrected information during follow-up. This would occur when new information related to the participant's baseline menstrual /medical history status is obtained after enrollment. If information is added to the PRE-1 CRF after enrollment, a chart note explaining the update is recommended.

7.1.3 Pre-existing Conditions Review and Update at the Enrollment Visit

Information documented on the Pre-existing Conditions CRF at the Screening Visit must be actively reviewed and updated at the Enrollment Visit, especially for those conditions that were ongoing at the Screening Visit. This includes a review and update of the condition's description, severity grade, and comments noted for the entry. Make sure the "Ongoing at Enrollment" field is completed for each entry prior to final eligibility confirmation. Chronic conditions should be marked as "ongoing" at Enrollment. 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.

If a pre-existing condition is resolved as of the Enrollment Visit, do not make any changes to the severity grade (similar to what is done when resolving adverse events). In this case the Ongoing at Enrollment question must be marked "no." If a pre-existing condition first identified at the Screening Visit, is ongoing at Enrollment, assess the severity at the Enrollment Visit and update the severity grade (up or down) as applicable to reflect the severity at the time of enrollment/randomization.

7.1.4 Baseline Medications

The MTN 023/IPM 030 protocol requires documentation of all medications taken by study participants beginning at the Screening Visit and continuing throughout follow-up. The Concomitant Medications Log is used to document all concomitant medications in this study. Medications include the following:

- Prescription and "over-the counter" medications and preparations
- Vaccinations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations

Study staff should use the information obtained during the review of the medical history to probe for additional medications that the participant may have forgotten to report.

If a participant is unable to provide the exact name of a medication, record the type or class of medication as the medication's name with the text "name unknown". For example, if the participant knows she takes a blood thinner, but cannot provide the exact name, use "anti-coagulant – name unknown" for the medication name field.

7.2 Clinical Instructions for Checking Ring Placement

At the enrollment visit, following insertion of the vaginal ring, the study clinician or designee should check placement of the vaginal ring, regardless of who inserted it, to confirm correct placement. The study clinician may also check placement of ring at follow-up visits, if needed. The following is the procedure that the IoR or designated clinic staff should use to verify ring placement:

- After ring placement, the participant should walk around prior to verification of correct ring placement.
- The participant should then lie comfortably on the examination table in supine position (on her back).
- Upon genital inspection, the ring must not be visible on the external genitalia. If the ring is visible, the placement is not correct.
- The ring should not press on the urethra.
- On digital or bi-manual examination, the ring must be placed at least 2cm above the introitus beyond the Levator Ani muscle.
- 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.

After correct placement is confirmed, the clinician 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.

7.3 Tanner Assessment

Participant self-report of Tanner development will be used to determine stage of puberty at the Screening visit. The sites should provide the participant with the Tanner Assessment Tool, located on the MTN-023/IPM 030 Study Implementation Materials webpage, for this purpose. Participants will be asked to identify the pictures which most closely resemble themselves. While the Tanner Assessment is intended to be self-report, participants may ask for clinician assistance if they would prefer to undergo an examination for clinical assessment. If the participant identifies herself at a particular stage and the clinician assesses the participant at a differing stage, then the clinician's assessment will be utilized to

determine if she meets the eligibility criteria. The final outcome of the assessment will be documented in chart notes or other site specific tool.

7.4 Medical and Medication History Review at Follow-Up

The Baseline Menstrual History CRF and Pre-existing Conditions CRF can be updated with new or corrected information during follow-up. This would occur only in instances when new information related to the participant's baseline medical history status is obtained after Enrollment. If information is added to either after Enrollment, a chart note explaining the update is required.

7.4.1 Participant-reported Follow-up Medical History

An updated participant self-reported medical history is required at each scheduled visit during follow-up. A history should also be performed at interim visits when a participant presents complaining of symptoms or when the purpose of the visit is to re-assess previously-identified adverse events (AEs). One purpose of the participant-reported follow-up history is to determine whether previously-documented conditions have changed with regard to severity or frequency. A second purpose is to determine whether new symptoms, illnesses, conditions, etc., have occurred since the last medical history was performed. Documentation that this history was taken is required; this can be done in chart notes, the Follow-Up Medical History Log or in a site-specific tool if desired. If no symptoms, illnesses, conditions etc., are reported, the participant chart should reflect this.

All newly-identified participant-reported symptoms and conditions will be documented on the Adverse Experience Log (AE-1) CRF (see Section 8 for details regarding AE documentation).

For purposes of this study, "newly-identified" is defined as a condition that:

- was not present at baseline (enrollment);
- is ongoing at baseline but has now increased in severity or frequency (includes ongoing baseline conditions or adverse events that increase in severity or frequency during follow-up);
- was ongoing at baseline, resolves/returns to baseline status during follow-up, and then re-occurs.

Any symptoms reported by the participant should be further probed and evaluated. Be sure to ask about ongoing baseline symptoms as well as any symptoms listed as "continuing" on an AE-1 CRF.

If during follow-up, a baseline symptom resolves or increases in severity or frequency from baseline, this will need to be documented either in chart notes or using a Follow-up Medical History Log (non-DataFax). Such information should not be added to the Pre-existing Conditions CRF, as that form represents a snapshot of the participant's status at baseline.

7.4.2 Review of Medications History

At each follow up visit, review the participant's Concomitant Medications Log CRF page(s) and record any new medications the participant reports starting since her last medications assessment. Review all previous entries that are ongoing and ask the participant whether she is still taking the medication (and at the same dose and frequency). It is important to ask whether the participant has taken any new medications, including herbal or therapies, since her last medications assessment. Ensure that concomitant medications mentioned in previous parts of the visit are rectified with the Concomitant Medications CRF so that records are not discrepant.

7.5 Physical Exams

7.5.1 Considerations at Screening and Enrollment

The goal of the physical exam during Screening and Enrollment is to collect detailed information on baseline conditions, as well as to evaluate eligibility. A complete physical exam will be conducted at the Screening and Enrollment visit and a targeted (abbreviated) physical exam for all subsequent scheduled visits except for the Week 2 Visit. Per protocol Section 7.9, the following assessments are required at the Screening and Enrollment physical exam. It will be documented on the applicable Physical Exam CRF.

- General appearance
- Weight (see Section 7.5.3 for further guidance)
- Vital signs:
    - Temperature
    - Pulse
    - Blood pressure (See section 7.5.5 for further guidance)
    - Respirations
- Abdomen
- Head, Eye, Ear, Nose and Throat (HEENT)
- Height (See section 7.5.4 for further guidance)
- Lymph nodes
- Neck
- Heart
- Lungs
- Extremities
- Skin
- Neurological

Assess any other medical condition that would make participation in the study unsafe or interfere with interpreting the study data or achieving the study objectives.

7.5.2 Physical Exams Conducted at Follow-up

Physical exams performed during follow-up are documented using the Physical Exam CRF. Abnormal physical exam findings newly-identified during follow-up are recorded and tracked using the Adverse Experience Log (AE-1) CRF. Refer to Section 7.4.1 for a definition of "newly-reported". The abbreviated physical exam at follow-up must include the following components:

- General appearance
- Weight (see Section 7.5.3 for further guidance)
- Vital signs:
    - Temperature
    - Pulse
    - Blood pressure (See section 7.5.4 for further guidance)
    - Respiratory rate
- Abdomen
- Head, Eye, Ear, Nose and Throat (HEENT)

Other components of the physical exam may be conducted at any time for clinical care.

7.5.3 Weight

Participant weight must be measured as part of each scheduled physical exam and additionally when clinically indicated. Weight should be measured in kilograms and should be rounded to the nearest whole number. Scales should be calibrated at least twice per year, and more frequently if required per local practice standards.

7.5.4 Height

Participant height must be measured as part of the full physical exam at Screening and Enrollment only. Height should be measured in centimeters and should be rounded to the nearest whole number.

7.5.5 Blood Pressure

Blood pressure must be measured as part of each scheduled physical exam and may also be measured at other visits as clinically indicated. Blood pressure devices are expected to be calibrated regularly per manufacturer's directions.

7.6 Pelvic Exam Overview

The pelvic exam during the Screening and Enrollment visits is necessary to evaluate protocol exclusion criteria and to collect detailed information on baseline genital/genitourinary conditions. Guidance on the conduct of pelvic exams can be found in the remainder of this section. Pelvic exams are documented on the non-DataFax Pelvic Exam Diagrams form and the Pelvic Exam CRF.

SPECIAL NOTE:

The findings below could potentially warrant a product hold should the participant enroll in the study. Therefore, study staff is asked to particularly assess for the following during the screening pelvic exam (some of which may be exclusionary):

- Deep epithelial disruption (ulceration)
- Generalized erythema or severe edema: area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema
- Cervicitis (including findings on exam such as inflammation and/or friability)

Note that cervical bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the Investigator of Record (IoR)/designee is not exclusionary.

7.6.1 Pelvic Exam Technique

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.

Exams During Bleeding: Routine pelvic exams, i.e., those required at protocol-specified time points, should be avoided during menses-like bleeding, as the presence of blood may interfere with visualization of the vagina and cervix, elevate the vaginal pH, and complicate interpretation of vaginal assays. If a participant is experiencing mild spotting, it is reasonable to proceed with a pelvic exam and collection of samples. If she is experiencing greater than mild bleeding when she presents for a visit in which a routine pelvic exam is required, perform other protocol-specified procedures at the visit and schedule the participant to return for the pelvic exam as soon as possible after menses, within the visit window (as part of a split visit). If this is not possible and the pelvic exam is missed, this procedure should be made up at her next scheduled clinic visit. If a participant is experiencing genital bleeding when she presents for an interim visit complaining of genital symptoms, every effort should be made to perform a pelvic exam to evaluate her symptoms at that time.

7.6.2 Detailed Procedural Instructions

Prior to the Exam: Prepare all required equipment, supplies, and paperwork; label specimen collection supplies as needed. Verify that all equipment is in good working order. 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. The study clinician should remove the VR just prior to speculum insertion.

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, if applicable, and vagina.

Collect Specimens: Collect specimens in the order listed on the pelvic exam checklist. The order of specimen collection is critical to ensure that first specimen collections do not affect subsequent specimens. Collect specimens away from apparent abnormalities and/or previously swabbed areas.

- At Screening, the 24-Week visit and when clinically indicated, collect a vaginal sample to test for **trichomonas** with the rapid test kit or Gen-Probe Aptima.
- At Enrollment, 4-Week, 12-Week and 24-Week, collect two vaginal swabs for **quantitative vaginal culture assessment**.
- At Enrollment, 4-Week, 12-Week and 24-Week, collect one vaginal swab for **Gram stain** evaluation.
- At Enrollment, 4-Week, 12-Week and 24-Week, collect one vaginal swab for **pH** assessment.
- At Enrollment, 4-Week, 12-Week, and 24-Week, collect one vaginal swab for **biomarker analysis**.
- At Enrollment, 12-Week, and 24 Week, collect **cervicovaginal fluid (CVL) for biomarker analysis**. Please refer to sections 7.6.3 and 10.7.1 of this manual for further details regarding preparation, sample collection and processing and storage requirements.
- At 2-Week, 4-Week, 12-Week and 24-Week, collect vaginal swab for **PK analysis**. See Sections 7.6.4 and 10.8.8 of this manual for further information.
- If indicated and per site standard of care, send fluid from a suspicious lesion for additional **herpes testing**.
- If clinically indicated, collect vaginal swab for saline prep and/or KOH wet mount for evaluation of **vaginitis** (yeast or BV).

Removal of Visual Obstruction: After collection of vaginal and endocervical specimens, any obstruction (e.g., mucus, cellular debris) may be removed with 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.

Complete 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.

7.6.3 Collection procedure for CVL

At Enrollment, 12-Week and 24 Final Clinic/Early Termination visits, cevicovaginal fluid (CVL) will be collected from participants. Prior to CVL, have all necessary materials readily available on exam cart or counter near exam table, and check expiration of sterile saline prior to use.

A training video is available at: http://www.mtnstopshiv.org/node/773

Sample Collection:

1. Draw 10mL of sterile normal saline into the 30mL syringe (size of syringe is not required to be exactly 30 mL, but it must be large enough to retrieve the saline after lavage from the vagina plus any additional vaginal fluid).
2. Carefully insert tip of syringe into the vagina using care not to touch vaginal walls with syringe. With tip of syringe aimed at the cervix or upper end of the vagina, dispense all 10mL of saline onto the cervix, or the vagina if the cervix was removed. Gently tilt speculum if necessary to avoid leakage of saline.
3. Place tip of a 2mL pipette onto posterior blade of the speculum and draw fluid into pipette, using care not to touch the vagina or cervix, if applicable.
4. Use the 10mL of saline to lavage the cervix, fornices and vaginal walls. Be sure to lavage each side wall at least twice. Only use the original 10mL of saline. Do not use any additional saline to perform lavage.
5. The saline must be in contact with the vaginal vault for at least 1 minute.
6. After at least 1 minute of contact, remove lavage fluid with 30mL syringe and sterile tubing or 2mL pipette.
7. Save lavage fluid for analysis. Transfer fluid to a 15mL conical centrifuge tube that has an affixed SCHARP label.

7.6.4 PK Vaginal Fluid Collection

At the 2-Week, 4-Week, 12-Week, and the 24-Week Final Clinic/Early Termination visits, vaginal fluid will be collected from participants. One (1) dacron swab will be collected within one hour of the PK blood draw from the area residing closest to the vaginal ring, near the cervix on the mid-lateral vaginal wall. At the 2-Week Visit, no other pelvic specimens are collected, and as such, a speculum pelvic exam is not required to collect the vaginal fluid for PK. With the participant in dorsal lithotomy position, the clinician can use one hand to separate the labia and the other hand to collect the specimen. Because the swab is prepackaged and cut short, the clinician will have to hold the swab with an instrument, such as a ring forcep.

The UAB, Pittsburgh, and Fenway sites will be weighing vaginal fluid swabs. These instructions are only for sites weighing vaginal fluid swabs.

- Note: These sites must determine whether each tube will be labeled with the appropriate SCHARP provided PTID label prior to or following weighing of cryovial (with screw lid).

- Site staff should weigh each cryovial and document the pre-collection weight on the LDMS Tracking Sheet. Following collection of the vaginal swab for PK assessment, site staff should place the pre-cut swab back in the designated pre-weighed cryovial, obtain the post weight for each cryovial containing the PK swab using an analytical balance, and document the post weight on the LDMS Tracking Sheet.

Refer to section 10 of this manual for further instructions on processing and storage of the swab for PK.

7.6.5 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, anatomical location, and severity grade) to ensure appropriate assessment can be provided during the next pelvic exam.

All abnormal findings during Screening and Enrollment 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. All newly-identified abnormal pelvic exam findings will be documented on an Adverse Experience Log (AE-1) CRF (see Section 7.2 for a definition of "newly-identified"). 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

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 Pelvic Exam CRF. For findings in which the finding term marked on the Pelvic Exam CRF is more specific than the corresponding term on the FGGT, use the more specific term.

7.7 STI/RTI/UTI

7.7.1 Considerations at Screening/Enrollment

Participants diagnosed during Screening and Enrollment with an STI may not be enrolled. However, they should be provided or referred for treatment. This should be documented in chart notes. If a participant is diagnosed with a UTI or RTI during screening they should be offered treatment. If the treatment has been completed and all symptoms have resolved during the screening window, they may be enrolled. Please see Exclusion Criteria #2 in Protocol Section 5.3.

7.7.2 STI/RTI/UTI Diagnosis

Clinical and laboratory evaluations for STI/RTI/UTIs, except Trichomonas, are only conducted if indicated after Screening. If identified during follow-up, they should be recorded as AEs. 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.

Genital HSV: No laboratory testing is required for herpes simplex virus (HSV-1 or HSV-2) during the study but may be done if indicated and per local standard of care. Per the FGGT, the term 'genital herpes' may only be used for adverse event reporting if laboratory testing is conducted or has been performed in the past; otherwise sites are encouraged to use the most appropriate row in the FGGT which most closely resembles the clinical findings (ulceration, for example).

Urinary tract infections (UTIs): UTIs may be diagnosed in MTN 023/IPM 030 based solely on the presence of symptoms indicative of a possible UTI and graded per the infection row of the DAIDS Toxicity Table. The following symptoms are considered indicative of a possible UTI:

- 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

Other methods of diagnosis (i.e. urine culture or dipstick) may be performed per site standard of care per site SOP. Results must be documented in chart notes and/or on other site-specific source documents. If culture or urinalysis is used, UTI should be graded per the UTI row of the FGGT if criteria are fulfilled.

7.7.3 STI/RTI/UTI Management

Treatment: All participants diagnosed with UTI based on the presence of symptoms should be provided treatment per site standard of care and applicable site standard operating procedures (SOPs).

All STIs/RTIs should be managed per current CDC guidelines, site standard of care and applicable site standard operating procedures (SOPs). Current CDC guidelines can be accessed at: http://www.cdc.gov/std/treatment/

Asymptomatic BV does not require treatment per current CDC guidelines. Asymptomatic vaginal candidiasis also should not be treated. During screening, these asymptomatic infections are not exclusionary and during follow-up these asymptomatic infections are not considered AEs.

Syndromic Management: Syndromic management of STIs is acceptable per site SOP and local standard of care; however, a thorough laboratory evaluation is expected in the context of this research study so that a specific diagnosis might be uncovered.

Test of Cure: STI/RTI tests of cure are not required in MTN 023/IPM 030, but may be recommended per local guidelines.

7.8 Vaginal Discharge

Both participant complaints and clinical findings of abnormal vaginal discharge are common in microbicide studies. While the evaluation of abnormal vaginal discharge may not differ between the two, whether treatment is offered and how the abnormality is reported may. Abnormal vaginal discharge may be associated with yeast and/or bacterial vaginosis among other conditions. Site clinicians are encouraged to thoroughly evaluate complaints and/or findings of abnormal vaginal discharge as per their discretion. Whether to treat the underlying cause of the abnormal vaginal discharge will depend on:

1. What the underlying diagnosis is; and,
2. Whether the participant is symptomatic.

If the evaluation reveals an underlying sexually transmitted infection such as trichomoniasis, the participant and her partner(s) should be offered treatment regardless of symptoms. If the evaluation reveals bacterial vaginosis or yeast, the participant should be offered treatment only if she is symptomatic.

Section 8 details the reporting of vaginal discharge adverse events. Briefly, sites are encouraged to distinguish whether the discharge was initially reported by the participant ("vaginal discharge by participant report") or noted only on pelvic exam by the clinician ("vaginal discharge-clinician observed"). Importantly, in instances when the evaluation of clinician observed vaginal discharge reveals asymptomatic bacterial vaginosis or asymptomatic yeast, an adverse event should be reported for "vaginal discharge-clinician observed." Even though asymptomatic yeast and bacterial vaginosis are not considered adverse events per protocol, in these instances, the clinician observed vaginal discharge should be captured as an adverse event.

7.9 Genital Bleeding Assessment

At each scheduled follow-up visit, study staff will actively ascertain whether any genital bleeding (menstrual or non-menstrual) was experienced since her last visit. In addition, participants will be counseled to report all occurrences of unusual genital bleeding to study staff as soon as possible after identification of the bleeding.

Study participants will undergo pelvic exams at Screening, Enrollment, 4-Week, 12-Week and 24-Week visits to evaluate any participant report of genitourinary complaints (including bleeding) that are different from baseline. The assessment of genital bleeding should begin by determining whether the bleeding (menstrual or non-menstrual) is consistent with baseline bleeding patterns. Refer to the Screening Menstrual History CRF and Pre-existing Conditions CRF (PRE) for information on the participant's bleeding pattern at baseline.

Note that any menorrhagia, metrorrhagia, or menometrorrhagia events ongoing at the time of randomization are marked as "not gradable" on the PRE. This is because the FGGT grades

these events relative to each participant's baseline bleeding pattern. In the "Comments" field of the ongoing PRE entry, sites should include text similar to what is in the FGGT row to describe the severity and frequency. For example, for an ongoing event of menorrhagia, mark "not gradable" and in the PRE Comments, record "no interference with participant's usual activities" (similar to text used to describe Grade 1 severity). Adding such text to the Comments of the PRE entry will help ensure that increases in the severity or frequency of bleeding relative to the participant's baseline bleeding pattern are identified and reported appropriately as AEs.

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. Additonal details on genital bleeding assessment and AE reporting may be found in 8.2.1.

7.10 Management of Laboratory Test Results

Serum Chemistries and CBC with platelets testing will be performed at Screening and the 24-Week/Final Clinic Visit. For each study participant, the IoR or designee is responsible for reviewing and monitoring these test results and for ensuring appropriate clinical management of all results. IoR or designee review of laboratory test results should be documented on the lab results report (provided by the lab to the clinic) and/or in chart notes.

In addition to participant-reported conditions, record all abnormal Screening Visit lab values, regardless of grade, on the Pre-existing Conditions CRF (as identified on the Laboratory Results CRF).

At a minimum, all test results of severity grade 3 and higher judged to be related and all results requiring product hold, should be urgently reported to a study clinician.

The IoR or designee should routinely review participant study records to ensure proper monitoring and clinical management of laboratory test results, and documentation thereof.

7.11 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), and management of STI/RTI (Sections 9.5), HIV infection (Sections 9.7), pregnancies (Section 9.8), and early study termination (Section 9.9). A summary of the criteria for product hold or permanent discontinuation can be found in the section appendix 7-1. Flow sheets outlining product management procedures can be found in appendix 7-2.

All specifications of protocol Sections 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.

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. Product holds and discontinuations must be communicated to site pharmacy staff using the Vaginal Ring Request Slip, as described in Section 6 of this manual. Product holds and discontinuations also must be documented on Product Hold/Discontinuation CRF.

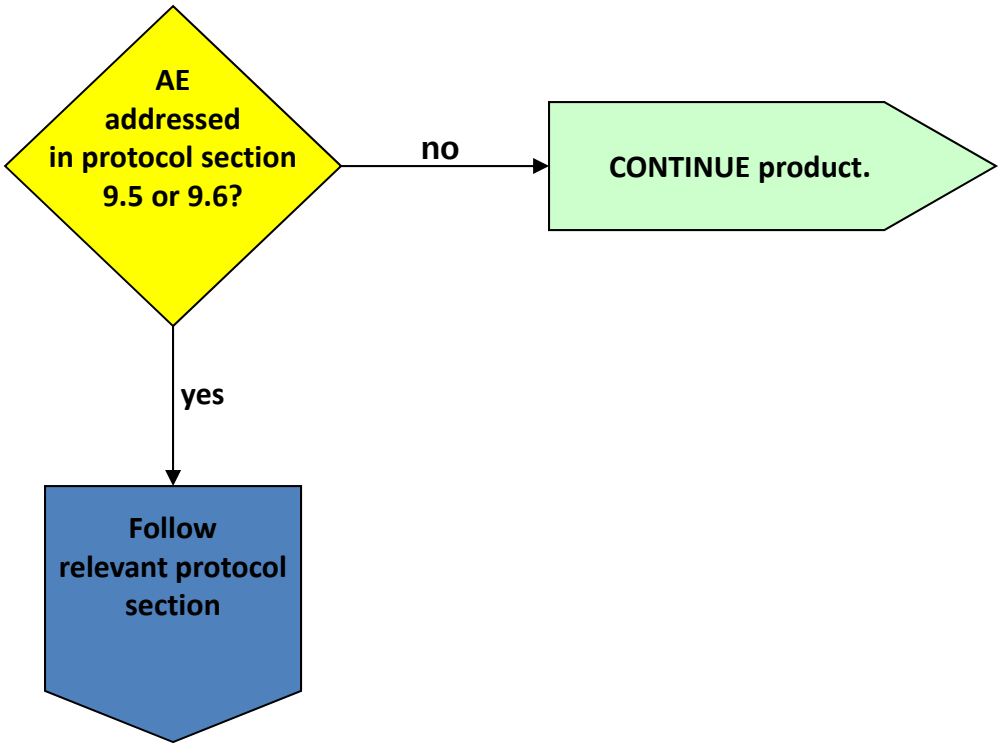
Appendix 7-1: Conditions Requiring Product Hold or Permanent Discontinuation

Condition	Temporary Hold	Permanent Discontinuation
Positive HIV Rapid	X	
Confirmed HIV infection		X
Allergic Reaction to the Vaginal Ring		X
Pregnancy		X
Breastfeeding		X
Use of PEP for HIV Exposure		X
Use of PrEP for HIV prevention		X
Non-therapeutic injection drug use		X
HIV-positive partner		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	
Grade 3 AE **Related** to study product use not otherwise specified in protocol section 9	X	
Grade 4 AE not otherwise specified in protocol section 9	X	
Superficial epithelial disruption (abrasion/peeling) **which has worsened** after re-evaluation in 3-5 days	X	
Deep epithelial disruption (ulceration)	X	
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	
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	
Cervicitis (inflammation and/or friability)	X	

**See Protocol Section 9 for complete guidelines on clinical management and study product holds. Note that when a product hold is performed, complete the Product Hold/Discontinuation CRF.*

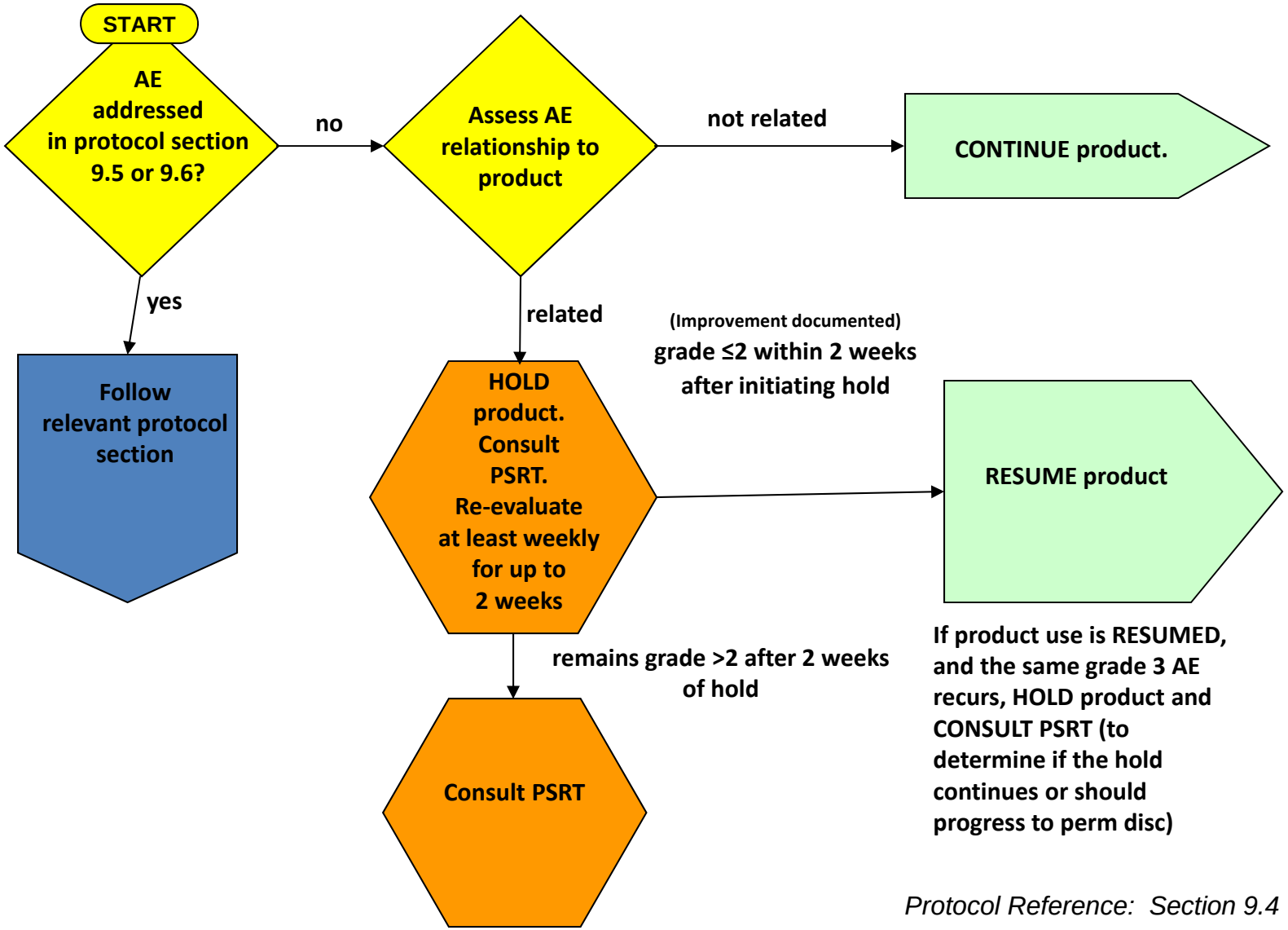
Appendix 7-2: Product Use Management Flow Sheets

Product Use Management: Grade 1 and Grade 2 Adverse Events



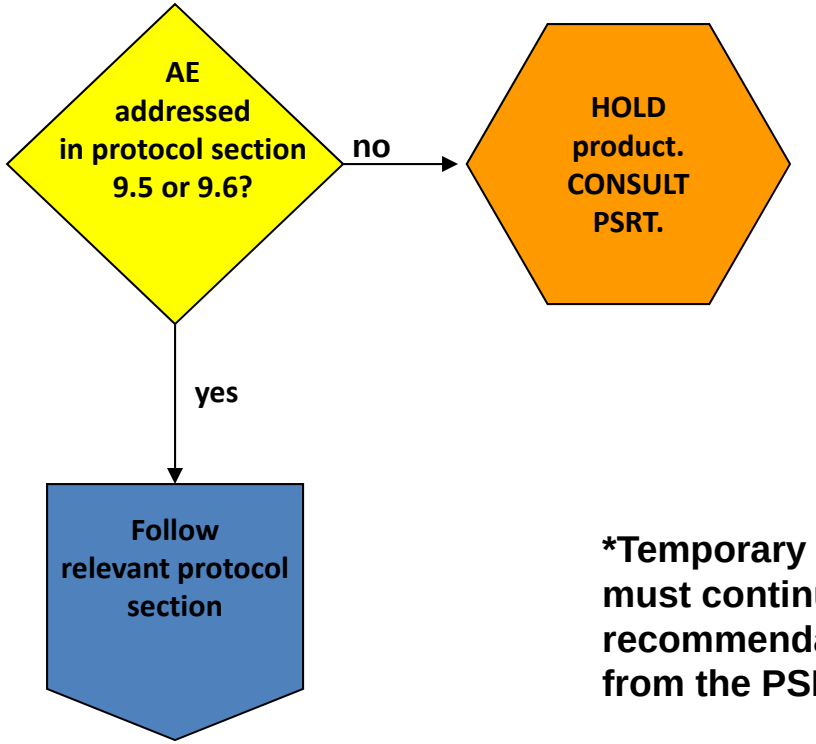
Protocol Reference: Section 9.4

Product Use Management: Grade 3 Adverse Events



Protocol Reference: Section 9.4

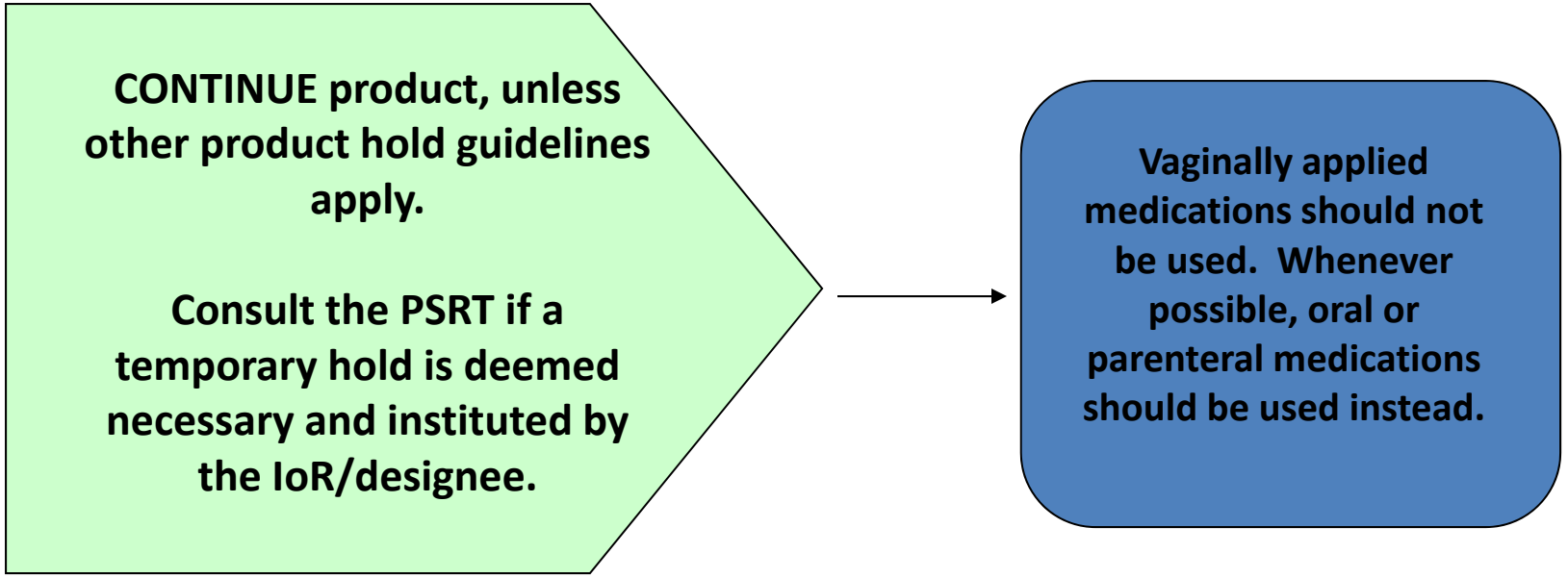
Product Use Management: Grade 4 Adverse Events



***Temporary product hold must continue until a recommendation is received from the PSRT.**

Protocol Reference: Section 9.4

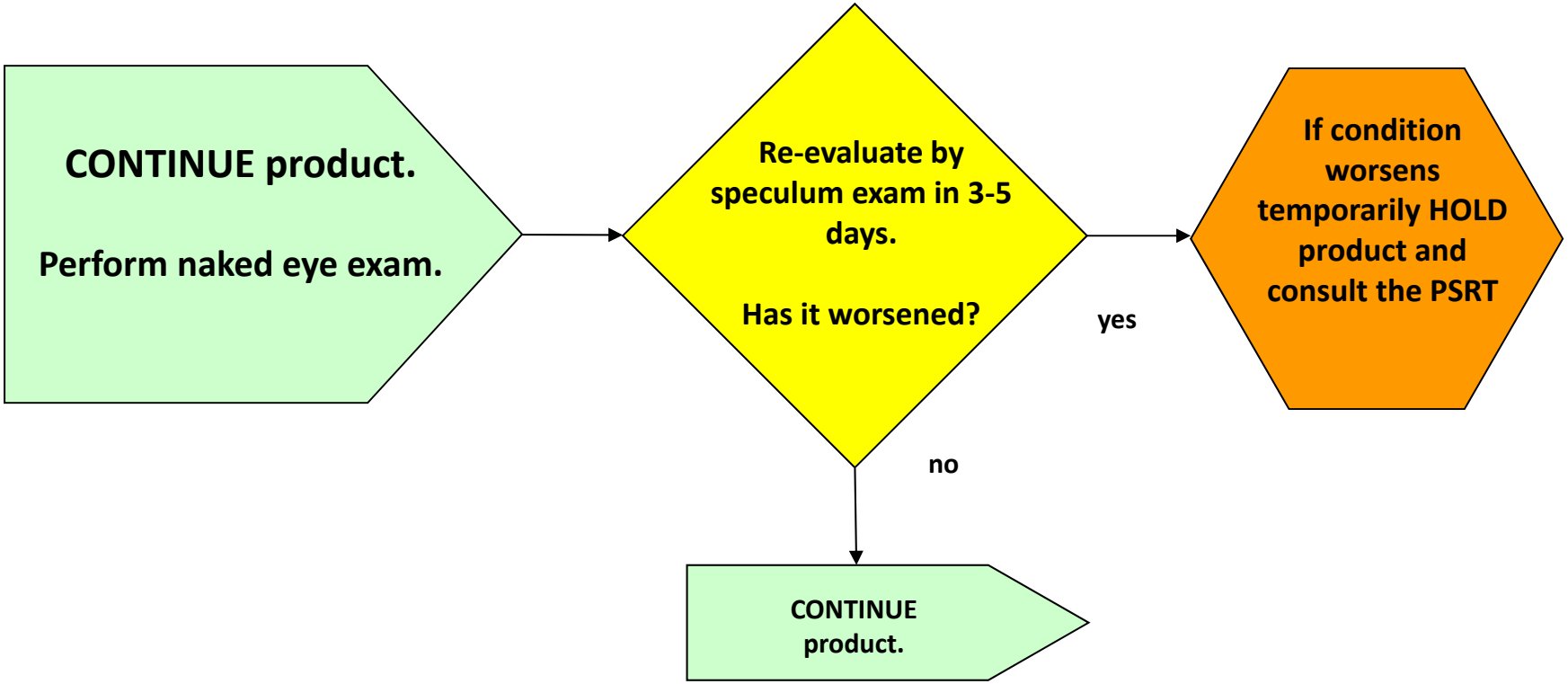
Product Use Management: Sexually Transmitted Infections and Reproductive Tract Infections



***Treat per CDC guidelines, using observed single dose regimens whenever possible.**

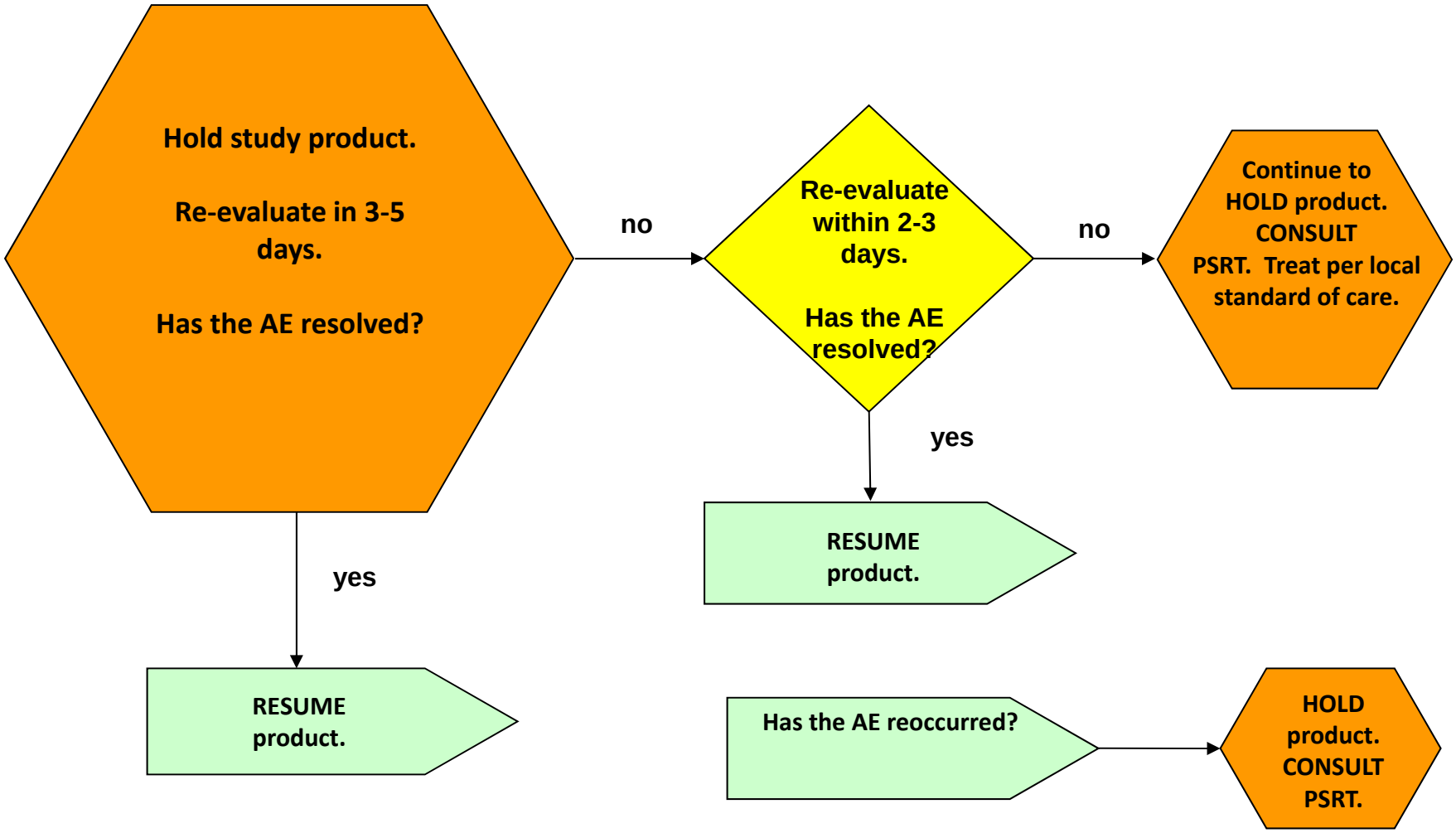
Protocol Reference: Section 9.5

Product Use Management: Superficial epithelial disruption (abrasion/ peeling)



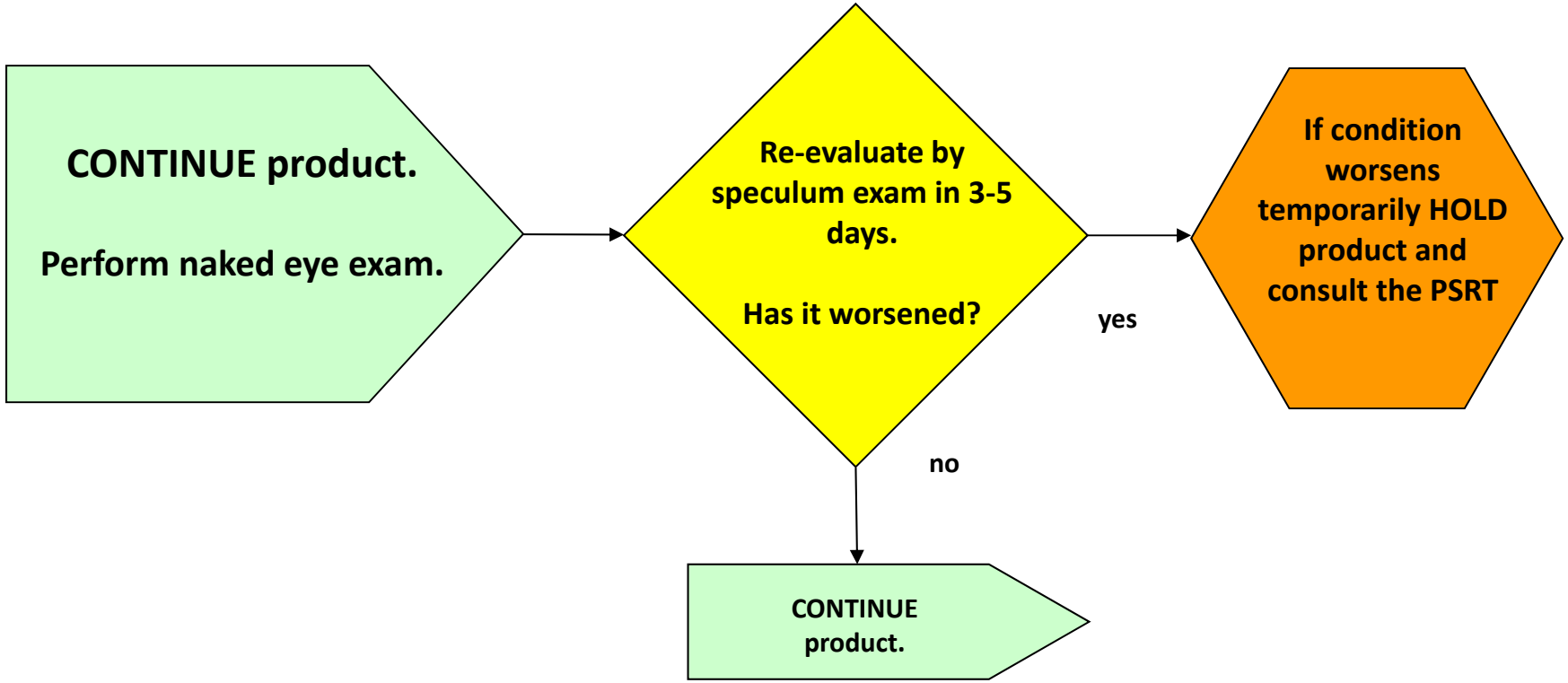
Protocol Reference: Section 9.6

Product Use Management: Deep epithelial disruption



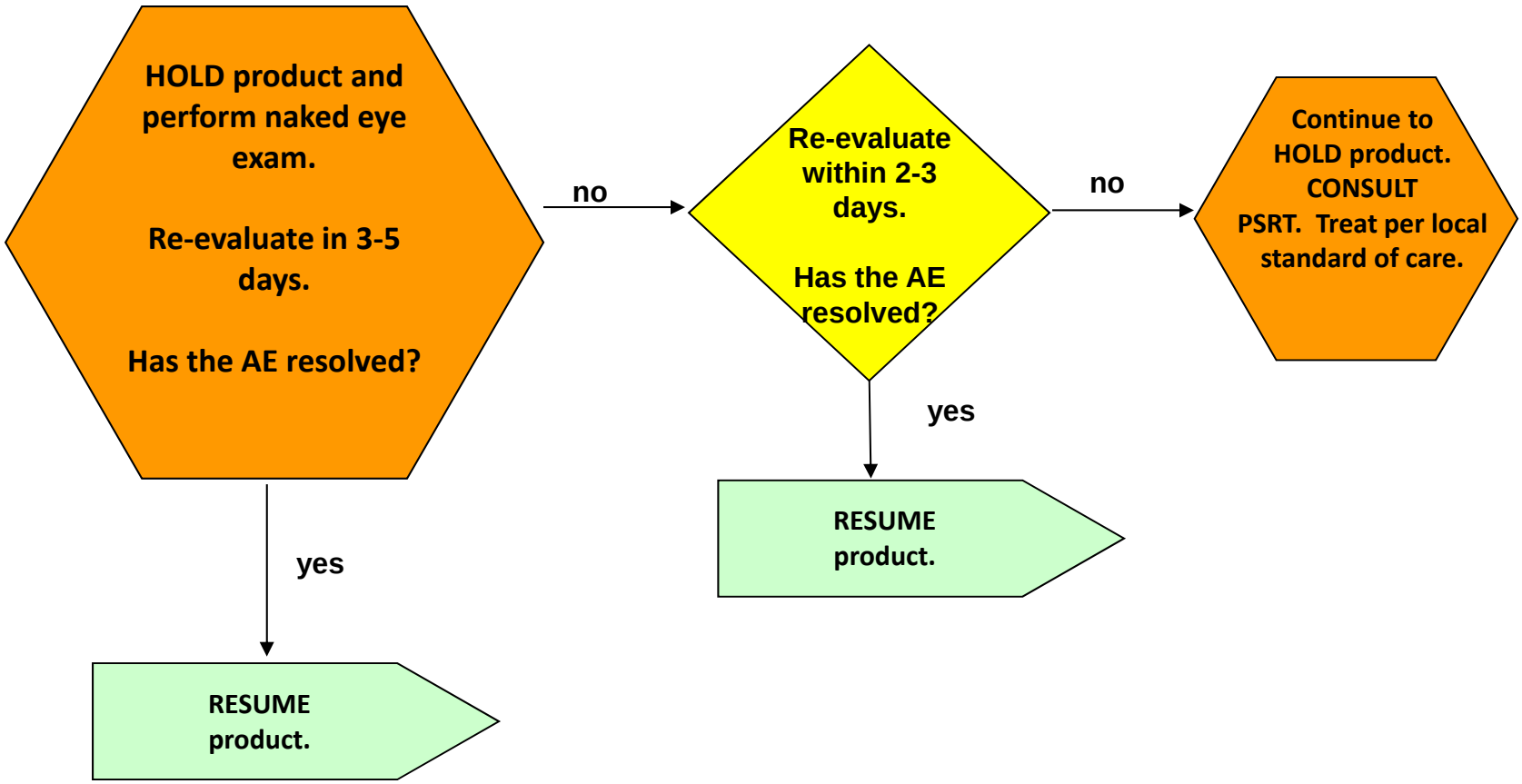
Protocol Reference: Section 9.6

Product Use Management: **Localized erythema or edema (area < 50% of vulvar surface or combined vaginal and cervical surface)**



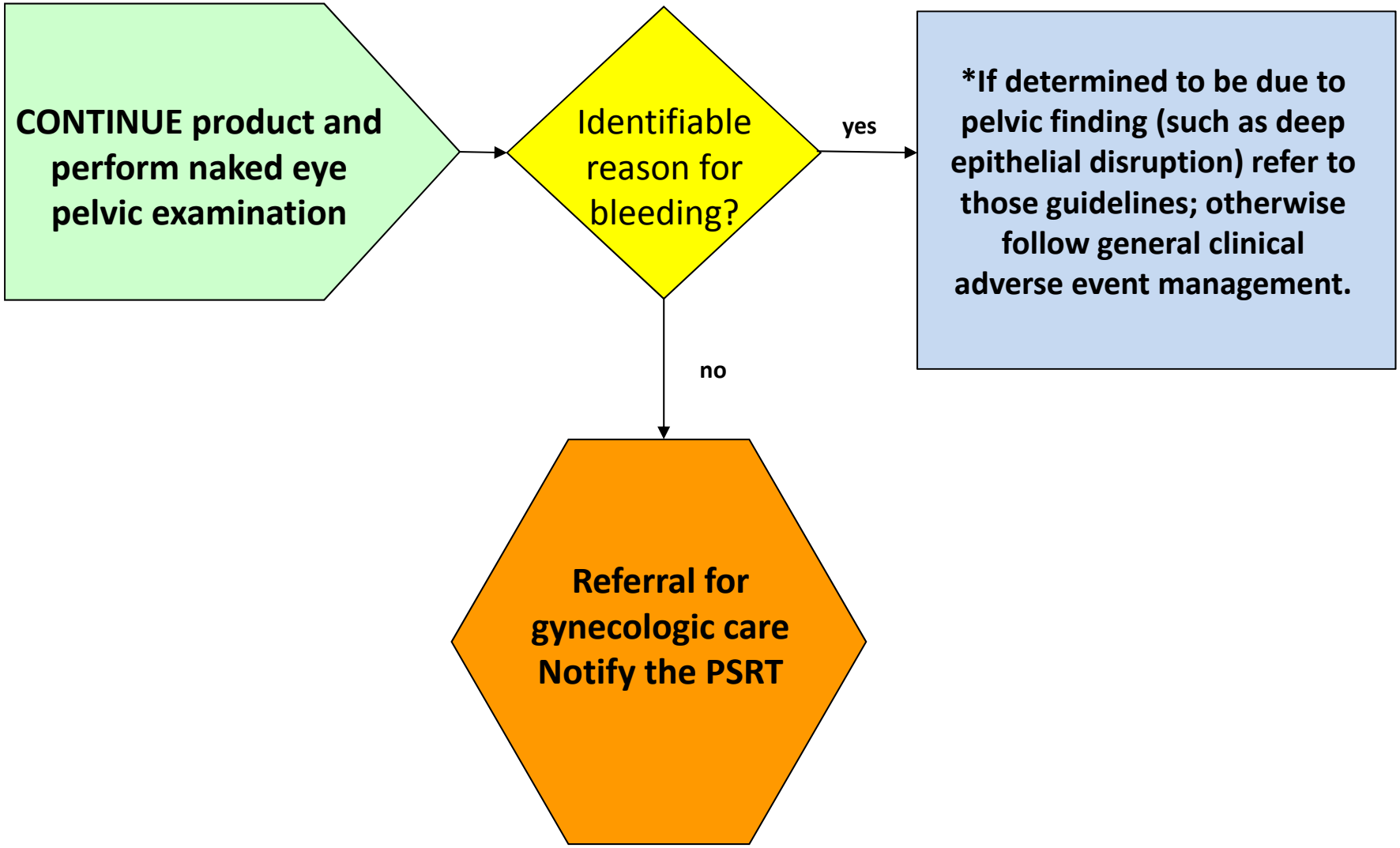
Protocol Reference: Section 9.6

Product Use Management: Generalized erythema or severe edema (area > 50% of vulvar surface or combined vaginal and cervical surface affected by erythema)



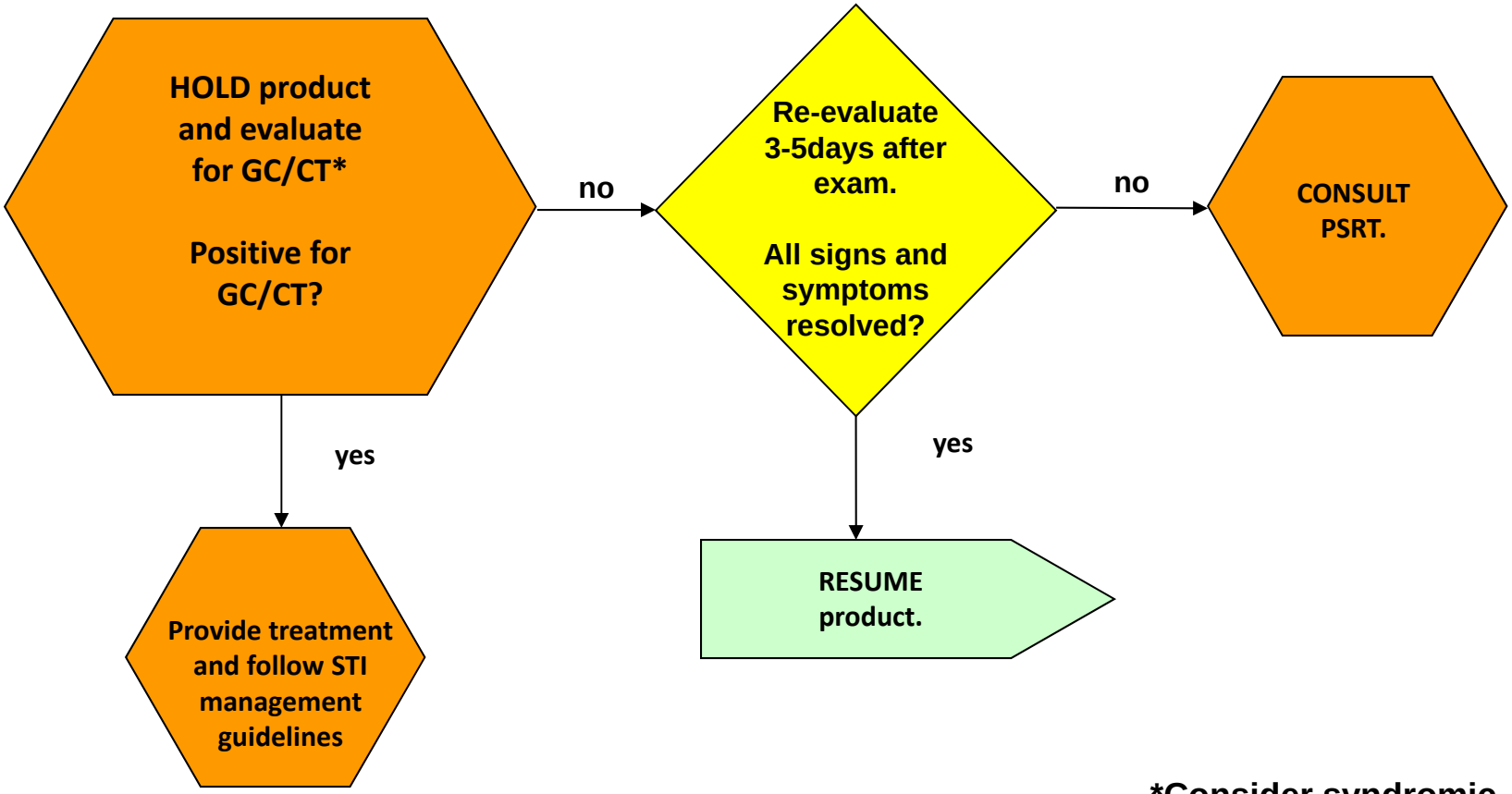
Protocol Reference: Section 9.6

Product Use Management: Unexpected genital bleeding



Protocol Reference: Section 9.6

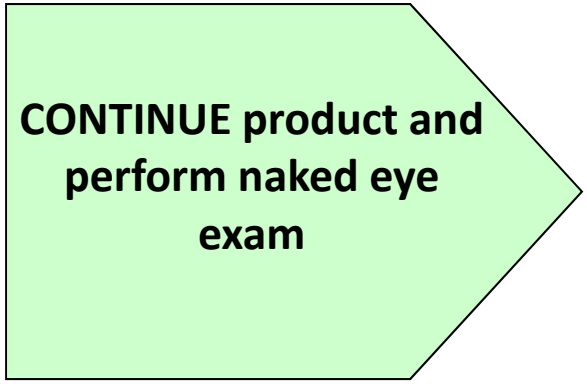
Product Use Management: Cervicitis (including findings on exam)



***Consider syndromic management pending results of testing and per clinician discretion.**

Protocol Reference: Section 9.6

Product Use Management: Genital petechia(e), genital ecchymosis



Protocol Reference: Section 9.6

Section 8. Adverse Event Reporting and Safety Monitoring

Table of Contents

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN 023/IPM 030. Please also refer to Section 8 of the protocol and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table)
- Addendum 1-DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT)
- Manual for Expedited Reporting of Adverse Events to DAIDS
- DAERS Reference Guide for Site Reporters and Study Physicians
- Investigator's Brochure for Dapivirine Vaginal Ring

Note: Both MTN and ATN sites will use the above DAIDS tools and the DAERS reporting system for AEs/SAEs/EAEs.

8.1 Definitions and General Reporting Guidance

8.1.1 Adverse Event (AE)

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines an 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 023/IPM 030, the same definition is applied to both study groups, beginning at the time of random assignment through when she terminates from the study. Study staff must document in source documents and case report forms all AEs reported by or observed in study participants, beginning at the time of random assignment and throughout the period of study implementation, regardless of severity and presumed relationship to study product.

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. Pre-existing conditions must be graded and are assigned severity grades just as AEs. If a pre-existing condition worsens (increases in severity or frequency) after randomization, the worsened condition is considered an AE and is reportable on the AE Log CRF. If a pre-existing condition resolves after randomization, but then recurs at a later date, the recurrence is considered an AE.

8.1.2 Reporting Adverse Events

Per Section 8.3 of the MTN 023/IPM 030 protocol, study staff will report on the AE Log CRF all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. Due to some of the clinical procedures, study participants may experience some expected AEs. These may include bruising from a blood draw or small amount of vaginal bleeding from pelvic examination, for example. Expected AEs must also be captured on the AE Log CRF.

Each site's SOP for source documentation should define the extent to which the AE Log CRF will be used as the source document for these data elements.

Documentation of site-specific delegation of duties should designate study staff authorized by the IoR to complete the AE Log CRF. Regardless of who initially completes these forms, a clinician listed on the site's FDA Form 1572 should review each AE Log CRF to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

If, at any time, site staff has questions about participant safety or reporting clinical events, they should send an email to the MTN 023/IPM 030 Safety Physicians at mtn023safetymd@mtnstopshiv.org

8.1.3 Serious Adverse Events (SAEs)

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

1. Results in death,
2. 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. When determining whether a grade 4 event meets the ICH definition of "life threatening", consider the event in the context of any related symptoms the participant may have experienced.
3. Requires inpatient hospitalization or prolongation of 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) or admission for diagnosis or therapy of a condition that existed before randomization AND has not increased in severity or frequency since baseline.
4. Results in persistent or significant disability/incapacity,
5. Is a congenital anomaly/birth defect,

6. Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition 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 and that "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 in the definition above" should also be considered serious. SAEs are a subset of all AEs. For each AE identified, an authorized study clinician must determine whether the AE meets the definition of SAE. The AE Log CRF includes an item to record this information.

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.

8.1.4 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 023/IPM 030, 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. The definition of a "reporting day" is as follows:

- Monday through Friday
- Saturday and Sunday are not considered reporting days.
- Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday
- A reporting day starts at 12:00 AM (midnight) and ends at 8:59 PM local time (in the site's time zone).
- The day site personnel become aware that an AE has met the definition of an EAE shall count as day 1 if that day occurs on a reporting day (i.e., Monday through Friday). This is true, regardless of the time of the day site personnel become aware of the EAE. If the day site personnel become aware of the EAE is a non-reporting day (i.e., Saturday or Sunday), then the next reporting day shall count as day 1.

For questions or other communications regarding submission of EAE Reports, see below.

Website:	http://rsc.tech-res.com
Office Phone:	301-897-1709 or toll free in the US: 800-537-9979
Office Fax:	301-897-1710 or toll free in the US: 800-275-7619
Office Email:	DAIDSRSCSafetyOffice@tech-res.com
Office Hours:	Monday through Friday, 8:30 AM to 5:00 PM ET

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., AE verbatim term, onset date, severity grade, relationship to study product, and status/outcome) 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).

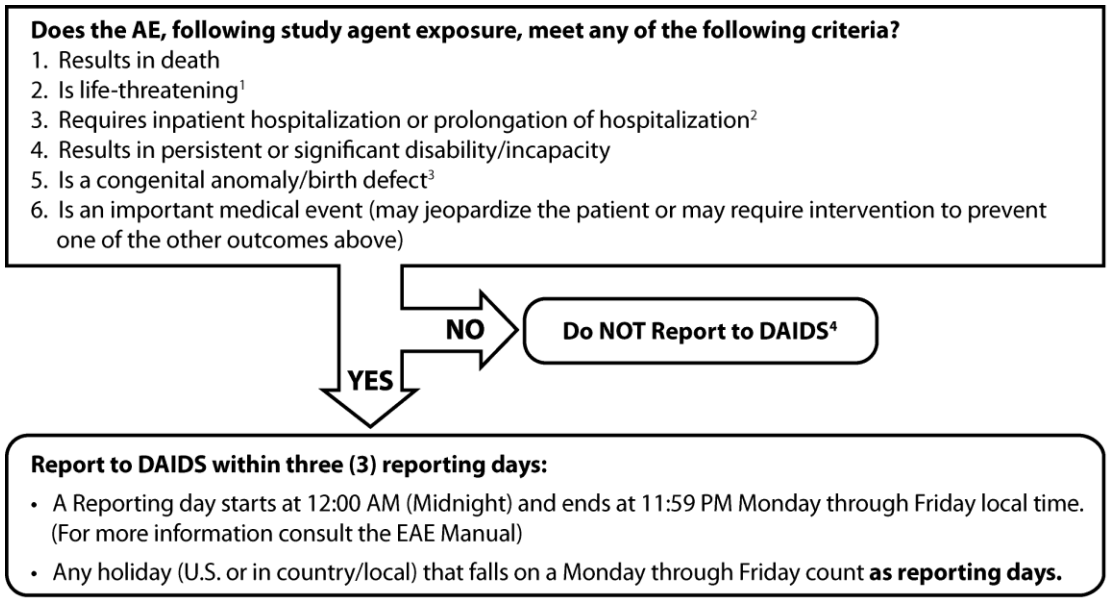
In the event that DAERS cannot be accessed (e.g., due to poor internet connectivity), paper-based EAE reporting should be used, per instructions provided in the Manual for Expedited Reporting of Adverse Events to DAIDS. Completed paper EAE Forms may be faxed or digitally scanned and emailed to the DAIDS RSC via email. The EAE Form and form completion instructions are available on the DAIDS RSC web site (http://rsc.tech-res.com). Contact details for submission of EAE Forms to the RSC are provided in the Manual for Expedited Reporting of Adverse Events to DAIDS.

For each EAE reported to DAIDS, sites are required to submit an updated report to DAIDS as soon as significant additional information becomes available. Note that updates made to EAE reports should also be made to the corresponding AE Log CRF documenting the AE, as applicable. Similarly, any updates made to an AE Log CRF should also be made to the corresponding EAE report, as applicable. EAE follow-up information should be reported to the DAIDS RSC, using the update function in DAERS, under the following circumstances:

- Requests from DAIDS for additional information
- A change in the relationship between the AE and study product by the study physician
- Additional significant information that becomes available for a previously reported AE (this is particularly important for new information addressing cause of death if the initial assignment was “pending”)
- Any change in the assessment of the severity grade of the AE
- An update including the final or stable outcome, unless the initial SAE submitted had a final or stable outcome noted already.
- Results of re-challenge with the study product, if performed

Note: A new EAE form does not need to be submitted for any change in the assessment of the severity grade or the relationship between the AE and the study product. However, the increase in severity must be reported as a new AE to the SDMC (as described previously).

Figure 8-1
Expedited Adverse Event Reporting Requirements for MTN 023/IPM 030



Contact Information for the DAIDS Safety Office:
Website: http://rcc.tech-res.com • **E-mail:** RCCSafetyOffice@tech-res.com
Office Phone: 1-800-537-9979 (U.S. only) or +1-301-897-1709 • **Fax:** 1-800-275-7619 (U.S. only) or +1-301-897-1710
(Office Phone and Fax are accessible 24 hours per day)
Mailing Address: DAIDS Safety Office 6500 Rock Spring Drive, Suite 650, Bethesda, MD 20817

[1] "Life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does NOT refer to an event that hypothetically might have caused death if it were more severe.

[2] Per the ICH SAE definition, hospitalization is NOT an adverse event (AE), but is an outcome of the event. **DO NOT REPORT**: Any admission unrelated to an AE (e.g., for standard labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep); protocol-specified admission (e.g., for a procedure required by protocol); admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) **and** has not increased in severity or frequency as judged by the clinical investigator. (**NOTE**: A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and **would be** reportable.)

[3] Clinically insignificant physical findings at birth, including those regarded as normal variants, do NOT meet reporting criteria. If a clinically significant anomaly is reported, all findings (including those of no individual significance) should be included in the same report. For example, do NOT report an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant. But if either finding occurred with a major cardiac defect, report all findings in the SAE Report.

[4] Please ensure that any other protocol-specific reporting requirements are met.

8.2 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in MTN 023/IPM 030. 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 abnormal cervical bleeding as a result of the speculum exam, then "cervical bleeding due to speculum exam" should be submitted as an AE. "Cervical bleeding" maps to "Reproductive system and breast disorders" System/Organ Class (SOC) whereas "Cervical bleeding due to speculum" 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. 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 **<u>not</u> due to the act** of study ring insertion or removal, do not include mention of the ring in item 1.

- 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.

It is fine to include text in the "Comments" field explaining why the AE has been judged "related", but such text is not required.

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.

8.2.1 Reporting Genital, Genitourinary, 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 (see below). The verbatim term from the FGGT should be used to distinguish if vaginal discharge was clinician observed versus participant reported.

PARAMETER	Grade 0 NORMAL	Grade 1 MILD	Grade 2 MODERATE
Vaginal discharge by participant report **	Participant's usual amount of discharge, regardless of color or quantity	Mild-moderate increase in amount above participant baseline - no sanitary protection required	Profuse increase in discharge requiring pad use or other hygienic intervention
Vaginal discharge as observed by clinician ** (red or brown discharge should be reported under bleeding, not discharge)	Slight amount of discharge, any color	Mild-moderate increase in amount	Significant increase in amount with pooling in vagina on examination

** 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 and is not pictured here.) If they are the same grade, report 'vaginal discharge by participant report' as the AE term.

Genital bleeding: Genital bleeding other than menstrual bleeding, often referred to as intermenstrual bleeding (IMB) is a common occurrence among reproductive age women, and often is of physiologic or benign etiology. Some women normally experience mid-cycle bleeding or pre-menstrual bleeding. IMB is common in hormonal contraceptive users, particularly new and/or inconsistent users. IMB also may be associated with traumatic injury to the cervicovaginal epithelium (e.g., due to speculum insertion, product applicator insertion, sexual activity).

During follow-up, the following types of genital bleeding are reportable as adverse events on an AE Log CRF:

- each new instance of heavy or prolonged menstrual bleeding or intermittent bleeding (as compared to the participant's baseline bleeding pattern), regardless as to whether it may be attributed to the initiation of new contraception
- postcoital bleeding (bleeding associated with sexual intercourse) should be reported if not present at baseline

Note that the above conditions are consistent with the parameters set out in the FGGT under the heading 'abnormal uterine bleeding unrelated to pregnancy'. Heavy, prolonged or intermittent bleeding episodes during follow-up that are consistent with a participant's baseline bleeding pattern are considered expected and are not reportable as AEs. Note that shorter than baseline menses is not included in the FGGT, and should not be considered an adverse event.

Vaginal and/or cervical bleeding associated with study procedures: Vaginal and/or cervical 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 adverse event. 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 'post procedural bleeding'. The severity of the AE should be graded per the vaginal abrasion 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, and there is bleeding attributable to the laceration, 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 CRF, and may also be noted in the comments section of the Adverse Experience Log CRF. The term metrorrhagia should not be used to document the AE.

If a newly-identified bleeding episode is determined to be different from a participant's baseline bleeding pattern (i.e., longer, heavier, more frequent), and not associated with an observed abnormal pelvic exam finding, record the episode on an Adverse Experience Log (AE-1) CRF. One of four terms to describe the bleeding event should be used:

- menorrhagia
- metrorrhagia [Note: 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.
- menometrorraghia
- post coital bleeding

Note that a shorter than baseline menses is not considered an AE per the FGGT, though infrequent genital bleeding may be an AE. Grade the episode per the applicable row of the FGGT provided below. 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.

PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ABNORMAL UTERINE BLEEDING UNRELATED TO PREGNANCY					
Menorrhagia [2] (prolonged and/or heavy menstrual bleeding)	Participant report of normal bleeding relative to her baseline	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Metrorrhagia [2] (intermenstrual or frequent bleeding)	None or any expected nonmenstrual bleeding	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Postcoital bleeding	None	Occasional (< 25% of coital acts) OR Increase from usual with no or minimal interference with usual social functioning (including sexual functioning)	Frequent (25-75% of coital acts) OR Increase from usual with moderate interference with usual social functioning (including sexual)	Consistent (> 75% of coital acts) OR Incapacitating or severe interference with usual social functioning (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock

Recurrent bleeding AEs in follow-up: Once a bleeding AE has been reported, each subsequent bleeding episode should be assessed to determine whether the episode is consistent with previously reported bleeding AEs, or if it is the first of its kind. Clinician discretion should be used to determine if a new AE needs to be documented or if a previously reported AE is ongoing.

- As needed, update the AE Log CRF to be 'continuing'. The dates of each irregular bleeding episode do not need to be recorded on the AE Log CRF, but should be captured in source documentation.
- If reviewing files in retrospect, mark for deletion any AE Log CRFs completed for bleeding episodes that can be subsumed under the AE that was initially reported for the event. When/if any AEs are deleted, clearly document the rationale in the relevant source documents.
- If applicable, review the CM-1 CRF "Taken for a reported AE?" and "AE Log page" to ensure that no deleted AEs are reflected on the form.
- If a participant has an ongoing (recurrent) bleeding adverse event, a pelvic exam is not required each time the participant reports the same ongoing bleeding, provided that the clinician assesses the bleeding to be consistent with the bleeding captured by the ongoing adverse event. If the AE increases in severity, a new AE Log CRF should be completed to document this change in severity.

8.2.2 STIs/RTIs

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 Amsels 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 023/IPM 030, 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: The criterion for diagnosing genital herpes per the FGGT is below. 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.

PARAMETER	Grade 0 NORMAL	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	Grade 4 POTENTIALLY LIFE-THREATENING
Genital herpes	No lesions	Characteristic ulcerative or vesicular lesions confirmed by culture, PCR, Tzanck prep or other diagnostic test of lesion or previous type-specific serology, covering < 25% of vulva, vagina, or cervix	Same criteria as mild but covering 25-50% of vulvar, vaginal, or cervical surface	Same criteria as mild but covering > 50% of vulvar, vaginal, or cervical surface	Symptoms of significant systemic involvement, e.g., encephalitis, hepatitis

- 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).
- 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

8.2.3 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”).

If the pain is assessed as reproductive in nature and a specific anatomic location is known, the term reported on the AE Log CRF should be described as such (e.g., “uterine adnexal pain”, “ovarian pain”).

If the pain cannot be localized to a specific organ, it should be described on the AE Log CRF using terms that identify a reproductive or genitourinary anatomical location (e.g., “pelvic pain”, “urinary tract pain”).

8.2.4 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.

8.3 Adverse Event Severity Grading

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in MTN 023/IPM 030 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 023/IPM 030 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:

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

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 treatment, it must automatically be graded at Grade 2 or higher.
- Urinary tract infection (UTI), which is expected to be diagnosed on the basis of symptoms should be graded according to the "infection (other than HIV infection)" row of the Toxicity Table. If culture and/or microscopy are done per site standard of care, Grade 1 and Grade 2 UTI can be graded per the UTI row of the FGGT.

PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Intraepithelial Neoplasia by biopsy (VIN, CIN, VAIN)	None	Intraepithelial Neoplasia 1 (IN1)	Intraepithelial Neoplasia 2 (IN2)	Carcinoma in situ (CIS)	Invasive carcinoma
Pap (use this category only if treatment performed without diagnostic testing, otherwise use biopsy category above)	nl PAP	ASCUS or LSIL	HSIL	Carcinoma in situ or Carcinoma	NA

8.4 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.

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

Study staff should give a reason for their determination of the relationship of the AE to the study product. When an AE is assessed as "not related" to the study products, an alternative etiology, diagnosis or explanation should be provided in the "Comments" line on 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'.

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

All AEs identified in MTN 023/IPM 030 must be followed clinically until they resolve (return to baseline) or stabilize (persist at a certain severity grade (above baseline) for two consecutive monthly evaluations.

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 two consecutive monthly evaluations. 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." 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.

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

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. The IoR or designee must establish a clinically appropriate follow-up plan for the AE.

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

At a minimum, the above listed AEs 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. 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 Protocol Safety

Review Team (PSRT) (see Appendix 8-1) at the time of reassessment. The MTN 023/IPM 030 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.

8.6.1 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.

Regular occurrences of the same adverse event that are expected in follow-up are not typically considered separate adverse events.

8.7 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. There is no CRF for the reporting of social harms. 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. 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, and with community representatives, 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 023/IPM 030, if required per IRB/EC guidelines.
- Consult the Protocol Safety Review Team (PSRT) for further input and guidance as needed.

8.8 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 Leadership 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.

8.9 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN 023/IPM 030 protocol for a complete description of the participant safety monitoring procedures in place for MTN 023/IPM 030. Section 13 of this manual is a reference for a description of the reports prepared by the MTN SDMC in support of MTN 023/IPM 030 safety monitoring procedures.

Participant safety is of the utmost importance in MTN 023/IPM 030. 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 via DAERS to the RSC, such 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, DAIDS PSB Medical Officer, and NICHD Medical Officer, will review all EAE Forms received for MTN 023/IPM 030 and follow up on these reports with site staff, the MTN 023/IPM 030 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 periodically review study data with a focus on performance indicators such as participant accrual and retention, protocol adherence, and data quality. 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.

Appendix 8-1: MTN 023/IPM 030 Protocol Safety Review Team

Roles and Responsibilities of the PSRT

The roles and responsibilities of the MTN 023/IPM 030 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 and/or re-joining of study participant's which previously withdrew consent (Protocol Section 9.8)

PSRT Composition

The following individuals comprise the MTN 023/IPM 030 PSRT:

- Kathleen Squires, Protocol Chair
- Katherine Bunge, Protocol Co-Chair
- Devika Singh, MTN Protocol Safety Physician
- Ken Ho, MTN Protocol Safety Physician
- Lydia Soto-Torres, DAIDS Medical Officer
- Bill Kapogiannis, NICHD Medical Officer
- Annalene Nel, IPM Medical Officer
- 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 NICHD Medical Officer (or designee) the Protocol Chair or Protocol Co-Chair and 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 (mtn023psrt@mtnstopshiv.org) will be used to facilitate communication with the PSRT.

Site consultation with the PSRT will be facilitated using the MTN 023/IPM 030 PSRT Query Form, which is available in the Study Implementation Materials section of the MTN 023/IPM 030 web page. Site staff will email completed query forms to the Protocol Safety Physicians (mtn023safetymd@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 023/IPM 030 Emergency Phone Contact form (available in the Study Implementation Materials section of the MTN 023/IPM 030 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. Counseling Procedures

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This section contains guidance on the following types of counseling provided in MTN-023/IPM 030: HIV pre/post-test counseling, HIV/STI risk reduction and male condom counseling, contraceptive counseling, study product adherence counseling, and protocol adherence counseling.

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 to allow for appropriate tailoring and targeting to an individual participant's needs at a given point in time. 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. Sites are encouraged to use flags or alert notes in participant study charts to highlight issues requiring follow-up at subsequent visits.

All counseling and referrals should be documented in participant study records per site SOPs. Proper documentation may be achieved through the use of counseling worksheets, and/or chart notes.

Sample counseling worksheets are available on the MTN-023/IPM 030 website for HIV testing, risk reduction, study product adherence and protocol adherence counseling.

9.1. HIV Pre and Post Test Counseling

HIV testing is required at Screening, Enrollment, 12-Week, and 24-Week Final Clinic/Early Termination Visit. HIV testing is performed when clinically indicated at all other visits. HIV pre-test and post-test counseling are required at visits when HIV testing is required or when performed if clinically indicated. Referrals should be provided when indicated. Sites are required to develop and follow SOPs for HIV testing and counseling considerations.

All HIV counseling should be provided in accordance with local counseling standards and study staff who provide HIV counseling should be trained to do so per local practice standards. Counseling staff should also be trained on study-specific HIV testing methods and interpretation of test results per the testing algorithm in protocol Appendix II. Further information on interpretation of screening and follow-up test results is provided in Table 9-1 below. This informational resource should be referenced as needed when providing pre-test and post-counseling.

Client-centered approaches should be used to assess participant knowledge of relevant information, dispel misconceptions, ensure participant readiness for HIV testing, and ensure participant understanding of test results. Information should be provided in a manner that is respectful and interactive. Participants should be informed of when their

test results will be available. 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.

Table 9-1
Interpretation of HIV Test Results Per Protocol Appendix II

Test Result	Interpretation
HIV Immunoassay negative	HIV-uninfected; test results indicate that you are not infected with HIV.
HIV 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.
Sample 1 Confirmatory Test positive	If Screening or Enrollment Visit: HIV-infected; test results indicate that you are infected with HIV. If Final Visit: HIV-infected; test results indicate that you are infected with HIV; however, additional testing is needed for study purposes.
Sample 1 Confirmatory Test negative or indeterminate	HIV status not clear; additional testing is needed to determine your status.
Sample 2 Confirmatory Test positive	HIV-infected. Test results have confirmed that you are HIV infected.
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.

A sample HIV pre- and post-test counseling worksheet is available for use on the MTN-023/IPM 030 webpage under Study Implementation Materials. This worksheet provides a guide to the minimum requirements for HIV testing and counseling sessions; this worksheet may be tailored for use at each study site.

9.2. HIV/STI Risk Reduction and Male Condom Counseling

Risk reduction counseling is required at every scheduled in-clinic visit. As part of risk reduction counseling, male condoms should be offered to all study participants, as needed. Male condom counseling is required at screening and when clinically indicated at all other visits and should include skills building to ensure participant understanding of correct condom use.

Participant-centered approaches should be used when assessing participant risk for HIV/STI 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 reported risk factors and barriers.

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 further risk reduction. For participants whose risk reduction barriers are significant, risk reduction plans may need to be incremental. For participants whose risk reduction strengths and 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, prevention strategies and risk factors previously identified should be used to lead to a risk reduction plan. These plans will be reviewed at subsequent sessions and discussed with the participant to determine:

- What was her experience since her last session?

- How did the strategies in the risk reduction plan from last visit work or not work for her?

Counselors use this opportunity to reinforce effort, not outcomes, and to frame the current discussion as an opportunity to continue exploring protecting one's sexual health.

Risk reduction plans identified and agreed upon with the participant at the current session should then build on experience since the last session:

- Successful strategies should be continued;
- Additional strategies may be identified to achieve further risk reduction;
- Alternative strategies may be identified if strategies tried since the last session was not successful.

Risk reduction counseling sessions should also offer skills-building to the participant when indicated, e.g., 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.

A sample HIV/STI Risk Reduction Counseling worksheet which may be tailored for use is available on the MTN-023/IPM 030 Study Implementation Materials webpage under Counseling Tools/Worksheets.

9.3. Contraceptive Counseling

Contraception counseling is required at all in-clinic study visits. All contraception counseling should be provided in accordance with local counseling standards.

At screening and enrollment visits, contraception counseling should be provided in the context of assessing study eligibility criteria. Per MTN-023/IPM 030 inclusion criteria, a potential participant must agree to use an effective method of contraception for at least 30 days prior to enrollment and throughout the duration of her participation. Counseling provided at these visits should explain which methods are acceptable for study purposes and emphasize that if she cannot commit to using of these methods for at least 25 weeks of follow-up, she should not enroll in the study.

Effective methods include:

- Hormonal methods, except for the contraceptive ring
- IUD
- Sterilization (of participant, as defined in site SOPs)

During follow-up visits, client-centered counseling should continue. 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 but should always provide clear method use instructions and always reinforce key adherence messages. For participants with issues or problems with their current method, counseling sessions during follow-up may require more time. In some cases, only counseling and reassurance may be required to address the issues or problems. In other cases, consideration of method switching may be indicated.

Some participants may wish to discontinue use of a contraceptive method during follow-up. In these cases, counselors should explore the participant's reasons for this and determine if other options would be acceptable to her. If no other options are acceptable, the participant may remain in the study, and continue using study product, even if she

discontinues contraceptive use. However, the possibility of resuming contraceptive use should be re-visited at each subsequent visit to determine whether the participant's circumstances may have changed.

Study staff who provide contraception counseling should be trained to do so per local practice standards and should also be trained on MTN-023-IPM 030 protocol specifications related to contraception. Contraception may be provided on site; however, sites may opt to refer participants to non-study providers for contraception. All sites are strongly encouraged to obtain credible medical records as part of their verification procedures for participant reported contraceptive methods.

All contraception counseling should guide and support each participant in making the best contraceptive method choice for her and in maintaining adherence to an effective method. When providing information on various contraceptive methods to study participants, standard information should include how each method is taken or administered, mechanism of action, and level of effectiveness.

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. Detailed counselors notes or counseling worksheets will be required to document counseling sessions. All sites are strongly encouraged to use flags or flyers in participant study charts to highlight contraception issues requiring follow-up at subsequent visits.

9.4. Ring Use Adherence Counseling

Participants will be provided ring use adherence counseling for the first time at the Enrollment visit. Ring use adherence counseling will also be provided at the 4-Week, 8-Week, 12-Week, 16-Week and 20-Week visits and interim visits if a new ring is provided. Prior to receiving this counseling at monthly visits, participants will receive their dispensation of the vaginal ring and insert the vaginal ring at the study clinic. Study participants will be given detailed instructions in the clinic on proper vaginal ring insertion and removal procedures.

In addition to verbal instructions, a copy of the illustrated instructions should be provided to each participant. Vaginal ring insertion instructions are available on the MTN-023/IPM 030 webpage under Study Implementation Materials. Other visual aids, such as sample vaginal rings and pelvic models should be used as needed when providing instructions to help ensure participant understanding of proper product use.

Adequate time should be taken to thoroughly explain the product use instructions and answer any questions the participant may have. Any questions or concerns raised by the participant should be documented in her study records so this information is easily available for reference at follow-up visits. Site staff should help ensure participant understanding, comfort, and confidence with vaginal ring use from the very beginning of study participation. In particular, any questions or concerns that arise in the context of ring insertion can be addressed by study staff before the participant leaves the clinic.

A Ring Use Adherence Key Messages worksheet is available for use on the MTN-023/IPM 030 Study Implementation Materials webpage. This worksheet provides a guide to the minimum requirements for product use counseling sessions; this worksheet may be tailored for use. Key messages outlined on the Vaginal Ring Insertion Instructions are further detailed on the Ring Use Adherence Key Messages worksheet should be discussed with the participant. As each point is addressed, site staff should mark each message on the worksheet. Discussion points, participant questions should also be noted on page 3 of the worksheet and/or in chart notes and used for future counseling sessions.

9.4.1. 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 insert 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.

If the participant has difficulty inserting the ring herself, the study clinician can assist the participant with insertion. If assistance is required, study clinicians should take time, talk through each step, and whenever possible, demonstrate the insertion steps by guiding the participant through the process.

At each visit when a ring is dispensed, staff should also confirm that the participant is able to remove and reinsert the vaginal ring. This is to encourage comfort with removal procedures, and additional practice in case the vaginal ring is removed or accidentally falls out prior to her next clinic visit.

Participant instructions for ring removal (provided verbally to participants):

- Before removing the ring, wash and dry your hands.
- Choose a comfortable position (can reference ring insertion instructions for illustrations of different positions).
- Put a finger into your vagina and hook it through the ring.
- Gently pull down and forward to remove the ring.
- 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, rinse the ring and place the used ring in the bag provided by clinic staff or other suitable container if the bag is not available. Store the ring a safe and private area out of reach of children or other occupants of the home.
- Wash your hands.
- Bring used ring with you to the clinic during your next study visit.

After the vaginal ring 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 on the ring use adherence worksheet and/or in chart notes so the information is easily available for reference at study follow-up visits. Clinicians will check for proper ring placement. Instructions to clinicians can be found in SSP Section 7.2.

9.5. Follow-up Study Product Use Adherence Counseling

Study product adherence counseling is required at the 4-Week, 8-Week, and 12-Week, 16-Week, and 20-Week visits (unless the participant is on a product hold or permanent discontinuation) or at interim visits where a new ring is dispensed. At these follow-up visits, adherence counseling should focus on exploring participant's experiences with ring use, including what makes it easier or harder for her to use the vaginal ring as recommended. Discussion of experiences is framed as an opportunity to gain an understanding from participants of how well this ring may "fit" into the daily and sexual lives of women using it. With that, it is important to gain a sense of what seems to help it be a good "fit" and what seems to make it a poor "fit." Additionally, as the ability to come to the clinic for scheduled visits is directly related to product use, these counseling sessions should also include a check-in about facilitating attendance to study visits.

Staff can review the vaginal ring insertion instructions and important information as needed during follow-up visits. As a participant becomes more experienced with ring use, time spent on this information can be tailored to suit participant needs.

During follow-up, adherence counseling should occur after completion of ACASI and administration of the Ring Adherence and Vaginal Practices CRFs.

Note: In order to promote an open and neutral environment, it is recommended that staff conducting the adherence counseling be different than those who conduct the adherence assessment questionnaires (Ring Adherence CRF).

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 and not receive product.

Further guidance for the adherence counseling session 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 self-reported adherence since her last counseling session. Note how often the participant reports having removed or expelled the study ring. This will help guide the adherence counseling that she will receive.

When providing adherence counseling:

- Ask the participant what her experience has been using the ring. If it was bad, ask why and when. If it was good, ask how and why.
- Review and discuss with the participant any current barriers/challenges or concerns related to ring use.
- When needed, review ring use insertion instructions 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.
- 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, and work with the participant in a client-centered manner to identify operational strategies to assist her in inserting the ring, and removing the ring if necessary. She should be encouraged to ask questions and raise issues or problems at any time. Each counseling session should be fully documented in chart notes as needed.

9.6. 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 vaginal ring.

Protocol adherence counseling is required at Enrollment, 2-Week, 4-Week, 8-Week, 16-Week, and 20-Week visits. Per protocol section 6.7, participants should be counseled to avoid the following practices:

- Refrain from using non-study provided or approved vaginal products or objects during study participation
- Refrain from using tampons, sex toys, and engaging in vaginal intercourse 72 hours (3 days) prior to each monthly scheduled visit.

Should the participant report that she has engaged in any of the above, this should be documented on the Vaginal Practices CRF.

Participants should also be counseled to abstain from using the following products:

- Spermicides
- Diaphragms
- Contraceptive vaginal rings
- Menstrual cups
- Cervical caps
- Vaginal douches
- Lubricants

If a participant reports a prohibited practice as listed above and in protocol section 6.7, the participant should be counseled regarding the use of alternative methods. Counseling and discussion of any issues related to protocol adherence may be documented on the Protocol Adherence Worksheet, located on the MTN-023/IPM 030 webpage under Study Implementation Materials or other site-specific worksheet.

Section 10. Laboratory Considerations

Table of Contents

10.1. 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/

Laboratory procedures may be performed in the study site clinics or laboratories, approved commercial laboratories and in the MTN Laboratory Center (MTN LC), including the MTN Pharmacology Core at Johns Hopkins University Clinical Pharmacology Analytical Laboratory (JHU CPAL). Table 10-1 is an overview of the specimens that are collected. Table 10-2 highlights storage and shipment requirements of specimens (including derivatives of initial specimens) that are stored. Table 10-3 lists the tests to be performed at each visit. Regardless of whether tests are performed in clinic or laboratory settings, study staff that performs the tests must be trained in proper, associated QC procedures prior to performing the tests for study purposes; training documentation should be available for inspection at any time.

Sites are responsible to ensure that specimen volumes do not exceed what is described in the informed consent process. The MTN LC may request details of collection containers and volumes for this purpose.

Note: Additional blood may be collected for any clinically indicated testing.

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.

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.

Table 10-1
Overview of Laboratory Testing Locations, Specimen Collection, and Methods for MTN-023/IPM 030

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	Quidel Quick Vue, Fisher HealthCare Sure-Vue Urine hCG, Cardinal Health hcG Cassette Rapid Test, or OSOM Card Pregnancy Test
Urine Culture or Dipstick[1]	Local lab	Urine	Plastic screw top cup	Local methodology
Urine or vaginal NAAT for GC/CT[2]	Local lab	Urine or vaginal swab	Kit specific Transport tube	BD Probetec or Gen-Probe Aptima
CBC with Platelet	Local Lab	Whole Blood	EDTA 4-mL tube	Local methodology
Chemistries (AST, ALT, Creatinine)	Local Lab	Serum or Heparinized plasma	Plain or serum separator 4-mL	Local methodology
HIV antibody screen and confirmatory test	Clinic/Local Lab	Plasma, serum, or whole blood	EDTA or plain tube 4-mL or greater	FDA approved tests
Blood PK (Dapivirine)	JHU CPAL	Plasma	EDTA 5-mL or greater tube	JHU CPAL collection procedure
Syphilis Serology	Local Lab	Serum or Plasma	EDTA tube, plain or serum separator, 4-mL or greater	Local methodology
Plasma Archive or HIV Confirmation & Resistance Testing	Clinic/Local Lab/MTN Virology LC	Plasma	EDTA 4-mL or greater tube	MTN LC procedure
Cervicovaginal Lavage (CVL) for biomarkers & Cell Pellet	MTN LC	Fluid & pellet recovered from CVL	15-mL Conical Tube	MTN LC Procedure
Vaginal Swab(s) for biomarkers	MTN LC	Vaginal Swab	2.0-mL cryovial with 400-uL PBS	MTN LC procedure
Vaginal Swab for PK	JHU CPAL	Swab	2.0-mL Cryovial	JHU CPAL collection procedure
Trichomonas Rapid Test	Local lab or in clinic	Vaginal swab (supplied with kit)	OSOM: Sterile tube with no additives Aptima: kit swab and transport tube	OSOM kit or Aptima[2]
Vaginal pH	In clinic	Vaginal swab	N/A	S/P pH Indicator Strips
Quantitative Vaginal Culture	MTN LC	Vaginal swab	BD Port-a-Cul transport tubes	MTN LC procedure
Vaginal smear for Gram stain	MTN LC	Vaginal Swab	Slides	MTN LC procedure
Used Vaginal Ring (VR) for PK residual assessment	Parexel, South Africa	Used VR	Biohazard labeled amber bag	Parexel, South Africa lab procedure
Vaginal saline wet preparation (for BV and/or KOH wet mount)[1]	In clinic	Vaginal swab	tube with 6 drops of saline	MTN LC procedure
Herpes Lesion Testing[1]	Local lab	Local method	Local method	Local methodology

1. Perform only if clinically indicated per local SOP.
2. If Trichomonas is being tested with Gen-Probe Aptima, GC/CT Gen-Probe Aptima NAAT can also be performed using the same vaginal swab.

Table 10-2: Overview of Specimens for Storage and Shipment

Stored Specimens	Storage Tube Type or Size (recommended)	Processing	Ship to:	Shipping schedule
Plasma for archive or Confirmation of HIV Resistance Testing	2-mL cryovial	Pipet two 1-mL aliquots of plasma into tubes. Freeze at ≤ -70°C within 24 hours after blood draw, if blood refrigerated, or within 4 hours if blood left at room temp	MTN LC	Store frozen at site until notified by MTN LC
Plasma for blood PK (Dapivirine)	2-mL cryovial	Pipet two ≥ 1-mL aliquots of plasma into tubes. Freeze at ≤ -70°C within 8 hours after collection	JHU CPAL	Store frozen at site until conclusion of study
Cervicovaginal Lavage (CVL) supernatant: Biomarker	2-mL cryovial	Refrigerate CVL until processing. Aliquot 1-mL supernatant into one tube for CVL biomarkers and ≥ 5 tubes labeled 'extra CVL'. Freeze at ≤ -70°C within 8 hours of collection.	MTN LC	Store frozen at site until notified by MTN LC
CVL Cell Pellet	2-mL cryovial	Refrigerate CVL until processing. Add 0.5-mL normal saline to cell pellet. Freeze at ≤ -70°C within 8 hours of collection	MTN LC	Store frozen at site until notified by MTN LC
Used Vaginal Ring for PK residual assessment	3"×5" amber Zippit pouch	Place VR in pouch	MTN LC	Room temp. storage at site until conclusion of study
Vaginal Swab(s) for biomarkers	2-mL cryovial	Keep refrigerated until frozen at ≤ -70°C within 8 hours of collection	MTN LC	Store frozen at site until notified by MTN LC
Vaginal Swab for PK	2-mL cryovial	May be kept on ice until frozen. Freeze at ≤ -70°C within 2 hours of collection	JHU CPAL	Store frozen at site until conclusion of study
Vaginal smear for Gram-stain	2 slides	Allow to air dry. Store at room temp,	MTN LC	Ship one slide with Port-a-cul to MTN LC. Store 2nd slide at site until conclusion of study
Vaginal Swabs for Quantitative Vaginal Culture	2 swabs in transport tube	Place swab in BD Max V or Port-a-Cul & break off shaft. Refrigerate until shipped.	MTN LC	Ship on ice packs to MTN LC for next day delivery. [1]

[1] If specimens are collected after the last FedEx pickup, store the Port-a-cul tube at 4°C and ship the following day. Check with your local FedEx office for last pickup times and the options for Saturday pickup or drop off locations.

Table 10-3: Overview of Laboratory Tests by Visit for MTN-023/ IPM 030

	SCR	ENR	2-Wk Visit	4-Wk Visit	8-Wk Visit	12-Wk Visit	16 Wk Visit	20 Wk Visit	24-Wk Final Clinic Visit/Early Termination Visit	1-Wk and 25- Wk Termination Phone Call
LABORATORY										
Urine hCG	X	X	X	X	X	X	X	X	X	
Urine or vaginal NAAT for GC/CT	X	*	*	*	*	*	*	*	X	
Dipstick UA and/or urine culture, per local standard of care	*	*	*	*	*	*	*	*	*	
Serum chemistries (4 mL) ♪	X	*	*	*	*	*	*	*	X	
CBC with platelets (4 mL) ♪	X	*	*	*	*	*	*	*	X	
HIV-1 serology (4 mL) ♪	X	X	*	*	*	X	*	*	X	
PK- Blood (Plasma) (5 mL) ♪			X	X	*	X	*	*	X	
PK-Vaginal fluid			X	X	*	X	*	*	X	
Syphilis serology (4 mL) ♪	X	*	*	*	*	*	*	*	*	
Plasma archive (4 mL) ♪		X	*+	*+	*+	*+	*+	*+	*+	
Gram stain		X		X		X			X	
Vaginal pH	*	X	*	X	*	X	*	*	X	
Vaginal swab for quantitative vaginal culture		X		X		X			X	
Vaginal swab for biomarkers		X		X		X			X	
CVL for biomarkers		X				X			X	
Vaginal swab for Rapid Trichomonas	X	*	*	*	*	*	*	*	X	
Vaginal swab for Trichomonas/GC/CT	X	*	*	*	*	*	*	*	X	
Saline wet mount for BV	*	*	*	*	*	*	*	*	*	
KOH wet mount for candidiasis	*	*	*	*	*	*	*	*	*	
Herpes lesion testing	*	*	*	*	*	*	*	*	*	
STUDY PRODUCT										
Collect study product			*	X	X	X	X	X	X	
Approximate Total volume of blood needed-may vary depending on local laboratory requirements.♪	16 mL	20 mL	21 mL	21 mL	16 mL	21mL	16mL	16mL	21 mL	

X = required, * = if indicated/needed, X~ = sites to reference SOPs, +=Plasma for confirmation of HIV viral load and resistance testing.

♪ Maximum volume needed for study requirement, if all specimens are collected including "if clinically indicated".

10.2. 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. The date the specimens are collected should also be included on the label. Use an indelible ink pen (e.g., Sharpie) if information is handwritten, such as the date.

Microscope slides used for evaluation of vaginal fluids also will be labeled with PTID labels provided by SCHARP. PTIDs are pre-printed on these labels; however, study staff must write the specimen collection date on each label. The visit code also may be written on the label.

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 10-4 for specimens that will be entered into LDMS and labeled with LDMS-generated labels.

10.3. 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.

In cases where additional specimens need to be recollected either due to a laboratory error (lost, broken tube, clerical, etc.) or clinic 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 compromised specimen integrity
- Any situation that may indicate a protocol deviation

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

10.4. Use of LDMS

The Laboratory Data and Management System (LDMS) is a program used for the storage and shipping of laboratory specimens. LDMS must be used at all sites to track the collection, storage, and shipment of the sample types described in Table 10-4. An LDMS tracking sheet listing the sample types in Table 10-4 is initiated by the clinical staff at time of sample collections and is transported with the primary samples to the LDMS laboratory. The LDMS laboratory logs the specimens into LDMS, which formats appropriate labels for sample derivatives. It is crucial to be aware of proper label formats to ensure that specimens are correctly labeled.

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).

Each site will be required to:

- Maintain the current version of LDMS
- Monitor updates relating to the use of LDMS
- Back up their LDMS data (frequency determined by site) locally
- Export their data to FSTRF at least on a weekly basis.

Exported data are used by the MTN Statistical Data Management Center (SDMC) to:

- Generate a monthly specimen repository report
- Reconcile data entered in LDMS with data entered on study case report forms (CRFs)
- Create 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 time frame 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 the 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.

Questions related to use of LDMS in MTN-023/IPM 030 may be directed to Lorna Rabe or LDMS Technical (User) Support. Usual business hours for LDMS User Support are 7:00 am - 6:00 pm (ET) from Monday through Friday. All other hours and weekends, an on-call LDMS User Support specialist will be available:

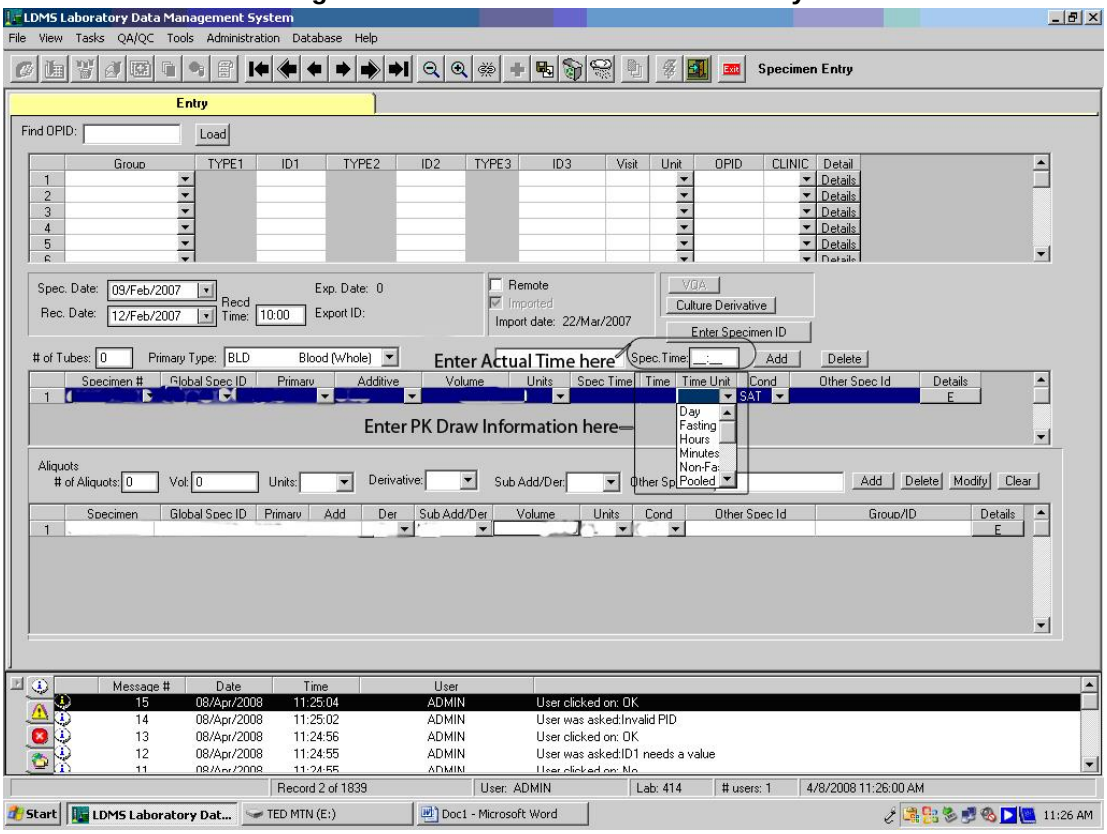
Email: ldmshelp@fstrf.org
Phone: +716-834-0900, ext 7311
Fax: +716-898-7711

Off-Hours Contact Information:
If you are locked out of your LDMS or are experiencing errors that prevent you from completing your LDMS lab work during off-hours, page LDMS User Support using the LDMS Web Pager utility. Alternatively, you may e-mail the paging system directly: ldmspager1@fstrf.org. Please allow at least 15 minutes to get a response before sending another e-mail to the paging system.

10.4.1. Logging in PK Samples:

- Enter the actual time in the Specimen Time area (See Figure 10-1).
- Enter the PK time point information in Time and Time Unit area (See Figure 10-1).

Figure 10-1: LDMS Screen for Time Entry



10.4.2. Entering weight measurements of vaginal swabs for PK in LDMS: For UAB, Pittsburgh, and Fenway sites only

The volume field in LDMS can be 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 figures 10-2 and 10-3.

- In the primary sample field (section A), enter the sample(s) information. Make sure to place the correct draw 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 10-2).
- To enter the actual weights, make an aliquot as in Section B for the primary sample. In the "# of Aliquots" field, enter 1. For "Volume", enter the net-weight and change the "Units" to MG (milligrams). Enter the correct derivative and Sub-Add/Der, and click the add button (See Figure 10-2).

Example: Pre-weight Swab: 1972.1 mg, Post weight Swab: 2097.4 mg, Net weight of Swab is 125.3 mg (2097.4 - 1972.1 = 125.3). Place the 125.3 under "Volume" and change "Units" to MG, the "Derivative" to SWB, change the Sub-Add/Der to N/A, and press add. The finished aliquot should look like Figure 10-3.

Figure 10-2: LDMS Screen for Weight Entry

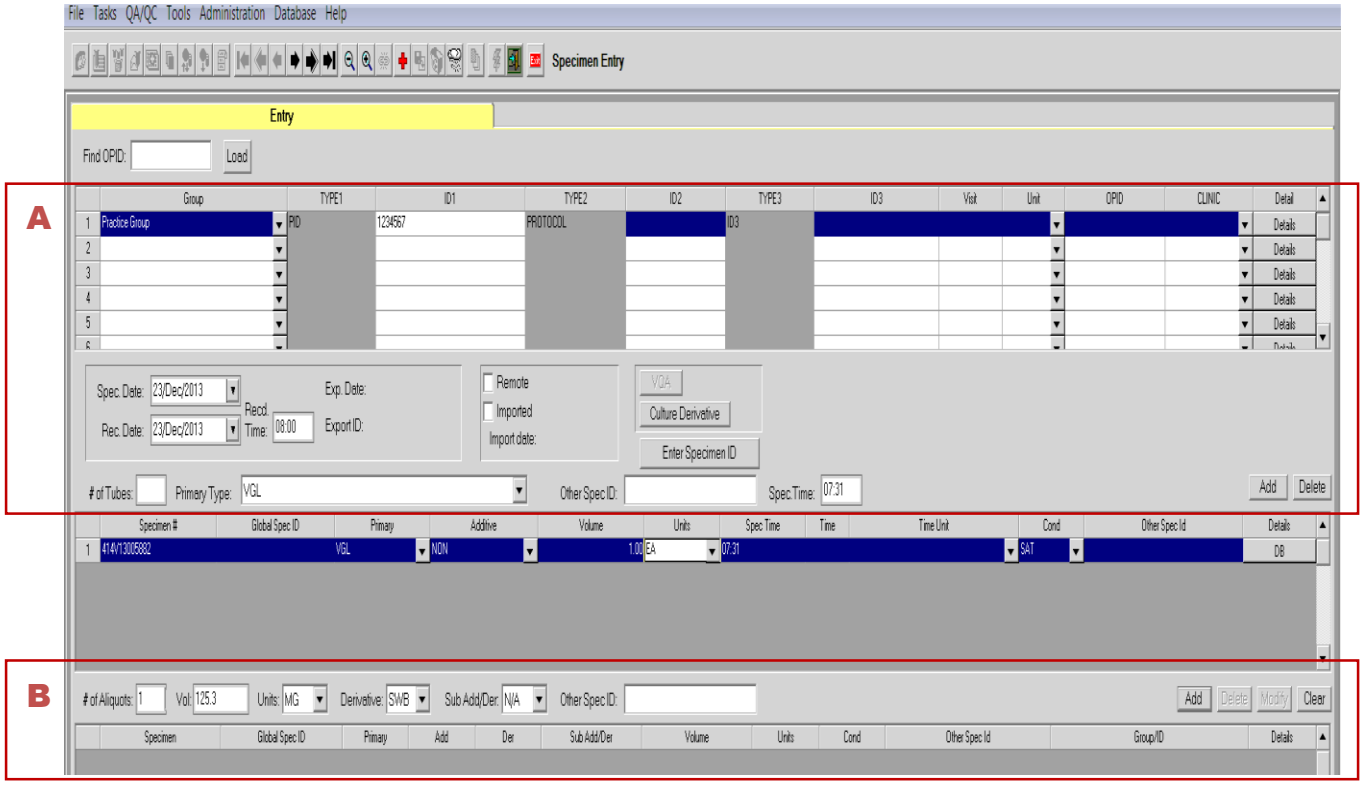
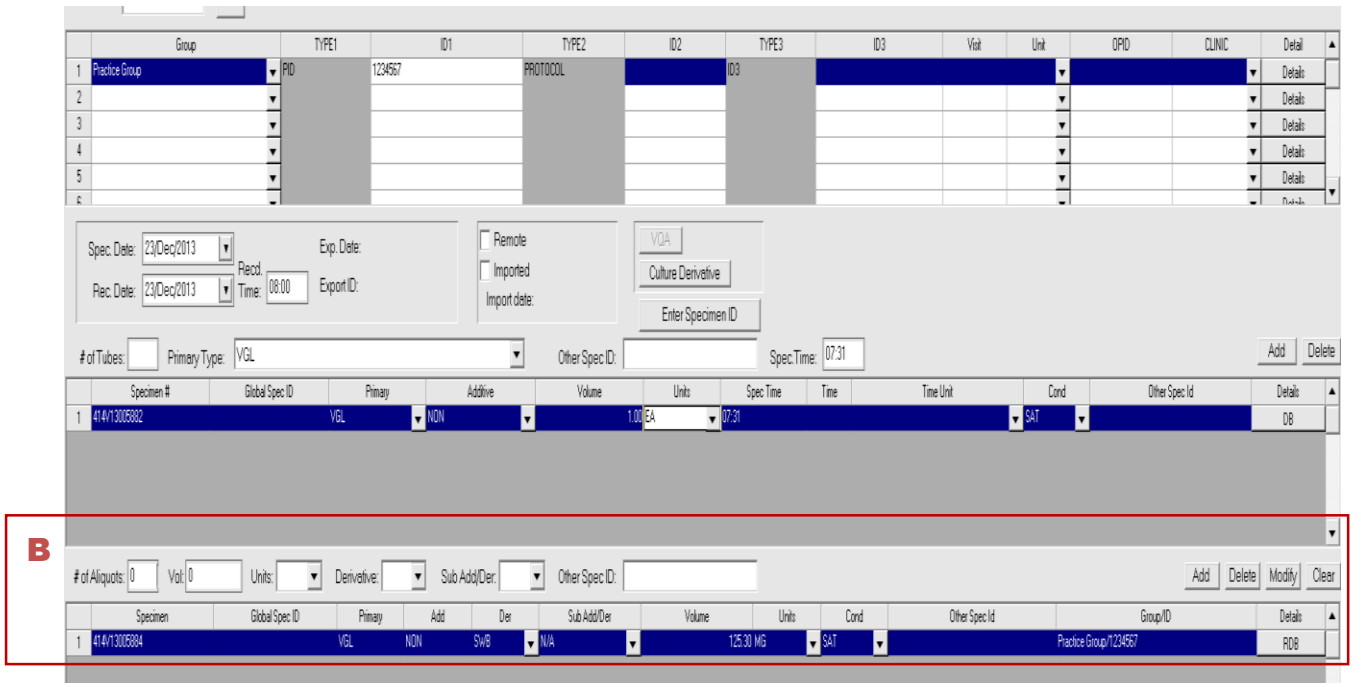


Figure 10-3: LDMS Screen for Weight Entry Example in 10.4.2



10.4.3. LDMS Codes for specimen log in

The table 10-4 should be used as a guide when logging in MTN-023/IPM 030 specimens into LDMS. When logging in specimens for each sample type listed, please use the LDMS codes listed below:

BLD: Whole Blood	IVR: Used Intravaginal Ring	PBS: Phosphate buffered saline
CEN: Cell Pellet	N/A: Not Applicable	PL1/2: Single or double spun plasma
GRS: Gram stain slide	NON: No Additive	SWB: Swab
EDT: EDTA	NSL: Normal Saline	VGL: Vagina
FLD: Fluid Supernatant	PAC: Port-a-Cul	CVL: Cervicovaginal lavage

Tracking sheets can be found in the Study Implementation Materials section on the MTN-023/IPM 030 webpage.

Table 10-4 LDMS Specimen Management Guide to Logging in MTN-023/ IPM 030 Specimens

SAMPLE TYPE	PRIMARY SPECIMEN	PRIMARY ADDITIVE	ALIQUOT DERIVATIVE	ALIQUOT SUB ADDITIVE/ DERIVATIVE	Aliquot volume	Units
Plasma for Storage (archive) or HIV confirmation	**BLD**	**EDT**	**PL1 or PL 2**	**N/A**	1.0-mL	mL
Plasma for PK (Dapivirine)	**BLD**	**EDT**	**PL 1 or PL 2**	**N/A**	>1.0-mL in 2-mL cryovial	mL
Cervicovaginal Lavage (CVL) supernatant	**CVL**	**NSL**	**FLD**	**N/A**	1-mL in 2-mL cryovial	mL
Cervicovaginal Lavage (CVL)Cell Pellet	**CVL**	**NSL**	**CEN**	**NSL**	1-mL in 2-mL cryovial	mL
Vaginal Swab(s) for biomarkers	**VGL**	**PBS** (400-uL PBS)	**SWB**	**N/A**	1 swab in 2-mL cryovial	Each
Vaginal Smear for Gram Stain	**VGL**	**NON**	**SLD**	**GRS**	2 smears	Each
Vaginal Swab for Quantitative Culture	**VGL**	**PAC**	**SWB**	**N/A**	2 swabs in 1 Max V transporter	Each
Vaginal PK Swab	**VGL**	**NON**	**SWB**	**N/A**	1 swab	Each or MG
Used Vaginal Ring for PK residual assessment	**IVR**	**NON**	**IVR**	**NA**	1 pouch	Each

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

Testing for chlamydia and gonorrhea is performed at screening and final visits 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.

10.5.1. Urine

10.5.1.1 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 not to clean the labia prior to specimen collection.
- Collect the first 20-30 mL of voided urine (not midstream urine) in a sterile collection cup if testing for GC/CT, pregnancy, or urinalysis dipstick.
    - Note: If a culture is required, then also collect midstream urine.
- Instruct the participant to screw the lid tightly onto the cup after collection.

10.5.1.2 Urine Processing for Testing

The laboratory that is performing the test must provide the clinic with the appropriate transport tube for the test being performed: ProbeTec or Gen-Probe.

- Open the kit and label the transport tube with the participants PTID number and date.
- Hold the transport tube upright and firmly tap the bottom of the tube on a flat surface to dislodge any large drops from inside the cap.
- Use the transfer pipet provided in the kit to fill the transport tube with urine to the level indicated by the black lines on the tube. Do not under fill or overfill the tube.
- Transport to the local laboratory according to the specific manufacturers recommendations.
- Testing will be done at the local laboratories according to the site SOP.

10.5.2 Vaginal Swab (option if using Gen-Probe Aptima for Trichomonas testing)

10.5.2.1 Specimen Collection

- Affix SCHARP-provided label on tube from GenProbe Aptima vaginal sample collection kit. Collect the specimen for GC/CT testing by rotating the swab from the Aptima collection kit several times over the lateral wall of the vagina. Insert swab into foil top GenProbe Aptima tube. Store at room temperature until testing.
- Transport to the local laboratory according to the specific manufacturers recommendations.
- Testing will be done at the local laboratories according to the site SOP.

10.6 Urine Testing for Pregnancy and Urinary Tract Infection

10.6.1 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 not to clean the labia prior to specimen collection.
- Collect the first 20-30 mL of voided urine (not midstream urine) in a sterile collection cup if testing for GC/CT, pregnancy, or urinalysis dipstick.

- Note: If a culture is required, then also collect midstream urine.
- Instruct the participant to screw the lid tightly onto the cup after collection.

10.6.2 Pregnancy Testing

The Quidel QuickVue One-Step hCG urine, Quidel QuickVue Combo hCG urine/serum, Fisher HealthCare Sure-Vue Urine hCG, Cardinal Health hCG Cassette Rapid test, or OSOM Card Pregnancy test must be used at all sites. Perform the test according to site SOPs and the package insert. Do not perform any other urine pregnancy tests for confirmatory purposes.

Pregnancy status is a critical participant safety consideration in MTN-023/IPM 030. 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.

If the urine pregnancy test cannot adequately be interpreted because of interfering factors, for example 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 a participant becomes pregnant, refer to section 7.5.2 of the SSP.

10.6.3 Urinary Tract Infection

Urine Dipstick and/or Culture: Perform only if indicated and by local standard of care. Instruct participant to collect midstream urine. However, the first 20-30 mL of voided urine must also be collected if GC/CT testing is needed.

10.7 Blood Specimens for Chemistry, Hematology, HIV testing, Syphilis, Plasma Archive, Blood Dapivirine

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.

10.7.1 Specimen Collection and Initial Processing

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

- Allow plain tubes (no additive or serum separator tubes) to clot, then centrifuge per site SOPs to yield serum for syphilis and/or HIV testing.
- EDTA tubes should be gently inverted at least eight times after specimen collection to prevent clotting. EDTA tubes are used for hematology, HIV testing, Dapivirine quantification, and plasma archive. 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.

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.

10.7.2 Chemistry (Alanine transaminase, Aspartate aminotransferase, and Creatinine), and Hematology (CBC with Platelets)

Testing will be performed per the local standard of care. Tests performed for Chemistry are: Alanine transaminase (ALT), Aspartate aminotransferase (AST), and Creatinine. Hematology tests are: Hemoglobin, Hematocrit, Platelets, MCV, and White blood cell count (WBC).

10.7.3 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 10-1 in this section or appendix II of the MTN-023/IPM 030 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 and sent to the MTN Virology LC for confirmation.

HIV test result interpretation is as follows:

- If the Sample 1 immunoassay result is negative, the participant will be considered HIV-seronegative.
- If the Sample 1 immunoassay result is positive or indeterminate, a CLIA and FDA-approved confirmatory test should be performed on Sample 1. 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.

Screening Participants (to include HIV testing for enrollment visit)

- If the confirmatory test is negative, indeterminate or invalid, contact the virology LC for guidance at mtnvirology@mtnstopshiv.org. It is not recommended for participants with discrepant HIV testing results to continue enrollment into MTN-023/ IPM 030.
- If the confirmatory test is positive for the screening visit, the participant is considered seropositive and is not eligible for enrollment.

Follow-Up Participants

- If the confirmatory test on sample 1 is negative, indeterminate or invalid, contact the virology LC for guidance at mtnvirology@mtnstopshiv.org.
- If the confirmatory test is positive at a follow-up visit, a second specimen (Sample 2) will be drawn for additional confirmatory testing (HIV RNA and resistance testing) at the MTN Virology LC.
  - 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- 1.5-mL plasma into 2-mL cryovials and freeze at $\leq$-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.

10.7.4 Syphilis Testing

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

1. Rapid plasma reagin (RPR) screening 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 results must have a titer reported. For reactive RPR 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-023 Protocol Safety Physicians (mtn023safetymd@mtnstopshiv.org).

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

10.7.5 Plasma Archive

For plasma archive, affix SCHARP label on the 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 1.0-mL aliquots.
- 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 (relative centrifugal force in 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 two 1.0-mL aliquots that will be stored in consecutive locations in 'Plasma Archive' storage box.
  - If total volume is less than 0.5-mL, redraw as soon as possible.
  - If less than 1-mL of plasma is available, store the plasma and contact the MTN LC for instruction.
  - If samples are hemolyzed, store the aliquots as per normal and enter comments in LDMS.
  - If plasma is for HIV confirmation and resistance testing store at least three vials with at least 1.0mL each.
- The MTN LC will send instructions to the site when shipping and/or testing is required.

10.7.6 Blood for PK (Dapivirine)

Affix SCHARP label to a 5-mL or greater EDTA Vacutainer tube. Collect blood 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. Pipette ≥1.0-mL aliquots of the resulting plasma into two or more 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 for Plasma PK 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 aliquots are labeled and tracked using LDMS.
5. Store the samples at ≤-70˚C until shipped to MTN LC Pharmacology Core JHU CPAL.
6. Prior to shipping, prepare a shipment box (a foam chest) filled with dry ice sufficient for a 48 hour period with an appropriate shipping label.
7. Primary samples will be shipped to the MTN LC Pharmacology Core JHU CPAL and assayed for Dapivirine at conclusion of study unless informed otherwise. The back-up samples will be retained at the site until advised by the MTN-023/IPM 030 leadership group.

The shipping address for PK samples:
James Johnson
Johns Hopkins University
Division of Clinical Pharmacology
600 N. Wolfe Street, Osler 523
Baltimore, MD 21287

Lab Phone#: (410) 955-9710 or (410) 614-9978
Email: jjohnso6@jhmi.edu

10.8. Cervicovaginal Lavage (CVL) for Biomarkers, Aliquot storage, and Cell Pellet

CVL aliquots will be collected, processed, and used for testing of biomarkers, supernatant storage, and preservation of the cell pellet. See SSP Section 7.6.3 for CVL collection procedures.

10.8.1 Processing of the CVL Cell Pellet and Supernatant for biomarker and storage

The CVL aliquots and the cell pellet are labeled and tracked using LDMS.

1. CVL specimens are kept on wet ice or refrigerated and should be processed within 8 hours

of collection.

2. All the CVL liquid will be spun at 800×g for 10 minutes in the 15-mL conical collection tube.
3. Remove supernatant from the cell pellet in as many 1-mL aliquots as possible into 2-mL cryovials, assuring there are at least 1 aliquot for biomarker testing and a minimum of 5 back-up aliquots marked as 'Extra CVL'.
4. Re-spin the 15-mL conical tube containing cells for 10 minutes at 800×g.
5. Pull off and save any additional supernatant making sure not to remove any cells or debris.
6. Re-suspend the cell pellet in 0.5-mL normal saline in a cryovial.
7. Freeze all CVL aliquots and cell pellet at ≤-70˚C within 8 hours of collection and track in LDMS.
8. Prepare three sets of CVL storage boxes for shipment.
    - The one aliquot for biomarker testing is placed in a 'CVL for Biomarker' box. This set of boxes will be the first shipment of CVL's that will be requested.
    - The remaining supernatant aliquots are stored in consecutive locations, (i.e. all participant's 'Extra CVL' aliquots stored together) in another set of boxes for 'Extra CVL'.
    - The third set of boxes stores the CVL cell pellet.
9. The MTN LC will send instructions to the site when shipping is required.

10.8.2 Shipping of CVL Biomarkers and Cell Pellet

CVL supernatant aliquots for biomarkers and CVL cell pellet samples will be batched and shipped on dry ice to MTN LC at end of study to:

Pamela Kunjara
Magee-Womens Research Institute
204 Craft Ave, Room A540
Pittsburgh, PA 15213
Phone# 412-641-6157
Email: pkunjara@mwri.magee.edu

10.9 Vaginal Specimens for Herpes Lesions, Gram Stain, Microbiology Culture, Vaginal Fluid pH, Vaginal Wet Mount, Trichomonas, Swab for Biomarkers, Vaginal Secretions for PK, and IVR for PK

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.

10.9.1 Herpes Lesion Testing

Testing will be performed per the local standard of care.

10.9.2 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 labeled and logged using LDMS. The primary slide will be shipped to the MTN LC with the Max V or Port-a-Cul. The secondary slide will be archived on site until written notification that the slide may be discarded is received from the Statistical Center for HIV/AIDS Research & Prevention (SCHARP).

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 = VGL) 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 on the day when there is a culture collection. 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).

10.9.3 Microbiology: Vaginal Swab for Quantitative Culture

In addition to the wet mounts and gram stains, vaginal swabs will be collected for quantitative cultures and sent to the MTN LC. Shipping instructions follow.

- Collect the specimen for culture by rotating two Dacron swabs several times over the lateral wall of the vagina. Do not collect culture swabs in the exact same area that another sample was collected (i.e: If the PK swab was collected first, then collect in a different location in the vagina preferably closer to the introitus).If using the BD Max V transporter, insert the two swabs attached to the cap into the tube. If using the Port-a-cul transporter, insert swabs into one Port-A-Cul transport tube (labeled with a SCHARP label), submerging the swabs into the gel and breaking off the shafts of the swabs, and capping. (The BD Max V or Port-A-Cul transport tubes will be provided by MTN LC.)

- The specimen may be kept at controlled room temperature for up to 4 hours. It must be refrigerated after that and shipped with ice packs.
- Deliver the Max V or Port-A-Cul and the LDMS specimen tracking sheet to the local LDMS laboratory.
- Using the LDMS Tracking Sheet, log the slides into LDMS (specimen type = VGL) and label the Max V or Port-A-Cul tube with LDMS labels.
- Use LDMS to generate a shipping manifest for the cultures to be shipped.
- Shipping schedules:
    - Monday through Thursday, on the day of collection, for all samples collected prior to the FedEx pickup deadline, prepare shipment of the Max V or Port-A-Cul tube and the vaginal smear for gram stain for standard overnight next day delivery. If the samples are collected after the FedEx pickup deadline, refrigerate the Max V or Port-a-cul tube and include in the shipment for the following day.
    - All samples collected on Friday should be in a package marked for Saturday delivery.
        - If a site plans to have weekend clinic hours they should contact their FedEx office for drop off locations and hours on Saturday for Monday delivery.
        - Specimens collected on a Sunday can be refrigerated until shipped on Monday for Tuesday delivery.
- Place the Max V or Port-A-Cul in a biohazard bag and secure in the leak-proof container with absorbent material. Place the container, ice packs, slides, and a copy of the manifest in a cardboard box lined with Styrofoam.
- Use diagnostics packing code 650, UN3373.
- Confirm the address is correct (see below). Because the Research Institute is not open for delivery on the weekend, the specimens shipped on Friday must be sent to the *hospital* address for delivery on Saturday.

Shipping instructions to MTN LC:

If sending Monday through Thursday, send to the Institute:

Lorna Rabe
Magee-Womens Research Institute
204 Craft Ave, Room A530
Pittsburgh, Pa. 15213
Phone# 412-641-6042

If sending on Friday for Saturday delivery, send to the hospital:

Lorna Rabe, C/O Safety and Security
Magee-Womens Hospital
300 Halket St.
Pittsburgh, Pa. 15213

Phone # 412 641-4191 (this is the Safety and Security #)
Note: Check off Saturday delivery on the Fed Ex label.

Notify the MTN LC via email (lrabe@mwri.magee.edu and kstoner@mwri.magee.edu) when the shipment has been picked up from the site by the courier/shipping company and the tracking number. Attach the LDMS shipping manifest to the email notification.

10.9.4 Vaginal Fluid pH

Vaginal fluid pH will be assessed as part of on-site evaluations 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:

1. Obtained by the clinician during the pelvic examination
2. 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. It is not necessary to record pH values onto laboratory log sheets or other source documents prior to recording values onto case report forms.

10.9.5 Vaginal Fluid Wet Mount Testing, if indicated for bacterial vaginosis (BV) and KOH preparation for Yeast

Wet mount procedures for this study are only performed if indicated, and consists of two different preparations:

1. Potassium hydroxide (KOH) prep
2. Saline prep

These procedures are for diagnosis of BV and candidiasis as summarized in Table 10-5 below.

If wet prep slides are read in-clinic by clinical staff, results may be recorded directly on to appropriate case report forms. 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 case report form.

The MTN LC requires all wet mount readers are assessed by the LC for competency of the wet mount tests; therefore, the MTN LC will administer a web-based proficiency test approximately every six months. The MTN LC will post wet mount slides on the MTN web pages for this purpose every 6 months; results will be entered directly on the website (contact: Lorna Rabe: lrabe@mwri.magee.edu). The MTN LC will report results back to the Laboratory Manager and also specify any corrective action that may be needed based on the results. 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.

Table 10-5 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)

Note: BV will be diagnosed based on the presence of any three of the following Amsel's criteria: homogenous vaginal discharge, vaginal pH greater than 4.5, positive whiff test, at least 20% clue cells

Prepare and examine wet prep slides according to study site SOPs as follows:

- 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) and write the specimen collection date in indelible ink (e.g. Sharpie pen) on each label.
- 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.
- Apply one drop of 10% KOH to one slide and immediately perform whiff test for a "fishy" amine odor. Then apply cover slip. Examine the KOH slide at both 100X and 400X magnification for yeast and pseudohyphae.
- 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.

10.9.6 Test for *Trichomonas vaginalis*

Testing for Trichomonas can be done with either the OSOM Rapid Trichomonas test (manufactured by Sekisui Diagnostics) or the Gen-Probe Aptima. If using the Aptima test, GC/CT can be tested from the same swab, thus eliminating the need for a urine specimen for GC/CT.

10.9.6.1 OSOM Rapid Trichomonas test

- 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.

10.9.6.2 Gen-Probe Aptima NAAT (This same sample can be used 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

10.9.7 Vaginal Swab for Biomarkers

Biomarkers will be evaluated to determine the impact the intravaginal rings and drugs may have on innate immune mediators, cytokines, or other safety concerns. Vaginal fluids are collected from the posterior fornix using a Dacron swab with a plastic shaft for biomarker analysis at the MTN LC.

Procedure:

- Affix a SCHARP-provided PTID label to the provided 2-mL cryovial containing 400-µL PBS (1X Concentration)
    - Label should indicate vaginal biomarker or VGL PBS to distinguish this specimen from other vaginal specimens.
- Collect vaginal fluid using a Dacron swab from the posterior fornix.
- Place the swab into the 2-mL cryovial containing 400-µL PBS, break off swab shaft, and cap the vial.
- Immediately refrigerate or place vial on ice and freeze at ≤-70°C within 8 hours of collecting the sample collection.
- Mark this sample on the LDMS tracking sheet and transport to the LDMS laboratory.
- The sample will be labeled and tracked using LDMS.
- Batch ship on dry ice to MTN LC at end of study:

Pamela Kunjara
Magee-Womens Research Institute
204 Craft Ave, Room A540
Pittsburgh, Pa. 15213
Phone# 412-641-6157
Email: pkunjara@mwri.magee.edu

10.9.8 Vaginal Swabs for PK

Vaginal fluid for PK will be collected at all sites; however, Pittsburgh, UAB and Fenway sites will weigh the swabs before and after collection. The Memphis, Colorado and Bronx sites will not weigh the swabs.

10.9.8.1 Procedure for Vaginal Fluid Sampling for PK assessment and weighing swab (UAB, Pittsburgh, and Fenway sites only):

Materials:

2-mL Nalgene cryovials containing pre-cut Polyester-Tipped (Dacron) Swab
Hemostat or Ring Forceps (recommend 8 inches or longer)
Analytical scale (accurate to 0.1 milligrams)

1. PK swabs must be collected within one hour of PK blood draw.
2. Ensure that new, clean, or sterilized supplies (gloves, hemostat, swabs, tubes, etc.) are used for each sample, as Dapivirine is very sensitive to cross-contamination.
3. Before starting procedures, write participant identification information on a SCHARP label and affix the label to the cryovial containing the pre-cut swab.
4. Perform QC that would be required for the analytical scale to accurately weigh samples to a weight of at least 0.1 milligrams.
5. Perform Pre-Weight measurement by weighing the capped cryovial with pre-cut swab.
6. Record this pre-weight on the LDMS Tracking Sheet.
7. Uncap the pre-weighed cryovial. Put on new gloves and use a clean hemostat to clamp on to the exposed shaft of the swab to collect vaginal fluid. Use a clean gloved hand

to assist, if needed.

8. Insert the hemostat holding the swab into the upper vagina near the cervix to the location nearest to where the ring was residing. For 10-20 seconds, rotate in a circular motion touching all walls to absorb as much fluid as possible.
9. Immediately place swab tip into the cryovial after sampling and recap.
10. Perform Post Weight:
    - Weigh the capped cryovial containing the absorbed swab tip
    - Record on the LDMS Tracking sheet
11. Transport sample to the LDMS laboratory where the sample will be labeled and tracked using LDMS.
12. Record the pre and post weights into the "PK swab excel worksheet". This will automatically calculate the weight of the fluid collected. This worksheet will be sent to the PK lab along with the specimens at the end of the study.
13. Within 2 hours, place the sample tubes in the freezer at ≤-70˚C.

10.9.8.2 Procedure for Vaginal Fluid Sampling for PK assessment (No weighing of swabs, Colorado, Bronx and Memphis sites):

Materials:

2-mL Nalgene cryovials with affixed SCHARP label
Polyester-Tipped (Dacron) Swab
(The MTN LC will provide pre-cut Dacron swabs inserted into the cryovial. This is to assure consistent size of swabs for analysis)

PK swabs must be collected within one hour of PK blood draw.

1. Ensure that new, clean, or sterilized supplies (gloves, hemostat or ring forcep, swabs, tubes, etc.) are used for each sample, as Dapivirine is very sensitive to cross-contamination.
2. Before starting procedures, label the cryovial containing the pre-cut swab with participant study and sample identification information.

Collection of vaginal fluid:

1. Label the cryovial with SCHARP label with PTID, date, and visit number.
2. Use a clean gloved hand to handle the swab.
3. Open the cryovial and attach the pre-cut swab to hemostat or ring forcep.
4. Insert the swab into the vagina to the location nearest to where the ring was residing. For 10-20 seconds, rotate in a circular motion touching all walls to absorb as much fluid as possible.
5. Immediately place swab tip into the labeled cryovial after sampling and recap.
6. Record this sample on the LDMS tracking sheet.
7. Transport sample to the LDMS laboratory where the sample will be labeled and tracked using LDMS.
8. Within 2 hours, place the sample tubes in the freezer at ≤-70˚C.

10.9.8.3 Shipping of PK swab samples to MTN LC JHU CPAL

At the end of the study, ship PK swab samples on dry ice on Monday or Tuesday to the MTN LC JHU CPAL:

James Johnson
Johns Hopkins University
Division of Clinical Pharmacology
600 N. Wolfe Street, Osler 523
Baltimore, MD 21287

Lab Phone#: (410) 955-9710 or (410) 614-9978
Email: jjohnso6@jhmi.edu

10.10 Testing of Intravaginal Ring (IVR)

Used rings will be analyzed for residual levels of Dapivirine, and will be collected at visit weeks 4, 8, 12, 16, 20, and 24. 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.

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.

   *Use a disposable container or a reusable container that was cleaned using 10% bleach solution for 20 minutes or sterilized.
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.

¥ If the ring is removed by the participant prior to the clinic visit and will not be reinserted, then the used ring is still prepared for residual drug analysis. After the used ring is taken out of the participant's bag (bag or pouch they returned the ring in), follow directions starting with step 1.

Preparation of used ring for storage on-site:

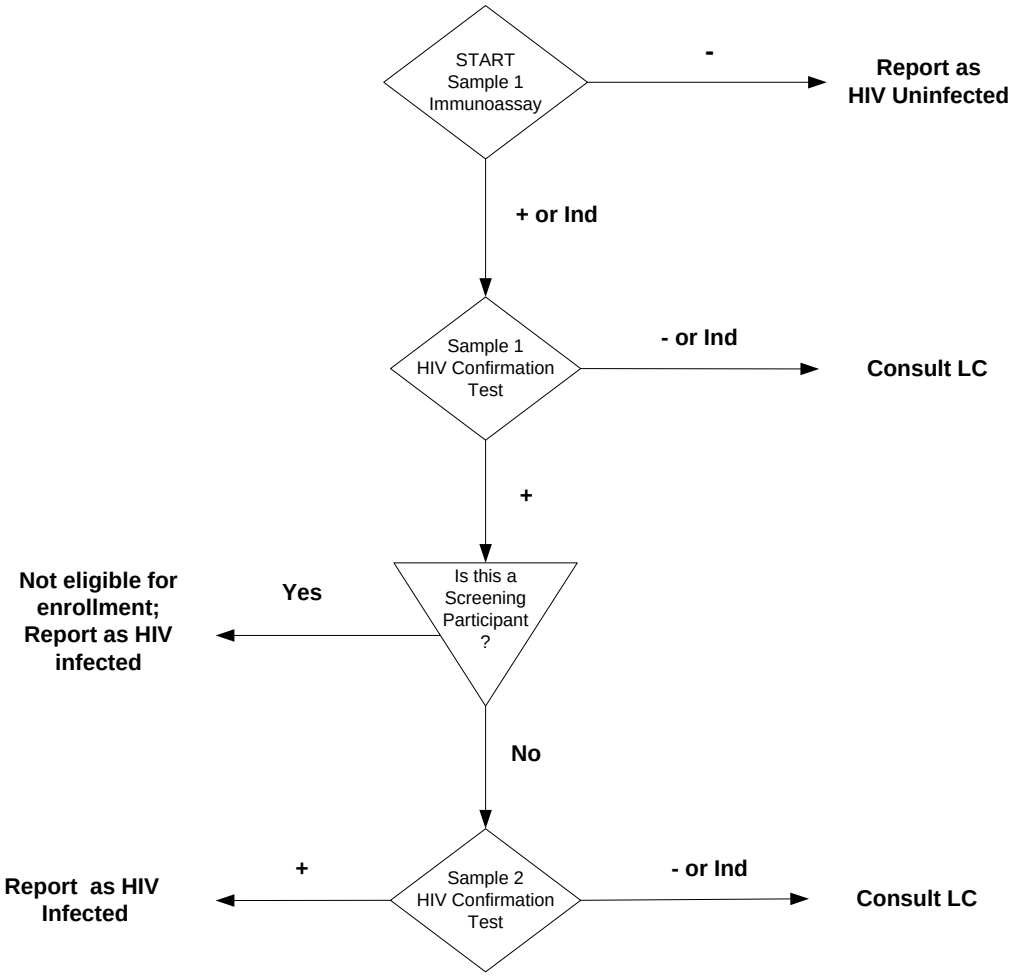
1. Site staff will place the ring into a new 3"X5" amber Zippit pouch (see figure 10-4) that was provided by LC to store the rings.
2. Label the pouch with a SCHARP label consisting of the participant ID number, visit number, and collection date.
3. Add a biohazard sticker if one is not already attached to the pouch, making sure not to cover the identifier information.
4. The use of LDMS is required to label and log in all used rings.
5. Store the used ring within the biohazard labeled amber pouch at room temperature.
6. At the end of the study, the MTN LC will contact site to coordinate shipment.

¥ If the ring is removed by the participant prior to the clinic visit and will not be reinserted, then the used ring is still prepared for residual drug analysis. After the used ring is taken out of the participant's bag (bag or pouch they returned the ring in), follow directions starting with step 1.

Figure 10-4
3"×5" amber Zippit pouch

Algorithm For HIV Testing

Appendix 10-1: HIV ANTIBODY TESTING ALGORITHM



Ind: Indeterminate test results
LC: Laboratory Center

Section 11. Data Collection

Table of Contents

The purpose of this document is to provide site staff with the information they need to successfully complete and submit MTN-023/IPM 030 Case Report Forms (CRFs). 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 SCHARP MTN-023/IPM 030 team members, along with their job role and e-mail address, are listed below.

MTN-023/IPM 030 Statistical and Data Management Center (SDMC) Staff

Job Role	Name	Email Address
Protocol Statistician	Jingyang Zhang	jzhang2@scharp.org
Project Manager	Melissa Peda	mapeda@scharp.org
Statistical Research Associates	Danny Szydlo Marla Husnik	dszydlo@fhcrc.org marla@scharp.org
Operations Programmer	Brad Fischer	hfischer@scharp.org
Data Coordinator	Jenn Schille	jens@scharp.org
Lab Programmer	Katie Snapinn	ksnapinn@scharp.org
Clinical Affairs Safety Associate	Jenny Tseng	jenny@scharp.org

11.1 DataFax Overview

DataFax is the data management system used by SCHARP to receive and manage data collected at study sites. The site faxes an electronic image of each CRF to SCHARP DataFax, and the original hard copy CRF is retained by the site.

CRF Transmission and Troubleshooting

Case report forms can be transmitted to SCHARP using a fax machine connected to the internet (fax to e-mail <datafax@scharp.org>).

SCHARP'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@scharp.org>. This group should also be contacted anytime the site has technical questions or problems with their fax equipment.

Data Entry/Quality Control

Once a CRF image is received by SCHARP DataFax, 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 members of SCHARP's Data Operations Group. 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 SCHARP DataFax.
- When the refaxed pages are received, SCHARP 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 SCHARP 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 SCHARP. Therefore, it is very important that the site refax updated CRF pages to SCHARP 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.

iDataFax View-only Access

Each site will be able to access and view its own MTN-023/IPM 030 CRF data via iDataFax view-only access (EDC view). With view-only access, sites can view their faxed CRF images and data, view their QCs and clinical queries, and identify missing CRF pages or visits. This will allow the user to review and resolve QCs even before they are included on a QC report. iDataFax view-only access may 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 CRF data, 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, each site must first download the iDataFax software by downloading version 4.0.3 from the Atlas site: https://atlas.scharp.org/cpas/project/iDataFax/How%20to%20Get%20Started/Getting%20Started/begin.view?

For questions or technical assistance with iDataFax, please contact support@scharp.org.

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 SCHARP 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.

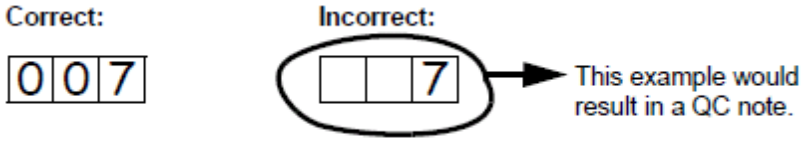
Mark only one response box for each item unless the "Mark all that apply" instruction is present.

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:

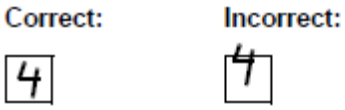
- Right justify **all** numbers and fill in any blank leading boxes with zeroes. If boxes are left blank, a QC note will be applied asking for the boxes to be filled in.

  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.

Easily Identified:

Difficult to Identify:

11.2.4 How to Record Dates

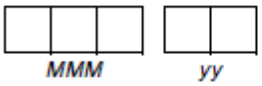
Dates are recorded using the "dd MMM yy" format, where "dd" represents the two-digit day, "MMM" represents the three-letter abbreviation of the month (in capital letters), and "yy" represents the last two digits of the year.

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 below:

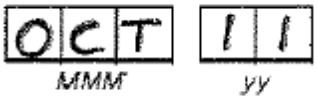
Month	Abbreviation	Month	Abbreviation
January	**JAN**	July	**JUL**
February	**FEB**	August	**AUG**
March	**MAR**	September	**SEP**
Month	**Abbreviation**	**Month**	**Abbreviation**
April	**APR**	October	**OCT**
May	**MAY**	November	**NOV**
June	**JUN**	December	**DEC**

For example, June 6, 2012 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:

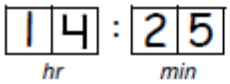


A diagnosis date of October, 2011 would be recorded as follows:



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
6:00 a.m.	06:00
7:00 a.m.	07:00
8:00 a.m.	08:00
9:00 a.m.	09:00
10:00 a.m.	10:00
11:00 a.m.	11:00

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 p.m.	18:00
7:00 p.m.	19:00
8:00 p.m.	20:00
9:00 p.m.	21:00
10:00 p.m.	22:00
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.

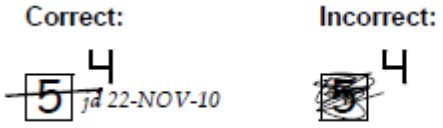
It is important to make these changes to the original CRF—*never* copy data onto a new form. After making the change, the CRF *must* be re-faxed to SCHARP DataFax. If an entire CRF must be marked for deletion, draw a diagonal line through the entire CRF, write "delete" and the reason for deletion in the white space, and initial and date. After refaxing to SCHARP DataFax, keep the deleted CRF in the participant binder; see section 11.2.9.

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.

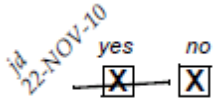
Whenever an entry on a DataFax CRF is changed, do the following:

- 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:

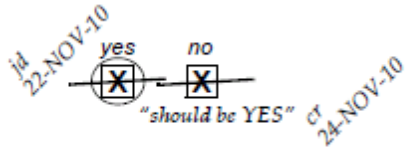
- draw a single horizontal line through the incorrectly marked box,
- mark the correct box, and
- initial and date the correction as shown below:



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

- draw a single horizontal line through the incorrectly marked box,
- circle the correct item,
- write an explanation in the white space near the item, and

- initial and date all corrections as shown below:

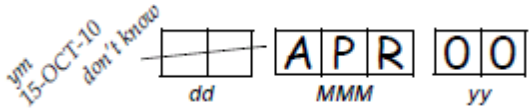


The standards above must ***always*** be followed whenever a CRF is changed, clarified, or amended, even if the change is made *before* the CRF is faxed to SCHARP for the first time.

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 SCHARP. 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 similarly to 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 it is faxed to SCHARP 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.

For sites wishing to confirm the receipt by SCHARP of faxed forms, the CRF Tracking System (CTS) is available. This system generates two types of e-mails listings: 1) the number of form pages received at SCHARP for each batch of forms faxed; and 2) which specific individual form pages were received at SCHARP for a given PTID and visit. Please contact the SCHARP DataFax Support Group (support@scharp.org) if you would like to use the CRF Tracking System or for more information about this fax confirmation system.

Once transmitted to SCHARP DataFax, keep all CRFs for every participant, even if the CRF was completed in error and/or has been marked for deletion from the database. Never destroy a form once it has been transmitted to SCHARP DataFax. In the rare event that a CRF is lost or destroyed after being transmitted to SCHARP DataFax, contact the SCHARP Project Manager for a copy of the electronic image saved in DataFax. This version will become the new "primary" and should be kept in the participant's binder. This CRF can be updated and retransmitted to SCHARP DataFax as needed. If the original is ever found, it should also be kept in the participant's file for documentation purposes only.

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, 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.

SCHARP can provide a template for use in creating notebook cover labels and spine labels. SCHARP can also provide a template that can be used to create tab divider labels.

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

- SCHARP data QC processes
- Electronically-captured study data
- Data storage

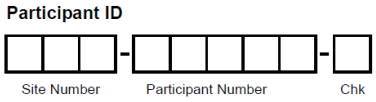
11.3 Study-Specific Data Collection Information

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 "WWW-XXXXX-Y." The PTID consists of four parts: the DataFax site number (WWW), the participant number (XXXXX), and the numerical check digit (Y). The check digit (Y) is a number generated by SCHARP with the participant number, and helps ensure that the correct PTID is recorded. Below are examples of the PTID structure used in MTN-023/IPM 030.



11.3.2 Study Visit Timing

Screening and Enrollment

The initial screening visit is defined as the first day the participant provided written informed consent to be screened for the study. The enrollment visit will be scheduled to take place within 56 days of the initial screening visit. The date the participant is enrolled is Study Day 0.

Screening Attempts (Re-screens)

If a participant's first screening attempt is unsuccessful, the participant may re-screen a maximum of one time for the study if she chooses. If she does re-screen, all screening procedures and forms must be repeated with the exception of PTID assignments. Once a PTID is assigned to a participant, that PTID is used for the re-screen procedures and forms completed for that participant.

If a participant re-screens and enrolls in the study, only case report forms from the successful screening and enrollment visits are faxed to SCHARP.

Follow-Up Visits

For each follow-up visit, 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 being Study Day 0.

Target Days and Visit Windows

Whenever possible, visits should be completed on the target day. If it is not possible to complete the visit on the target day, the visit should be completed within the visit window.

SCHARP will provide sites with a spreadsheet tool that may be used to generate participant follow-up visit calendars. The spreadsheet requires that the participant's enrollment date be entered. Once the enrollment date is entered, the target date and visit window for each required follow-up visit will appear. Please note that the final visit is dependent on the actual date of the previous visit. Therefore, the actual date of the 24-Week Final Clinic Visit must be manually entered in order to calculate the visit target date and windows for the 25-Week Follow-up Phone Call. The calendar can then be printed and added to the participant's study notebook.

Split Visits

A Screening Visit may be split as long as all screening procedures are completed within the allowable 56 day window before enrollment.

Enrollment Visits may not be split. Refer to the Accrual section of this manual for more information regarding Enrollment Visit procedures and timing.

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 visit window. For example, a participant comes in on her 4-Week Study Visit target date and completes most of the required evaluations. She comes back 7 days later 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 Visit Summary CRF is completed, and all CRFs completed for the visit are assigned the same visit month/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

Visit Code	Visit Type	Visit Window Opens	Target Day/ Comments	Visit Window Closes
1.0	Screening	N/A	No more than 56 days prior to planned Enrollment day	N/A
2.0	Enrollment	Day after Screening Visit	Day 0	56 days after Screening Visit
3.0	1-Week Follow-up Phone Call	Day 1	Day 7	Day 8
4.0	2-Week Visit	Day 9	Day 14	Day 20

5.0	4-Week Visit	Day 21	Day 28	Day 41
6.0	8-Week Visit	Day 42	Day 56	Day 69
7.0	12-Week Visit	Day 70	Day 84	Day 97
9.0	16-Week Visit	Day 98	Day 112	Day 125
10.0	20-Week Visit	Day 126	Day 140	Day 153
11.0	24-Week Visit	Day 154	Day 168	Day 181
12.0*	25-Week Follow-up Phone Call	1 day after the 24-Week/Final Clinic Visit	Varies	14 days after the 24-Week/Final Clinic Visit

** The Target Visit Date for the 25-Week Phone Call is based on the Actual Visit Date of the 24-Week Final Clinic Visit. Therefore, you must enter the Actual Visit Date for the 24-Week Final Clinic Visit on the Visit Calendar Tool in order to calculate the Target Date and Visit Windows for the 25-Week Phone Call.*

Missed Visits

In 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 2-Week Visit until 22 days after enrollment. 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, which is faxed to SCHARP.

Interim Visits

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

All interim visits/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 visit 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-023/IPM 030, there is no Interim Visit CRF. Instead, a Follow-up Visit Summary CRF is completed for interim visits/contacts as needed. The Visit Code of the Follow-up Visit Summary CRF will document whether the visit is a required (regular) visit or an interim visit.

11.3.3 Visit Codes and Page Numbers

Most 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. For CRFs completed only once per participant (the Enrollment CRF, for example), there is no place to record a visit code, as the visit code has been automatically assigned by SCHARP.

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	**1.0**
2	Enrollment	**2.0**
N/A	1-Week Follow-up Phone Call	**3.0**
3	2-Week Visit	**4.0**
4	4-Week Visit	**5.0**
5	8-Week Visit	**6.0**
6	12-Week Visit	**7.0**
7	16-Week Visit	**9.0***
8	20-Week Visit	**10.0**
9	24-Week Visit	**11.0**
NA	25-Week Follow-up Phone Call	**12.0**

**Under protocol version 2.0, there will be no visit code 8.0; visit code 8.0 is reserved for data collected at the 13-week follow-up phone call under protocol version 1.0.*

Visit Codes for Interim Visits

Note that interim visit codes are not used for visits/contacts between the Screening Visit and Enrollment Visit, as CRFs completed for screening and enrollment have the visit code automatically-assigned.

For interim visits occurring after the Enrollment Visit, 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 follow-up visit, *even if the visit was missed and/or if the participant is within the next visit's window.*

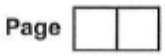
- For the box to the right of the decimal point:
  - #.1 = the first interim visit after the most recently-required follow-up visit,
  - #.2 = the second interim visit after the most recently-required follow-up visit,
  - #.3 = the third interim visit after the most recently-required follow-up visit, and so on.

Example #1: A participant completes her 8-Week Visit (Visit Code = 6.0) on the target date. The participant returns to the site 2 days later to report a new genitourinary symptom. This interim visit is assigned a Visit Code of 6.1:

Visit Code for this Interim Visit

Page numbers

Other CRFs, such as log forms (e.g., Adverse Experience Log, Concomitant Medications, or Protocol Deviations 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). Continue to 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-023/IPM 030 CRFs. Sites may either print CRFs (this is the preferred method) from PDF files provided by SCHARP (available on the MTN-023/IPM 030 Atlas web page), or via photocopy of hard-copy originals. CRF PDF files will include visit packets containing all of the CRFs required to be completed for the visit, as well as a file containing all of the CRFs created for the study.

SCHARP will also ensure sites have access to specimen labels (printed on-site). Specimen labels should be used for all primary specimen collection containers. Please

refer to the Laboratory section of the manual for more information on laboratory specimen collection and labeling.

11.3.6 Case Report Form Completion Schedule

The SCHARP-provided forms for this study include DataFax forms (forms that are completed and faxed to SCHARP DataFax) and non-DataFax forms (forms that are completed but not faxed to SCHARP DataFax).

Some SCHARP-provided forms are required to be completed at each visit, while other forms are required only at one visit or only when specifically indicated. Table 11-3 lists the DataFax and non-DataFax forms that are required to be completed at each study visit.

The following CRFs are completed only when specifically indicated: Clinical Product Hold/Discontinuation Log, Adverse Experience Log, Pregnancy Report and History, Pregnancy Outcome, Participant Transfer, Participant Receipt, Missed Visit, and Protocol Deviation Log.

Table 11-3: Schedule of Forms – CRFs Required to be Completed at Each Visit

Screening Visit: Visit Code 1.0	
DataFax forms	**Non-DataFax forms**
Baseline Menstrual History Concomitant Medications Log Demographics Eligibility Criteria Laboratory Results Pelvic Exam Physical Exam Pre-existing Conditions STI Test Results	Baseline Medical History Questions Sheet Pelvic Exam Diagrams Screening Behavioral Eligibility
Enrollment Visit: Visit Code 2.0	
DataFax forms	**Non-DataFax forms**
Enrollment Laboratory Results Pelvic Exam Physical Exam Ring Collection and Insertion Specimen Storage Vaginal Practices Version 2.0 Re-Consent (if applicable)	Baseline Medical History Questions Sheet LDMS Specimen Tracking Sheet Pelvic Exam Diagrams Enrollment Behavioral Eligibility
1-Week Follow-up Phone Call: Visit Code 3.0	
DataFax forms	**Non-DataFax forms**
Follow-up Visit Summary Version 2.0 Re-Consent (if applicable)	N/A
2-Week Visit: Visit Code 4.0	
DataFax forms	**Non-DataFax forms**
Follow-up Visit Summary Laboratory Results Pharmacokinetics Version 2.0 Re-Consent (if applicable)	Follow-up Medical History Log LDMS Specimen Tracking Sheet Pelvic Exam Diagrams (as needed)

STI Test Results (as needed) Ring Collection and Insertion (as needed) Vaginal Ring Storage (as needed) Pelvic Exam (as needed)	
4-Week Visit: Visit Code 5.0	
DataFax forms	**Non-DataFax forms**
Follow-up Visit Summary Laboratory Results Pelvic Exam Pharmacokinetics Physical Exam Ring Adherence Ring Collection and Insertion Specimen Storage Vaginal Practices Vaginal Ring Storage Version 2.0 Re-Consent (if applicable) STI Test Results (as needed)	Follow-up Medical History Log LDMS Specimen Tracking Sheet Pelvic Exam Diagrams
8-Week Visit: Visit Code 6.0	
DataFax forms	**Non-DataFax forms**
Follow-up Visit Summary Laboratory Results Pelvic Exam (as needed) Physical Exam Ring Adherence Ring Collection and Insertion Vaginal Practices Vaginal Ring Storage Version 2.0 Re-Consent (if applicable) STI Test Results (as needed)	Follow-up Medical History Log LDMS Specimen Tracking Sheet Pelvic Exam Diagrams (as needed)
12-Week Visit: Visit Code 7.0	
Follow-up ACASI Tracking Follow-up Visit Summary Laboratory Results Pelvic Exam Pharmacokinetics Physical Exam Ring Adherence Ring Collection and Insertion Specimen Storage Vaginal Practices Vaginal Ring Storage Version 2.0 Re-Consent (if applicable) STI Test Results (as needed)	Follow-up Medical History Log LDMS Specimen Tracking Sheet Pelvic Exam Diagrams
16-Week Visit: Visit Code 9.0	
Follow-up Visit Summary Laboratory Results Pelvic Exam (as needed) Physical Exam Ring Adherence Ring Collection and Insertion Vaginal Practices Vaginal Ring Storage STI Test Results (as needed)	Follow-up Medical History Log LDMS Specimen Tracking Sheet Pelvic Exam Diagrams (as needed)

20-Week Visit: Visit Code 10.0	
Follow-up Visit Summary Laboratory Results Pelvic Exam (as needed) Physical Exam Ring Adherence Ring Collection and Insertion Vaginal Practices Vaginal Ring Storage STI Test Results (as needed)	Follow-up Medical History Log LDMS Specimen Tracking Sheet Pelvic Exam Diagrams (as needed)
24-Week Final Clinic Visit/Early Termination Visit: Visit Code 11.0 (will vary for early termination)	
DataFax forms	**Non-DataFax forms**
Follow-Up ACASI Tracking Follow-Up Visit Summary Laboratory Results Pelvic Exam Pharmacokinetics Physical Exam Ring Adherence Ring Collection and Insertion Specimen Storage STI Test Results Vaginal Practices Vaginal Ring Storage	Follow-up Medical History Log LDMS Specimen Tracking Sheet Pelvic Exam Diagrams
25-Week Follow-up Phone Call: Visit Code 12.0	
DataFax forms	**Non-DataFax forms**
Follow-Up Visit Summary Termination	N/A

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 SCHARP. While DataFax CRFs are being reviewed, it is important that they are stored and tracked systematically.

Below are specific review guidelines that should be followed for these QC review steps.

11.3.9 MTN-023/IPM 030 QC Review Step #1

- Review CRFs based on participant responses to ensure completeness.

- For the Screening Visit, Enrollment Visit, and all follow-up visits review all required and completed CRFs as listed in Table 11-3 above. In addition, be sure to review any CRFs completed "as needed."

11.3.10 MTN-023/IPM 030 QC Review Step #2

This QC review step should occur before forms are faxed to SCHARP. Ideally, this review will happen once all lab results are available, so that all forms for a particular visit can be reviewed for consistency across documents. The goal, as outlined in the site's MTN Data Management SOP, is to correct data inconsistencies/errors prior to faxing forms to SCHARP so that QC notes are prevented.

General QC #2 procedures for all visits:

- Review visit checklist to ensure all required procedures were completed
- Ensure no participant identifiers other than the PTID are present on DataFax forms.
- Ensure the PTID is correct, and is the same on all forms/documents.
- Ensure the Visit Code assigned is correct, and is the same on all documents.
- Make sure a response has been recorded for each item, as required. Make sure skip patterns have been followed correctly.
- If a response box has a line for "other," "specify," or "describe," ensure text is recorded on the line.
- Make sure text responses are clearly recorded.

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.

Adverse Experience Log (AE-1)

- Do not wait until the AE resolves before faxing the form page to SCHARP.
- 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 SCHARP, 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 7. Any adverse experiences associated with the planned procedure or surgery, are AEs.
- If an AE is marked as “related”, please avoid putting additional detail regarding relatedness in the “Comments” section. Rather, provide as much relevant information as possible in item 1 (the text description of the AE). This will help avoid MedDRA coding queries during the study.
- For more details regarding how to report AEs please review SSP section 8.

11.5 Case Report Forms

The current version of the MTN-023/IPM 030 case report forms (not for actual data collection purposes use) can be found on the MTN-023/IPM 030 SSP web page on the MTN website (www.mtnstopshiv.org).

Sites can access and download the MTN-023/IPM 030 case report forms for on-site printing and data collection on the MTN-023/IPM 030 Atlas web page:

https://atlas.scharp.org/cpas/project/MTN/023%20and%20IPM%20030/begin.view?.

Section 12. Data Communiqués

For MTN-023/IPM 030, SCHARP will use “Data Communiqués” to document and communicate data decisions and procedural revisions during the study. By using Data Communiqués, SCHARP avoids having to redistribute 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 a copy in this section of each MTN-023/IPM 030 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-023/IPM 030 Data Communiqué #1

24 June 2014

This is official study documentation for MTN-023/IPM 030. Please circulate it among relevant staff for their review, print it, and place it in your MTN-023/IPM 030 SSP Manual in the Data Communiqués section. This document is considered part of the MTN-023/IPM 030 SSP manual.

REMINDERS

None.

CLARIFICATIONS

1. **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 her 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 4 is marked "not related", record "due to alternate 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.

UPDATES

1. **STI Test Results (STI-1), item 1c.**
   Clue cells should be reported and marked as "positive" if 20% or more of the cells observed are clue cells. The form and the instructions are currently incorrect in that they indicate that only if *more than 20%* of the observed cells are clue cells should it be reported as "positive."

2. **STI Test Results (STI-1), item 2.**
   The CRF reads "Trichomonas rapid test" for item 2, but the Bronx site is not using a rapid test for this study. Instead this site will be using a NAAT test. The results for the NAAT test should be recorded in item 2 as "not done/not collected," "negative," or "positive."

MTN-023/IPM 030 Data Communiqué #2

2 March 2015

This is official study documentation for MTN-023/IPM 030. Please circulate it among relevant staff for their review, print it, and place it in your MTN-023/IPM 030 SSP Manual in the Data Communiqués section. This document is considered part of the MTN-023/IPM 030 SSP manual.

UPDATES

1. New SCHARP Project Manager

   Melissa Peda has joined the SCHARP team as a Project Manager working on the MTN-023 study. Please include Melissa (mapeda@scharp.org) on any and all correspondences that you send to Karen Patterson.

2. New Visit Codes for Protocol Version 2.0

   Under protocol version 1.0, the length of follow-up was 3 months (13 weeks). This has been extended to 6 months (25 weeks) under protocol version 2.0, resulting in three additional study visits at weeks 16, 20 and 24.

   To accommodate these additional study visits, the visit schedule has been updated to the following:

Visit	Visit Code
Screening	**1.0**
Enrollment	**2.0**
1-Week Follow-up Phone Call	**3.0**
2-Week Visit	**4.0**
4-Week Visit	**5.0**
8-Week Visit	**6.0**
12-Week Visit	**7.0**
16-Week Visit	**9.0***
20-Week Visit	**10.0**
24-Week Visit	**11.0**
25-Week Follow-up Phone Call	**12.0**

*It should be noted that under protocol version 2.0, there will be no visit code 8.0; visit code 8.0 is reserved for data that was collected at the 13-week follow-up phone call under protocol version 1.0.

This information has been updated in Section 11-Data Collection of the SSP, which can be found on the MTN website (http://www.mtnstopshiv.org/node/5648).

3. Updated CRFs (dated 27-FEB-15) for Data Collected Under Protocol Version 2.0

In response to the release of protocol version 2.0, some of the MTN-023 Case Report Forms (CRFs) have been updated (dated 27-FEB-15), as specified in the sub-sections below. Please note that those CRFs that did not undergo any changes still maintain the original date of 19-FEB-14.

For those CRFs that have been updated, each site should continue to use the previous version (dated 19-FEB-14) to collect data under protocol version 1.0. Once a site obtains the necessary approvals to begin implementation of protocol version 2.0, the site should begin using the new versions of these CRFs (dated 27-FEB-15) *exclusively*, and dispose of blank copies of the older version to avoid any mix-up. For QC purposes, the site should **notify the SCHARP Project Managers of the date when the site first begins to use the updated version of these CRFs**.

Please note that version 2.0 CRFs (dated 27-FEB-15) should *not* be faxed to SCHARP until SCHARP sends notification to the protocol team confirming database readiness.

The updated CRFs, dated 27-FEB-15, and updated visit packets will be posted at the bottom of the MTN-023 Atlas web page: https://atlas.scharp.org/cpas/project/MTN/023%20and%20IPM%20030/begin.view?
.

a. Updated Visit Code Structure

In order to accommodate the additional study visits, the visit code structure has been updated from X.X to XX.X. The additional box allows sites to record study visit codes that have more than two digits (e.g., a participant comes in for her 20-week study visit, which has three digits and is classified as visit code 10.0). Below is an example, as shown on the updated Follow-up Visit Summary CRF.

The following CRFs have been updated with the new visit code structure:

1) Physical Exam (PX-1)
2) Follow-up Visit Summary (FVS-1)
3) Vaginal Ring Storage (VRS-1)
4) Ring Adherence (RA-1)
5) Ring Collection and Insertion (RCI-1)
6) Pelvic Exam (PE-1)
7) Laboratory Results (LR-1)
8) Specimen Storage (SS-1)
9) Follow-up ACASI Tracking (FCT-1)
10) Pharmacokinetics (PK-1)
11) Vaginal Practices (VP-1)
12) STI Test Results (STI-1)
13) HIV Confirmatory Results (HCR-1)
14) Pregnancy Report and History (PR-1)
15) Pregnancy Outcome (PO-1)
16) Pregnancy Outcome (PO-2)
17) Missed Visit (MV-1).

In addition, the visit code structure within the body of some CRFs has also been updated to the same format as mentioned above. For example, item 3 on the Vaginal Ring Storage CRF has an additional box in the visit code field structure as shown below.

The visit code field structures have been updated for the following CRFs:

1) Vaginal Ring Storage (VRS-1)—Items 2 and 3
2) HIV Confirmatory Results (HCR-1)—Item 2
3) Clinical Product Hold/Discontinuation Log (PH-1)—Item 1
4) Adverse Experience Log (AE-1)—Item 10
5) Participant Transfer (PT-1)—Item 3.

b. Updated Form Instructions

On the back of some CRF forms, instructions were updated to accommodate the additional study visits in protocol version 2.0. For example, on item 8 of the Enrollment CRF, the instructions have been updated to the following: “Record whether the participant has been randomized to complete the in-depth interview that takes place at the *24-week* Final Clinic Visit.” This was formerly the *12-week* final clinic visit.

The following CRFs have updated form instructions:

1) Enrollment (ENR-1) – Item 8
2) Follow-up Visit Summary (FVS-1) – Item 4
3) Pelvic Exam (PE-1) – Item 1
4) Pharmacokinetics (PK-1) – Items 1 and 2
5) Pelvic Exam Diagrams (non-DataFax) – General Information/Instructions.

c. Ring Collection and Insertion CRF (RCI-1), item 3a

The reference to the Final Clinic Visit was updated from Week 12 to Week 24, as shown below.

3a. Reason ring not dispensed:

- ☐ participant on clinical hold
- ☐ participant has been permanently discontinued from product
- ☐ participant declined study ring, specify: _____
- ☐ early termination
- ☐ 24-Week Final Clinic Visit
- ☐ other, specify: _____

d. Eligibility Criteria CRF (ECI-1), item 4d

Item 4d language was updated from "penile-vaginal" intercourse to "sexual" intercourse. This reflects the updated language in the Inclusion Criteria section in protocol version 2.0.

4. Reason(s) for ineligibility: *Mark all that apply.*

- ☐ 4a. <15 or >17 years old
- ☐ 4b. not Tanner stage 4 or 5 at Screening
- ☐ 4c. HIV infected at Screening or Enrollment
- ☐ 4d. no reported history of sexual intercourse at Screening

e. Enrollment CRF (ENR-1), item 8 and instructions

For Item 8, a third response option of "N/A" has been added. The form instructions have been updated to the following: "Mark 'N/A' if the participant was randomized to the in-depth interview, but was not selected to participate in the interview as the site had already completed all required interviews." This was done because, under protocol version 2.0, 6 participants per site will be randomized to complete in-depth interviews at the 24-Week Final Clinic Visit/Early Termination Visit. This was formerly 10 participants per site under protocol version 1.0. If a participant is randomized to the in-depth interview, but the site has already met their quota of 6 participants, mark "N/A".

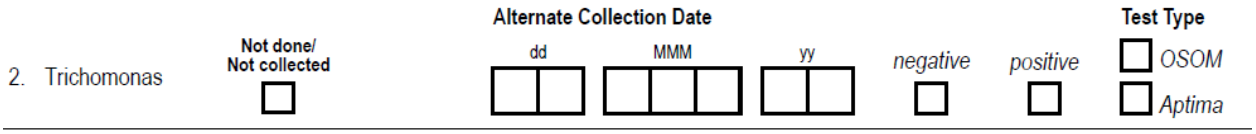
f. STI Test Results CRF (STI-1), items 1c and 2

i. Item 1c – Clue Cells

Per Data Communique #1, clue cells should be reported and marked as "positive" if 20% *or more* of the cells observed are clue cells. The 19-FEB-14 version of the form and its instructions incorrectly referenced ">" 20% clue cells.. The form has been corrected to show "≥" 20%.

ii. Item 2 – "Trichomonas" was updated to remove the "rapid test" line.

Also, the specific test types approved for study use - Aptima and OSOM - have been added. When recording a Trichomonas result, sites should mark which test type was used.



For previously documented Trichomonas results, sites will need to update the STI Results CRF (dated 19-FEB-14) by writing a note in the Comments section at the bottom of the form to indicate which test type was used.

g. New "Version 2.0 Reconsent" CRF

SCHARP has issued a new form, Version 2.0 Reconsent CRF, dated 27-FEB-15, to document whether a participant re-consents to protocol version 2.0. Completion of the form is required for each participant who provided informed assent/consent under protocol version 1.0 and is still participating in the study at the time her site begins implementation of protocol version 2.0 (regardless of whether or not the participant re-consents to protocol version 2.0).. (Participants who have already terminated from the study under protocol version 1.0 will not be asked to rejoin the study and will not be asked to re-consent under protocol version 2.0). The Version 2.0 Re-consent CRF should be completed at the visit when a participant either signs the version 2.0 assent/consent, or is asked but refuses to re-consent under protocol version 2.0. Completion of this form is expected at visits that fall between visit codes 2.0 and 8.0, inclusive.

The UAB, Fenway, Denver, and Bronx sites are expected to begin implementing the Version 2.0 Re-consent form when they begin implementing protocol version 2.0. This form is not applicable and should not be used at the Memphis and Pittsburgh sites, as they will receive site activation and begin study implementation under protocol version 2.0.

REMINDERS

None

CLARIFICATIONS

None

MTN-023/IPM 030 Data Communiqué #3

6 April 2015

This is official study documentation for MTN-023/IPM 030. Please circulate it among relevant staff for their review, print it, and place it in your MTN-023/IPM 030 SSP Manual in the Data Communiqués section. This document is considered part of the MTN-023/IPM 030 SSP manual.

UPDATES

1. Fenway, UAB, Denver, and Bronx Sites to Update In-depth Interview Item on MTN-023/IPM 030 Prescription

    a. Under protocol version 1.0, the in-depth interview was conducted at week 12. Under protocol version 2.0, the in-depth interview is conducted at week 24. As a result of this change, study prescriptions for participants at the UAB, Fenway, Denver and Bronx sites who reconsent to protocol version 2.0 will need to be updated. In addition, study prescriptions for participants at these sites who enroll under protocol version 2.0 will need to be updated (once a participant randomizes and the randomization envelope is opened). For these participants, please make the following update:

- In the "Participant selected to complete the in-depth interview at Week 12?" box, line through the "12" and write in "24". Initial and date the change. Please see below for an example.

Note: *this update does not apply to the following: participants who terminate the study under protocol version 1.0, participants who do not reconsent to protocol version 2.0, and participants at the Memphis and Pittsburgh sites.*

MTN-023/IPM 030 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:	University of Colorado Denver	CRS ID:	ATN Site 22
CRS Location:	Aurora, CO	Randomization #:	999
Participant selected to complete the in-depth interview at Week ~~12?~~ 24	No		

MP 27-MAR-15

b. Under protocol version 1.0, ten participants at each site were randomized to the in-depth interviews. Under protocol version 2.0, only six participants need to be randomized to the in-depth interviews. To account for this change, we ask that the Fenway, UAB, Denver, and Bronx sites complete six in-depth interviews each, according to the randomization assignments on the study prescriptions, then line through the "yes" randomization and write "no", initial and date, for all subsequent randomizations to the in-depth interview. Please see the example below.

Note: *this update does not apply to participants at the Memphis and Pittsburgh sites.*

MTN-023/IPM 030 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:	**University of Colorado Denver**	**CRS ID:**	**ATN Site 22**
CRS Location:	**Aurora, CO**	**Randomization #:**	**123**
Participant selected to complete the in-depth interview at Week ~~42~~? 24 MP 27-MAR-15	~~Yes~~ No MP 27-MAR-15		

2. SCHARP Staffing Update

Melissa Peda has assumed responsibility as sole SCHARP Project Manager on MTN-023/IPM 030. Please contact Melissa (mapeda@scharp.org) regarding any questions related to data collection or data management in MTN-023/IPM 030.

REMINDERS

None

CLARIFICATIONS

None

MTN-023/IPM 030 Data Communiqué #4

2 October 2015

This is official study documentation for MTN-023/IPM 030. Please circulate it among relevant staff for their review, print it, and place it in your MTN-023/IPM 030 SSP Manual in the Data Communiqués section. This document is considered part of the MTN-023/IPM 030 SSP manual.

REMINDERS

None.

CLARIFICATIONS

Documenting Abnormal and Normal Findings due to Unexpected or Expected Bleeding

Observation of any unexpected genital blood or bleeding is considered an abnormal finding. For example, bleeding that is prolonged or heavier than usual, per clinical judgment of the IoR or designee, this would be considered an abnormal finding. See SSP sections 7.9 and 8.2.1 for further guidance and clarification. "Abnormal findings" should be marked in Item 2 of the Pelvic Exam CRF and any associated findings should be marked in Item 2a. Unexpected genital bleeding should be documented as a reportable AE as well and an Adverse Experience Log (AE-1) CRF should 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, menstrual blood or cervical bleeding associated with speculum insertion or a vaginal swab and/or specimen collection judged to be within the range of normal, per clinical judgment of the IoR or designee, would not be reported as an abnormal finding. Thus, this is not a reportable adverse event. With expected bleeding, "no abnormal findings" can be marked on the Pelvic Exam (PE-1) CRF.

This guidance supersedes the current form instructions on the back of the Pelvic Exam CRF and should be used moving forward.

UPDATES

None.

Section 13. Study Reporting Plan

Table of Contents

The purpose of this reporting plan is to describe the reports that the MTN SDMC (SCHARP) plans to generate for MTN-023/IPM 030.

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 follow-up (if necessary) is taken; and
- To ensure the Protocol Team approves the plan prior to study initiation.

This reporting plan was prepared by the MTN-023/IPM 030 SDMC Project Manager in collaboration with other MTN-023/IPM 030 SDMC staff.

MTN-023/IPM 030 Statistical and Data Management Center (SDMC) Staff

Job Role	Name	Email Address
Protocol Statistician	Jingyang Zhang	jzhang2@scharp.org
Project Manager	Melissa Peda	mapeda@scharp.org
Statistical Research Associates	Danny Szydlo Marla Husnik	dszydlo@fhcrc.org marla@scharp.org
Operations Programmer	Brad Fischer	hfischer@scharp.org
Data Coordinator	Jenn Schille	jens@scharp.org
Lab Programmer	Katie Snapinn	ksnapinn@scharp.org
Clinical Affairs Safety Associate	Jenny Tseng	jenny@scharp.org

13.1 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 Atlas website, https://atlas.scharp.org

Following the tables is a description of each report that includes the purpose of the report, who will prepare the report, and specific components of the report.

Table 13-1: MTN-023/IPM 030 SDMC Reports Distributed via Email

Report Title	Distribution Frequency	Email Distribution List
Data Quality Control (QC)	Monthly, or as needed	• SDMC Project Manager • Site Staff as designated by each site
Clinical Data Quality Control (CQC)	As needed (as queries are identified)	• SDMC Project Manager • Site Staff as designated by each site
Subset of New Clinical Queries	Weekly	• SDMC Project Manager • PSRT members
Unresolved Adverse Experiences (AE) Listing	Monthly	• SDMC Project Manager • Site Staff as designated by each site
Unresolved Product Holds	Monthly	• SDMC Project Manager • Site Staff as designated by each site
LDMS Specimen Monitoring	Monthly	• SDMC Project Manager • Site Staff as designated by each site • Site LDMS Lab Staff • Network Lab Representative

Table 13-2: MTN-023/IPM 030 SDMC Reports Posted on Atlas

Report Title	Update Frequency	Atlas Viewing Area
Screen Out	Daily	Unsecure
Enrollment	Daily	Unsecure
Retention	Daily	Unsecure
Procedures Completion	Monthly	Unsecure
Data Management Quality	Monthly	Unsecure
Data Summary	Monthly	Unsecure
Missed Visit Listings and Summary	Daily	Unsecure
Protocol Deviations Listing and Summary	Daily	Secure

Protocol Safety Review Team (PSRT)	One week prior to PSRT call	Secure
Study Monitoring Committee (SMC)	As determined by the SMC	Secure

13.1.1 Data Quality Control (QC) Report

Purpose: To identify missing and inconsistent data.

Components: Quality control notes, overdue visit reminders, missing page reminders.

13.1.2 Clinical Data Quality Control (CQC) Report

Purpose: To identify inconsistencies/questions identified in safety or clinical data.

Components: Queries containing clinically-based questions about safety and clinical data.

13.1.3 Subset of New Clinical Queries

Purpose: To monitor a specific subset of AEs and product holds

Components:
- All Grade 3 or higher AEs including the lab events regardless of relationship
- All SAEs and AEs requiring an expedited report to DAIDs
- Any product hold CRF received with reason indicated

13.1.4 Unresolved Adverse Experiences (AE)

Purpose: To identify AEs which have been continuing for 90 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 more than 90 days.

13.1.5 Unresolved Product Holds

Purpose: To identify clinical product holds which have been continuing for 30 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 30 or more days.

13.1.6 LDMS Specimen Monitoring Report

Purpose: To identify inconsistencies in specimen storage data between information in LDMS and data recorded on CRFs.

Components: Site-specific listing of specimens with inconsistencies between the PTID, collection date, or visit month information in LDMS and the CRFs; specimens that are stored per CRF but not present in LDMS; specimens that are present in LDMS but not stored per CRF; specimens in LDMS from PTIDs who did not enroll.

13.1.7 Screen Out Report

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.

13.1.8 Enrollment

Purpose: To report participant accrual as reflected by data received and entered at the SDMC.

Components: Accrual data are presented 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.

13.1.9 Retention Report

Purpose: To report participant visit retention as reflected by data received and entered at the SDMC.

Components: By site and by visit, the number of expected participants who have completed the visit; who have not completed the visit; and have missed a required visit; the number of participants not expected.

13.1.10 Procedures Completion Report

Purpose: To provide information on completion of required study procedures during follow-up, and serve as an indication as to the amount of missing data from completed visits.

Components: Overall and by site, listing of number and percentage of required ("expected") study procedures that were completed at follow-up visits. Procedures are expected if the visit was completed (that is, not missed).

13.1.11 Data Management Quality Report

Purpose: To summarize site performance regarding key data management and data quality metrics.

Components: By site and overall, for cumulative and previous month time periods, the total number of CRF pages received, total number of QCs created, QC rate per 100 CRF pages,% QCs resolved (cumulative report only), % CRFs received within 7 days, and mean days to fax in AE Log.

13.1.12 Data Summary Report

Purpose: To summarize 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 monthly and cumulative data management quality data.

13.1.13 Missed Visit Listings and Summary

Purpose: To provide site-specific cumulative listings of all missed visits reported for the study, as well as summary reports (cumulative and for the past month) showing the total number of missed visits by site and for all sites total

Components: Site-specific cumulative listing of missed visits. A visit is considered missed if a Missed Visit CRF has been completed for that visit and the visit window has closed.

13.1.14 Protocol Deviations Listing and Summary

Purpose: To summarize reported protocol deviations reported at each site for a subset of the Protocol Team.

Components: Listing, by site, of reported protocol deviations as reported on the Protocol Deviation Log CRFs received at SCHARP. Frequency, by site, of the type of protocol deviations reported on the Protocol Deviation Log CRFs received at SCHARP.

13.1.15 Protocol Safety Review Team (PSRT) Report

Purpose: To help the Protocol Safety Review Team monitor study participant safety as reflected by adverse experiences reported to the SDMC.

Components: Cumulative AE, product hold, and pregnancy outcome data reported to SCHARP.

13.1.16 Study Monitoring Committee (SMC) Report

Purpose: To provide information on study conduct, ability to answer study objectives, and primary endpoint data to SMC members as required in preparation for scheduled reviews

Components: Summary by site and overall of study design and history, accrual, retention, demographics, baseline characteristics, data management quality, protocol deviations, and other components as requested by the SMC.

Section 14. Behavioral Measures

Table of Contents

This section contains information on behavioral research procedures performed in MTN-023; including the behavioral ACASI assessments, the In-Depth Interview (IDI) and SMS adherence assessment and correspondence.

14.1 Overview

Behavioral assessments will be captured through web-based ACASI, IDIs, and SMS assessments. All behavioral interviews are source documentation and must be maintained in accordance with the guidelines for other study documentation. As per Protocol Version 2.0, Letter of Amendment #01, dated 16 February 2016, all IDIs and SMS activities related to the secondary and exploratory endpoints of acceptability and adherence were discontinued in February 2016.

Table 1 outlines the timing (by study visit) and mode (by instrument) each behavioral assessment should be completed.

Table 1
Behavioral Assessments: Timing and Mode of Administration

Questionnaire	Mode of Administration	Visit
Baseline	ACASI	Enrollment (visit 2)
Follow-up	ACASI	12 & 24-Week Study Visit
In Depth Interview (IDI)*	Web Video interview	24-Week Final Clinic Visit or Early Termination Visit
SMS Messages*	Frontline Software & Cell Phone	Weekly

* Discontinued in February 2016

14.2 ACASI Behavioral Assessments

The baseline behavioral assessment and follow-up assessments will be captured through Audio Computer Assisted Self-Interview (ACASI) at the Enrollment visit and Weeks 12 and 24 study visits.

The baseline behavioral assessment will evaluate a participant's past sexual behavior, concerns about using the ring, HIV concerns and partner HIV status. Follow-up assessments will explore participant experience using the ring, concerns about the ring, partner experience and adherence. Adherence questions will evaluate the consistency and timing of treatment administration and factors influencing adherence.

Once the participant has been welcomed, staff should introduce themselves and complete the following:

1. Explain the ACASI procedure.
    a. Stress we are using ACASI to give as much privacy as possible.
    b. Emphasize the responses are kept confidential.
    c. Tell the participant what to expect during the ACASI interview.
2. Enter information into the Administrative Section.
3. Swivel the laptop's screen toward the participant.
4. Demonstrate the use of the touch-screen computer, headphones and stylus.
5. Verify the participant's comfort using the touch-screen computer and stylus.
6. Allow the participant to complete the practice questions, assisting her, if needed, to make sure she understands how to answer.
7. Once the practice has been successfully completed, ensure the participant has read and understands the statement encouraging her to respond to all questions as truthfully as possible.
8. Inform the participant that you will be just outside the interview room. Instruct her to let you know if she has questions and when she is finished with the questionnaire.
9. When ACASI is finished, thank the participant and make sure she returns the stylus or leaves it with the computer.
10. For ACASI questions or concerns, email: mtn023acasisupport@mtnstopshiv.org.

Detailed guidelines on ACASI equipment set-up, maintenance, trouble shooting and ACASI administration are addressed in the MTN 023 ACASI User's Manual, located on the MTN-023 Study Implementation Materials Webpage (http://www.mtnstopshiv.org/node/5444).

14.2.1 Data Collection: ACASI

Each participant will complete behavioral questionnaires by ACASI at the Enrollment, Week 12 and 24 visits. Each study site must have a computer connected to the internet and speakers with a headset. The computer must be in a private room where participants will not be interrupted or overheard. Select a location in a room with a door that closes to allow privacy for the participant.

Details on how to access the ACASI questionnaires are included in the ACASI User's Manual, located on the MTN-023 Study Implementation Materials webpage.

14.2.2 Missed Visits

Participants who miss their scheduled visit and ACASI may reschedule their visit, if within the visit window. Missed interviews should be noted in participant chart notes and every effort should be made to reschedule the interview. If the interview cannot be conducted within the visit window, the MTN-023 Behavioral Team coordinator (jndmoore@ucla.edu), and MTN-023 Management Team should be contacted to assess whether the interview should be conducted at a later date.

14.2.3 Interrupted Visits

Site staff should ensure that ACASI questionnaires are always completed at the appropriate scheduled visit, and that all ACASI data from a given questionnaire is collected during the visit. If a participant is interrupted and does not complete an ACASI questionnaire in one sitting, based on site staff judgment and length of interruption, she can complete the ACASI questionnaire later as long as it is **during the same visit**. In the case of a split visit, the ACASI may be completed on any day a participant is at the clinic during the same visit.

If participants need to briefly interrupt their computer sessions (i.e. attend to a call, go to the bathroom), at the discretion of the site staff, they can do so, and resume the ACASI where they left it, as long as the survey window remains open. However if the computer window is closed before the ACASI is completed, participants will need to start a **new** ACASI questionnaire from the beginning. If participants need to leave the clinic in the middle of the ACASI, resulting in a split visit, they must close the interview window and begin a new ACASI questionnaire when they resume the visit.

If duplicate ACASI questionnaires are present for the same PTID and date, the fully-completed ACASI questionnaire will be the one used in study analyses. These unique circumstances should be documented in the clinic chart notes and a brief description recorded on the applicable CRF (i.e. Enrollment, Follow- up ACASI Tracking).

14.2.4 Management of Errors on ACASI

Once an ACASI questionnaire is completed, no one can change the responses or administrative fields, including site staff. If errors are noted by site staff for the administrative section (or by participants to the site staff on the questionnaire section), notify the ACASI troubleshooting team via email at mtn023acasisupport@mtnstopshiv.org. Please include the following information in the message text: PTID, date, visit code, the name of the ACASI questionnaire and a description of the error. Also, to facilitate the troubleshooting process, please indicate in your email a description of the problem, including a copy of the error message(s), if any, and date and time of when the problem occurred. The ACASI troubleshooting team will assess the problem and communicate with

site staff about resolutions. If this occurs, it should be documented by keeping a record in the participant's file.

14.3 In-Depth Interview (IDI)

At the 24-Week Final Clinic Visit/Early Termination Visit, a subset of approximately 36 randomly selected participants across all sites, (approximately 6 per site) will complete an IDI. Participants are randomly assigned to the IDI via the randomization envelope and prescription at the Enrollment Visit. The interview will address study vaginal ring use and acceptability during the trial. These interviews will be conducted by a trained qualitative interviewer and will follow a semi-structured questionnaire guide and are anticipated to last approximately 45-60 minutes. These interviews will be conducted over the computer by a non-recorded video. If the participant consents, an audio recording will be made with a digital audio recording device that is operated by the qualitative interviewer (off-site at UCLA). The audio from the interview will be recorded and transcribed for analysis.

Through open-ended questions, this interview will explore the participant's overall experiences and feelings using the ring during the trial, including any physical, mental or emotional concerns or experiences she encountered; her experiences using the ring; her and her partner's attitudes towards the ring, including during sexual intercourse, preferences for HIV prevention.

The staff member should explain that these questions are being asked in person to more thoroughly explore the participant's feelings, and that her responses will be audio recorded but not video recorded.

Further description of the management of audio files, interview notes, debriefing reports and transcripts of the interviews is described below.

14.3.1 Scheduling the IDI

Study coordinators will email the off-site qualitative interviewer to inform her of all scheduled appointments so they can prepare for video calls. The interviewer will confirm the appointment via email. The interviewer should be informed of all changes or cancellations within 24 hours of the scheduled appointment, if possible. If last minute changes do occur, please notify the interviewer as soon as possible by phone or text message. Any scheduling changes will be confirmed by email.

To minimize scheduling conflicts between sites, the interviewer will enter available hours and confirmed appointments in an Outlook calendar shared between the sites. Study coordinators can view the calendar prior to scheduling appointments to make sure the interviewer will be available to do the interview.

To access the calendar, go to Outlook on the study provided laptop and sign in with account login below. Click on the "Calendar" tab at the bottom left.

For last minute changes to scheduling or to notify interviewer that participant is ready, call listed phone number or send text message. For non-urgent matters and advanced scheduling, use email.

Contact: Janell Moore Phone: (510)717-9952
Email: jndmoore@ucla.edu

Bronx Site Login
Email: Bronx023SMS@ucla.edu
Password: 023IDIConnect

Boston Site Login
Email login: Boston023SMS@ucla.edu
Password: 023IDIConnect

UAB Site Login
Email login: UAB023SMS@ucla.edu
Password: 023IDIConnect

Denver Site Login
Email login: Colorado023SMS@ucla.edu
Password: 023IDIConnect

Pittsburgh Site Login
Email: ph_pitt023sms@ucla.edu
Password: 023IDIConnect

Memphis Site Login
Email: ph_memphis023SMS@ucla.edu
Password: 023IDIConnect

14.3.2 Preparing for the IDI

Before each IDI the following should occur:

Qualitative Interviewer:

- Ensure the correct version of the guide and other supplemental tools (e.g. ring model or picture to use as a reference for describing issues related to the ring) are ready for use.
- Ensure the internet-based video system (ReadyTalk) is ready and connected and the interviewing space is ready.
- Contact the site to confirm the visit and time of the IDI.

Site:

- Ensure the participant was randomized to the IDI on the Randomization Envelope
- Ensure the computer with a webcam is available in a private space, and has a headset with microphone plugged into the computer that is operational.
- Ensure the internet-based video system (ReadyTalk) is ready and connected.

14.3.3 Data Collection: IDI

For the IDI, each study site must have a computer connected to the internet with a video camera and speakers with microphone or headset. The computer must be in a private room where participants will not be overheard during the interview. Select a location in a room with a door that closes to allow privacy for the participant and to allow the participant and interviewer to hear each other without noise disturbance. The participant should be able to sit comfortably and be seen on the video camera by the interviewer, and be able to see the interviewer on the screen. A neutral background behind the interviewer and the participant is preferable. To allow better viewing of the participant and interviewer, they should not be sitting in front of a bright window or other light that would disrupt the camera.

14.3.4 Initiating and Conducting the Video Interview

Prior to conducting any video interviews, the interviewer will verify that each site has completed video interview set up and ensure that all necessary add-on software is installed in the internet browser of the site's interview computer.

The site staff will contact the interviewer to let her know that the participant is ready. The interviewer will initiate a meeting in ReadyTalk and send an email invitation to the appointed site staff. The site staff will click on the link in the email from the study laptop to join the meeting, log into the meeting and turn on the video feed. Once the connection is established and the video feed is running, the site staff will click to enlarge the video window. The site staff should help the participant get set up at the computer with the headset. The site staff will then leave the room and close the door.

The interviewer will welcome the participant to the IDI and review the IDI introductory checklist which reviews the content, length and confidentiality of the interview and ensures that the participant agrees to audio recording the session. If she agrees, the interviewer will start the recording. Following the last question on the IDI, the recording will be stopped. If she does not agree to audio recording, the interviewer will take long hand notes.

At the end of the interview, the interviewer should quickly review the guide and her notes for completeness and clarify with the participant any unclear parts or gaps in the notes.

Once the interview is done, the interviewer will thank the participant, and ask that they bring the site staff back into the room. The interviewer will confirm with the site staff that the in-depth interview has been completed and the interviewer will then end the video meeting. The interviewer will inform site staff of any potential adverse events (AEs) or social harms (SH) reported during the IDI.

Then the interviewer can further expand her notes (on the same day) to ensure completeness of the information, and complete a Debriefing Report that will be circulated for review to the behavioral qualitative team.

If any participant randomized to the IDI discontinues study participation early, or has a modified 24- Week Final Clinic Visit, but has completed at least 1 month of study, she may complete the IDI at study exit.

14.3.5 Qualitative Data Management for IDIs

14.3.5.1 Audio Files

The audio recording will be made with a digital audio recording device that is operated by the qualitative interviewer off site (BRWG). The audio recording will be completely separate from the computer video conference (that is not recorded).

Following the interview or discussion, the audio file should be uploaded onto a password protected hard drive. Audio files of IDIs will be destroyed following finalization of transcripts (transcript finalization process described below). The destruction process will be the responsibility of the BRWG study team. The audio recordings will be deleted from the server and a log will be kept noting the file, the date deleted, the signature of the staff responsible for the deletion, and a signature of another team member who witnesses the deletion.

14.3.5.2 Interview Notes

When an IDI is conducted, notes will be taken during each session to supplement the audio recording (or replace, if recording doesn't work or is refused). Immediately following the IDI, the interviewer reviews the guide, and adds or expands on notes and comments as needed. Interview notes will be filed in participant files in the BRWG offices that will be stored in a locked cabinet.

14.3.5.3 Debriefing Reports

On the same day as the IDI, the Interviewer should complete a Debriefing Report (DR) which will list basic information about the session and provide a summary report of the interview that can be used in "real time." A DR template will be developed by BRWG Debriefing reports may be maintained electronically until final versions are provided by BRWG as described below.

At the BRWG, the DR will be read and reviewed by data team members and queries will be made on the DR using MS Word's comment feature within **one week** of receipt of the file. The following are examples of queries:

- Problems such as typos that lead to ambiguous meaning (e.g. "sore the medication" vs. "store the medication"), confusing terms or missing /potentially incorrect data
- Sentences that are unclear
- Clarification of local terminology or context
- Within **one week**, the Interviewer is asked to correct or clarify any problems identified directly in the DR text using track changes and confirm the status (e.g. 'done', 'corrected', 'not needed', etc.) of each query within a comment bubble.
- When the revised information is received, the reviewer, the Qualitative Data Manager or a designated qualitative data team member reviews the corrected areas and deems the issue resolved or further follows up with the Interviewer until all necessary changes are made on the DR.
- Once the BRWG finds no additional issues, the BRWG will accept all changes, remove all comment bubbles and email the final clean DR to the Behavioral Qualitative Team. This final version of the DR should be printed and filed in the participant chart with the BRWG.
- After the DR is finalized, it will be circulated to the appropriate members of the Protocol and Management Teams.

14.3.5.4 Transcription

The audio recordings will be transcribed and will undergo the following QC process:

- Each transcript will be reviewed by a member of the BRWG's data team, and queries will be made on the transcript using comment bubbles. The QC may include the identification of the following:
    - Problems such as typos that lead to ambiguous meaning, confusing terms or missing/ potentially incorrect data
    - Sentences that are unclear
    - Clarification of local terminology or context
- Responses to queries will be made by another member of the BRWG data team by listening to audio recordings if necessary, Responses will be recorded either through changes directly in the transcript using track changes or through using the comment bubble in the reviewing mode of MS Word, when in-text changes are unable to be made. When changes in the text reflect content that was not spoken verbatim by the participant or interviewer, they will be inserted in [brackets].
- A designated BRWG staff member reviews the corrected areas and deems the issue resolved or further follows up as needed until all necessary changes are made.

Once the BRWG finds no additional issues, the BRWG will accept all changes, remove all comment bubbles, and finalize the transcript.

14.3.5.5 File Naming Conventions

All data files should be named according to a standard naming format. Each time a document is edited, the editor should add their initials to the filename without changing any other part of

the filename. For the first iteration of the file that is sent to the BRWG for review, there is no need to include the editor's initials. It is only upon subsequent review (QCing) that this occurs.

File Naming Conventions:

Initial format: [Interview Mode]_[PTID]_[Data Type]_[Date of IDI]

Query format: [Interview Mode]_ [PTID]_[Data Type]_[Date of IDI]_[Initials]

Final format: [Interview Mode]_ [PTID]_[Data Type]_[Date of IDI]_FINAL

For example, when reviewed for the first time, the IDI transcript ***"IDI_1001_Transcript_18NOV14"*** would become ***"IDI_1001_Transcript_18NOV4_CM"*** and ***"IDI_1001_Transcript_18NOV14_CM_NM"*** for the second revision. Once the document is finalized, all initials will be removed from the name and replaced with the word "FINAL."

14.3.5.6 Data Tracking

A Qualitative Data Tracking Log will be completed by the BRWG to maintain record of each audio file, DR and transcript that is submitted along with details regarding the submission date, query status, and finalization date.

14.4 SMS Messaging

Detailed instructions for SMS adherence assessment and correspondence are located in Section Appendix 14-4.

14.5 Special Cases and Technical Issues

14.5.1 Technical Problems Preventing ACASI or IDI Completion

In the event of technical problems (i.e. server or power outage) that would preclude a participant's ability to complete an ACASI questionnaire online, hard copy versions of ACASI questionnaires will not be available. These unique circumstances should be documented in the chart notes and a brief description recorded on the applicable CRF (i.e. Enrollment, Follow-up ACASI Tracking).

In the event of technical problems that interrupt or hinder a participant's ability to complete an IDI, 3 attempts to reconnect will be made and if none are successful the IDI will be rescheduled. These unique circumstances will be documented in chart notes and a brief description of the cause of the rescheduling will be recorded in the applicable CRF.

14.6 Staff Training

14.6.1 ACASI

Site staff that will be assisting participants with ACASI is required to complete at least 2 practice sessions for each instrument.

For testing, please access questionnaires through the websites indicated above. The

following test PTIDs should be used:

Administrator ID's assigned by site:

- 100-199 – New York
- 200-299 – Birmingham, Alabama
- 300-399 – Denver, Colorado
- 400- 499 – Boston, Massachusetts
- 500- 599 – Pittsburgh, Pennsylvania
- 600- 699 – Memphis, Tennessee

Test PTIDs:

- 999-00062-2
- 999-00063-5
- 999-00064-8
- 999-00065-0
- 999-00066-3
- 999-00067-4
- 999-00068-9
- 999-00069-7
- 999-00070-1

Upon completion of testing at each given site, an email should be sent to the MTN-023 ACASI alias mtn023acasisupport@mtnstopshiv.org indicating the number and type of tests completed, name of staff members completing test questionnaires, and a description of any problems encountered.

14.6.2 IDI

Site staff that will be assisting participants with the IDI will be instructed in the use of the ReadyTalk video conference system. Prior to conducting any IDI at a site, the qualitative interviewer will assist site staff in setting up any software required to use ReadyTalk on the interview computer, and will instruct staff on how to connect participants to a video for the IDI. Site staff will participate in a mock interview with the qualitative interviewer to ensure the video system is operating correctly.

Prior to conducting any IDIs, clinic staff and the qualitative interviewer will be trained on the procedures for documenting and following up on reports of potential Adverse Events or Social Harms that participants may report during the IDI. The qualitative interviewer will be trained on the appropriate DAIDS procedures for safety reporting and file maintenance.

14.6.3 SMS

Site staff who will be assisting participants with the SMS will be provided detailed instructions on what information is needed by BRWG to set up messaging to participants. Prior to beginning SMS activities, a member of the behavioral team will walk site staff through the process. Site staff will participate in a test message exercise to ensure the system is operating correctly.

Detailed directions on the SMS setup and messaging procedures can be found in Appendix 14-4, at the end of this section. Site staff should familiarize themselves with these procedures

and are welcome to test out the system prior to their formal training dat

Section Appendix 14-1: Quick Tips for In-Depth Interview

Scheduling

1. Schedule IDI in Outlook calendar:

- **Login email:**

  For UAB: UAB023SMS@ucla.edu

  For Boston: Boston023SMS@ucla.edu

  For Aurora: Colorado023SMS@ucla.edu

  For Bronx: Bronx023SMS@ucla.edu
  For Pittsburgh: ph_pitt023sms@ucla.edu
  For Memphis: ph_memphis023sms@ucla.edu

- **Password for all sites (case sensitive):** 023IDIConnect

2. Interviewer will indicate available hours in the shared Outlook calendar and site staff will be able to see conflicts in scheduling between each site.
3. Each site should add their appointment with their assigned colors as follows:
   - UAB: Green
   - Boston: Blue
   - Aurora: Orange
   - Bronx: Purple
   - Pittsburgh: Pink
   - Memphis: Red
4. Interviewer will confirm the appointment via email.
5. Notify interviewer of all changes or cancellations within 24 hours of the scheduled appointment, if possible.
6. If last minute changes do occur, please notify interviewer as soon as possible, by phone or text message.

Preparing for Interview

- Ensure the computer with a webcam is available in a private space, and has a headset with microphone plugged into the computer that is operational.
- Ensure the video system is ready and connected.
- Once participant is ready, notify interviewer by phone.

Initiating the Video Interview

- Interviewer will initiate a meeting by sending an email to the designated site staff.
- Click on the link in the email to join the meeting, log into the meeting using the study laptop, click join via computer, and turn on the video feed.
- Once the connection is established and the video feed is running, click to enlarge the video window.
- Help the participant get set up at the computer with the headset.
- Leave the room and close the door.

Ending the Video Interview

- Participant will notify you when the interview is done.
- Disconnect from the meeting

Section Appendix 14-2: SMS Messaging Guidelines

This section contains information on behavioral research procedures performed in MTN-023 around SMS message texting of participants to assess ring adherence and provide clinic visit reminders.

1. Overview

- These directions are intended to guide site staff on how to collect participant contact information in order for the participant to receive weekly SMS from BRWG staff.

Under the MTN-023 protocol, SMS will be sent to participants, weekly for the duration of the study. While date and timing will vary based on participant preference, messages will be programmed to send on the same day and at the same time every week.

Once participant cell phone numbers are collected, staff will test the participant's phone with the participants at enrollment.

2. Testing Participant Phone

Each participant who has consented to participate in the SMS notification option will have their cell phone capability tested at enrollment. While the participant is present, staff will complete the following steps to ensure the information provided is accurate and the SMS system will work properly with the participant's phone. Complete the following:

Site staff will send a text to the participant. The text should read "Test". Site staff will wait with participant to make sure she receives the text.

Once test text is received, participant will then be asked to respond to the text. Participant should respond with any number, for example, "1"or "2".

Site staff will wait to assess if participant is able to respond to texts.

3. Saving BRWG Contact in Participant Phone

BRWG staff will send each participant a weekly text. In order for participants to recognize who is sending the text, site staff will instruct participants to save the number from which BRWG will send text as a contact in their phone.

BRWG will send participant weekly texts using the phone number **(510) 619-1067.** This number was generated by the web-based text messaging software company Frontline. This is not the official contact for BRWG staff. This number will be used for the sole purpose of sending and receiving text for the study.

Study staff will inform participants that they can save the number in their contacts under a name they are most comfortable with, for example, "BRWG" or "Study".

4. Sending BRWG Participant Contact Information

Immediately following the enrollment visit of each new participant, study staff will provide BRWG with the participant's basic contact information (date or enrollment, PID and cell phone number).

BRWG will provide each site with a SMS contact tracking form. Site staff will fill this form out at the end of each new enrollment visit and will email the form to BRWG staff Janell Moore at jndmoore@ucla.edu

5. SMS Problem Troubleshooting

The study staff should contact Janell Moore via email at jndmoore@ucla.edu if they have any problems or questions about testing the participant's phone or filling out the contract tracking form. BRWG staff will contact the site staff if there are any problems with the contact information provided by the participants or any issues with sending/receiving texts