Section 1. Introduction

Document Revision History

Version	Date	Summary of Changes	Author
V00.01	26 Mar 2018	Initial Draft	Amber Blackmon, Clinical Trial Lead
V00.02	13 Apr 2018	PM Review	Jessica Kappes Clinical Project Manager II
V00.03	30 Apr 2018	Revised per external team review	Jessica Kappes Clinical Project Manager II
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This section specifies the sources of procedural information available to study staff, the responsibilities of the Principal Investigator and the process by which the site will be approved to initiate implementation of MTN-044/IPM 053/CCN019.

1.1 Current Protocol Specifications

The table below documents the history of the MTN-044/IPM 053/CCN019 protocol, along with any Clarification Memos and Full Amendments, if applicable, all of which are considered Essential Documents. A copy of each document should be available to staff and a copy should be maintained in site essential files.

Document	Date
MTN-044/IPM 053/CCN019 Protocol, Version 1.0	20 February 2018
MTN-044/IPM 053/CCN019 Protocol, Version 2.0	07 June 2018

Protocol Version 1.0 was IRB approved. However, this version was considered a draft by IPM and the FDA. Protocol Version 2.0 is the final version.

Sites are expected to operate under the protocol version and associated Clarification Memos and/or Letters of Amendment that are currently approved by the local institutional review board/ethics committee (IRB/EC). To ensure this section reflects the current specifications of

the protocol, upon issuance of any future protocol Clarification Memo (CM) or Protocol Amendment, specifications listed above will be updated accordingly. These documents are available on the MTN-044/IPM 053/CCN019 LiveTrial Home.

1.2 Procedural Information

The Study Specific Procedures (SSP) Manual serves to supplement the protocol. It does not replace or substitute the protocol or its contents. In the event this manual is inconsistent with the information and guidance provided in the protocol, the specifications in the protocol will take precedence. In the event study implementation questions are not adequately addressed by the study protocol or this manual or if any inconsistencies between the two documents are identified, please notify the in-house CRA, Holly Rollins at hrollins@healthdec.com.

Sites should contact the in-house CRA first for general questions on protocol implementation or study procedures, including clinical, lab, product, and/or CRF completion guidance. If the in-house CRA cannot be reached, you may then contact the Clinical Trial Lead, Amber Blackmon at ablackmon@healthdec.com.

Contact details for all of the above listed individuals are listed on the MTN-044/IPM 053/CCN019 LiveTrial Homepage.

1.3 Principal Investigator Responsibilities

MTN-044/IPM 053/CCN019 must be conducted in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (GCP). In addition, MTN-044/IPM 053/CCN019 must be implemented in accordance with all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Copies of all such regulations, policies, and guidelines should be maintained in on-site essential document files.

The Principal Investigator at each study site must sign the Protocol Signature Page and a U.S. Food and Drug Administration (FDA) Form 1572 to formally indicate his/her agreement to conduct MTN-044/IPM 053/CCN019 in accordance with the provisions of the study protocol, and applicable US regulations. The Principal Investigator may delegate their obligations and responsibilities for conducting MTN-044/IPM 053/CCN019 to other study staff members. However, in doing so, this delegation does not relieve the Principal Investigator of his/her ultimate responsibility for all study procedures performed and all study data collected. Delegation of Principal Investigator responsibilities must be formally documented throughout the period of study implementation on the site's Delegation of Authority (DoA) log. The obligations and responsibilities assumed by the Principal Investigator when signing the FDA Form 1572 are listed on the form itself. No other staff member should fulfill the Principal Investigator's role in the Principal Investigator's absence. Full responsibility and authority over the protocol by anyone other than the Principal Investigator may only take place if an additional 1572 is completed and submitted.

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

Consistent with the regulations, guidelines, and policies cited above, the site Principal Investigator must obtain and maintain IRB/EC approval of MTN-044/IPM 053/CCN019 throughout the period of study implementation. All sites are encouraged to request an acknowledgement of receipt for all documents submitted to their IRBs/ECs and to request that IRBs/ECs note the effective and expiry dates of all approvals. Documentation of all correspondence to and from all responsible IRBs/ECs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in on-site essential document files.

1.4 Study Activation Process

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

- obtain approval to conduct MTN-044/IPM 053/CCN019 from all required local regulatory authorities and IRBs/ECs,
- complete study activation requirements, and be issued a Site Activation Letter from a representative at Health Decisions.

Detailed information on the requirements of pre-implementation steps are summarized in the MTN-044/IPM 053/CCN019 Activation Checklist. Health Decisions will notify sites (on a site-by-site basis), when all activation requirements have been met by issuing a Site Activation Letter.

Section 2. Documentation Requirements

Document Revision History

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V00.01	26 Mar 2018	Initial Draft	Amber Blackmon, Clinical Trial Lead
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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-044/IPM 053/CCN019.

2.1 Essential Documents

The HD SOP titled “Document Management” 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 site regulatory binder will be provided by Health Decisions. This 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.
- 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 2.4.
- 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-044/IPM 053/CCN019 Confidential Subject ID Log and Screening and Enrollment Log must be maintained throughout the duration of the trial.

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

2.2 Financial Disclosure Forms

Each clinical investigator listed on the Form 1572 must disclose any financial interests that may be affected by the outcome of the research or attest to the absence of relevant significant financial interests. Per 21 CFR 312.53, financial disclosure must be completed prior to study involvement. The Principal Investigator and site Regulatory Coordinator must ensure that ***prior to*** completing (adding or removing investigators) and signing the FDA Form 1572, all investigators listed on the form must complete and sign the study-specific financial disclosure form (FDF). In addition, investigators listed on the current FDA Form 1572 must submit a new FDF if their financial interest changes throughout the study.

A blank FDF is available on the MTN-044/IPM 053/CCN019 LiveTrial Homepage. All items can be entered electronically except for the signature and date.

At the beginning of the study and throughout study duration, whenever an FDF is completed, sites should send this form to Health Decisions In-House CRA, Holly Rollins, hrollins@healthdec.com.

2.3 Participant Research Records

MTN-044/IPM 053/CCN019 study sites must maintain adequate and accurate participant research records containing all information pertinent to each study participant. See protocol section 13.6 for further information regarding confidentiality of participant information; participant charts should be stored in locked file cabinets with access limited to authorized study staff.

2.3.1 Concept of Source Data and Source Documentation

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

The term **source data** refers to all information in original records and certified copies of original records related to clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the trial (including all screening and enrollment activities). Source data are contained in source documents (e.g., original records or certified copies).

The term **source document** refers to original documents, data, and records (e.g., hospital records; clinical and office charts; laboratory records and notes; memoranda; participants' diaries and/or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies of transcriptions certified after verification for accuracy and completeness; microfiche; photographic negatives; microfilm or magnetic media; x-rays; participant files; case report forms (CRFs), 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.

2.3.2 Required Source Documentation

For MTN-044/IPM 053/CCN019, participant research records should consist of the following source documents:

- Chart notes
- Documentation that the participant provided written informed consent to screen for and participate in the study prior to the conduct of any screening or study procedures
- Documentation that the participant met the study's eligibility criteria
- Prescription documentation
- A record of the participant's use of the investigational study product
- Pharmacy investigational product accountability, dispensing and chain of custody records (maintained in the study site pharmacy), as well as clinic study product accountability documentation (maintained in the study clinic)
- A record of all contacts, and attempted contacts, with the participant
- A record of all procedures performed by study staff during the study (e.g. on visit checklists and/or other site-specific procedural flow sheets or chart notes)
- Local laboratory testing logs and result reports, or any other document defined as a source document for a test result
- Study-related information on the participant's condition before, during, and after the study, including:
  - Data obtained directly from the participant (e.g., interview and/or other self-reported information)
  - Data obtained by study staff (e.g., exam and lab findings)
  - Data obtained from non-study sources (e.g., non-study medical records)
- Other source documents (e.g., site-specific worksheets, logs)

Detailed information on proper completion, maintenance, and storage of product dispensing documentation is provided in SSP Section 6 and in the MTN-044/IPM 053/CCN019 Pharmacy Study Product Management Procedures Manual. Detailed information on proper completion of CRFs, is provided in the CRF Completion Guidelines provided by SCHARP.

2.3.2.1 Chart Notes:

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

- Visit date at which a contact takes place or at which a particular procedure takes place
- Visit type (scheduled, interim, etc.)

- Purpose of the visit and location of the contact if other than the research clinic
- General status of the participant at the time of the visit

Chart notes should also be used to document the following:

- The screening and enrollment informed consent process (if an Informed Consent Coversheet is not used)
- Procedures performed that are not recorded on other source documents
- Additional information related to clinical exam findings to ensure appropriate follow-up
- Study-specific counseling sessions and any associated referrals that are not documented on other source documents
- Other pertinent data about the participant that are not recorded on other source documents and/or any clarifications or information needed to supplement data recorded on a CRF
- Reason(s) why protocol-specified procedures were not performed
- Contact attempts to follow up on participants who missed a scheduled study visit

2.3.2.2 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.

2.3.2.3 Case Report Forms (CRFs):

See SSP Section 11 for further details regarding the use of case report forms (CRFs) with the Medidata Rave data management system. As shown in the Source Documentation SOP template, CRFs have been designed to be used as source whenever possible. Prior to study activation, each study site will 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

2.3.3 Protocol Deviations

It is required that all protocol deviations be documented in participant records, along with efforts made to correct and prevent similar deviations in the future.

For this study, the Protocol Deviation Log CRF will be used to document each reportable deviation identified. Missed visits are considered protocol deviations, 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 non-adherence will be completed if a participant reports more than three days of non-product use during follow-up. Sites should document when the non-use occurred in the 'description' section of the Protocol Deviation Log CRF.

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

Protocol deviations should be reported within 7 days of site awareness, even if all of the actions/plans are still in-progress. If there is a question as to whether a deviation has occurred, or how it should be documented, the in-house CRA should be contacted at hrollins@healthdec.com.

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

2.3.4 Document Organization and Participant Confidentiality

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

Study-related documentation collected during the screening process should be stored in a file folder/binder for each potential participant. All screening documentation — for potential participants who eventually enroll in the study as well as for those who do not enroll or "screen fail" — 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.

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. 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 must be secured with password protected access systems. Any lists, appointment books, or other documents that link PTIDs to other participant identifiers should be stored securely (locked cabinet/drawer if hard copy; password protected if electronic). When in use, documents that link PTIDs to other participant identifiers should not be left unattended or otherwise accessible to study participants, other study clinic patients, or any other unauthorized persons.

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

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

Study clinic staff will contribute to the documentation of product provision and chain of custody as described in SSP Section 6.

The specifications related to document security and participant confidentiality described in Section 2.3.4 also apply to records maintained in the study pharmacies. All records must be stored securely in the pharmacies with access limited to authorized study pharmacy staff only.

The following essential documents should be maintained in study site pharmacies:

- Current Protocol
- Investigator's Brochure for the DPV-LNG ring: current version and any updates
- Current FDA Form 1572
- Current list of authorized prescribers and staff authorized to sign Prescriptions and Vaginal Ring Request Slips (names and signatures)
- Pharmacy Establishment Plan (MTN LOC Pharmacist approved)
- Pharmacy Study Product Management Procedures Manual and applicable SOPs for investigational study product management and Chain of Custody
- Product shipping and receipt documentation, product storage temperature logs, and investigational product accountability records
- Subject-specific records (including prescriptions and ring request slips, record of receipt of participant study product and documentation of unused product returns)
- Monitoring visit reports
- Communications with site clinic staff, communications with the MTN Pharmacist, IPM Clinical Supply Coordinator and/or product distributor
- Communications with site clinic staff, IPM, or other communications or locally-required administrative, operational, and/or regulatory documentation

2.5 Record Retention Requirements

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

All records must be retained on-site throughout the study's period of performance. Study product records must be stored in site pharmacies, with access limited to authorized study pharmacy staff only. 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 NICHD.

Section 3. Accrual and Retention

Document Revision History

Version	Date	Summary of Changes	Author
V00.01	09 Apr 2018	Initial Draft	Amber Blackmon, Clinical Trial Lead
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This section provides information on requirements and procedures for recruiting participants in MTN-044/ IPM 053/CCN019. This section also presents information related to definitions, requirements, and procedures for participant retention.

3.1 Pre-Screening Procedures

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

3.2 Participant Accrual

Approximately 24 participants will be recruited at one US site. The accrual period is expected to last approximately 6 months. Site staff should make every effort to complete accrual at a rate of about 4 participants per month.

Screening and enrollment data will be captured on case report forms (CRFs). Site staff will complete the Eligibility Criteria CRF (CRF) in the Medidata Rave study database for each participant once she enrolls or screen fails for the study. Please see Section 13 of this manual for more details on SCHARP Screen Fail and Enrollment Reports.

3.2.1 Accrual Tips

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

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

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

Staff responsibilities include the following:

- Designating someone who is responsible for tracking accrual rates and managing recruitment efforts over time
- Hold biweekly or monthly 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
- Likely to attend all study visits, respond to SMS messages, and adhere to protocol requirements, including abstaining from vaginal products/practices

3.2.2 Participant Accrual SOP

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

- Site-specific accrual targets

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

3.3 Participant Retention

The term "retention" generally refers to completion of follow-up visits and procedures as specified in a study protocol. This definition must be operationalized for any study, and operational definitions usually reflect the primary objectives and endpoints of a study. For MTN-044/IPM 053/ CCN019, two retention measures are planned to be used. Additional retention measures may be defined and used during the study if desired by the Protocol Chairs 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 the visit window) divided by the number of visits expected for all participants. A visit is considered expected for a participant once the visit 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 visit window, but make up missed visit procedures at an interim visit or at the next scheduled visit will not be considered retained for the missed visit. However, they will be considered retained for the next scheduled visit if it is completed within the visit window. Thus, retention rates can fluctuate over time and across visits.

3.3.1 Retention Requirements

The 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. Missed visits also result in missing laboratory evaluations. To avoid these problems, and thereby avoid bias in the study results, high participant retention rates must be maintained throughout the study.

3.3.2 Participant Retention SOP

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

- Site-specific retention goals
- Methods for tracking actual retention versus retention goals and for the timely evaluation of the utility of retention methods
- Site-specific definition of “adequate” locator information (for purposes of determining participant eligibility) and procedures for obtaining and updating locator information
- Visit reminder methods and timeframes
- Methods and timeframes for identifying when a visit has been missed and planned retention methods
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

3.3.3 Locator Information

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

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

Study staff should view every participants’ 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 and/or visit checklists that they reviewed the locator information with the participant at every visit. Any updates to the locator form should use standard GCP corrections with initials and date of the staff member making the changes.

3.3.4 Retention Tips

Some additional strategies for maximizing participant retention are as follows:

- Dedicate adequate staff time and effort to retention efforts.

- Emphasize the value of the participant's involvement in the study during the study informed consent process and subsequently at follow-up visits. When participants complete scheduled visits, acknowledge and compliment their commitment, time, and effort devoted to the study.
- Develop rapport and ensure participants feel welcome and comfortable during their visits.
- Consider comfort of the waiting area and clinic rooms, especially any areas where participants may spend long days while waiting to provide samples.
- Make use of all available contact methods (e.g. phone, mail, e-mail, etc.). Also make use of other available locator information sources, such as phone and postal directories and other public registries.
- Use tracking systems to identify when participants' scheduled visits are due and/or overdue. Establish routine mechanisms to remind both study staff and participants of upcoming scheduled visits.
- Prepare a calendar of scheduled visits for each enrolled participant, based on her enrollment date, or offer a planner/calendar as an incentive and note all study appointments in the planner/calendar. Note the dates of all scheduled visits in the participant's file for easy reference. Confirm the scheduling of the next visit at each follow-up visit and give the participant an appointment card with the scheduled visit date and time noted.
- For participants who demonstrate a pattern of late or missed appointments, schedule appointments as early in the day as possible and develop systems for providing extra reminders to these participants, if needed.
- Follow-up on missed appointments with an attempt to re-contact/re-schedule (preferably on the same day). Continue these efforts per the local retention SOP until contact is made.
- Keep participants and community members up-to-date on study progress to foster a sense of partnership and ownership of the study
- 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.

Section 4. Informed Consent

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This section provides information on informed consent procedures for MTN-044/IPM 053/CCN019. This study utilizes one study informed consent (Screening, Enrollment, and Long-term Storage and future testing).

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

4.1 Overview of Informed Consent Requirements and Procedures

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

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

Based on the technical and regulatory reviews that are completed as part of the protocol development and study activation processes, there is adequate assurance that once Health Decisions has activated a site for study implementation, site-specific informed consent forms specify all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate informed consent form. It is the responsibility of the Principal Investigator and designated study staff to perform the following:

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

4.2 Site-Specific Informed Consent Forms

A sample informed consent form (ICF) is provided by the study team. Sites are responsible for adapting the sample as needed for local use. Local adaptation may include reformatting the consent forms in accordance with local IRB/EC requirements. All must be reviewed and approved by Health Decisions prior to IRB/EC submission.

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

4.3 SOP for Obtaining Informed Consent

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

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

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

4.4 Informed Consent for Screening and Enrollment

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

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

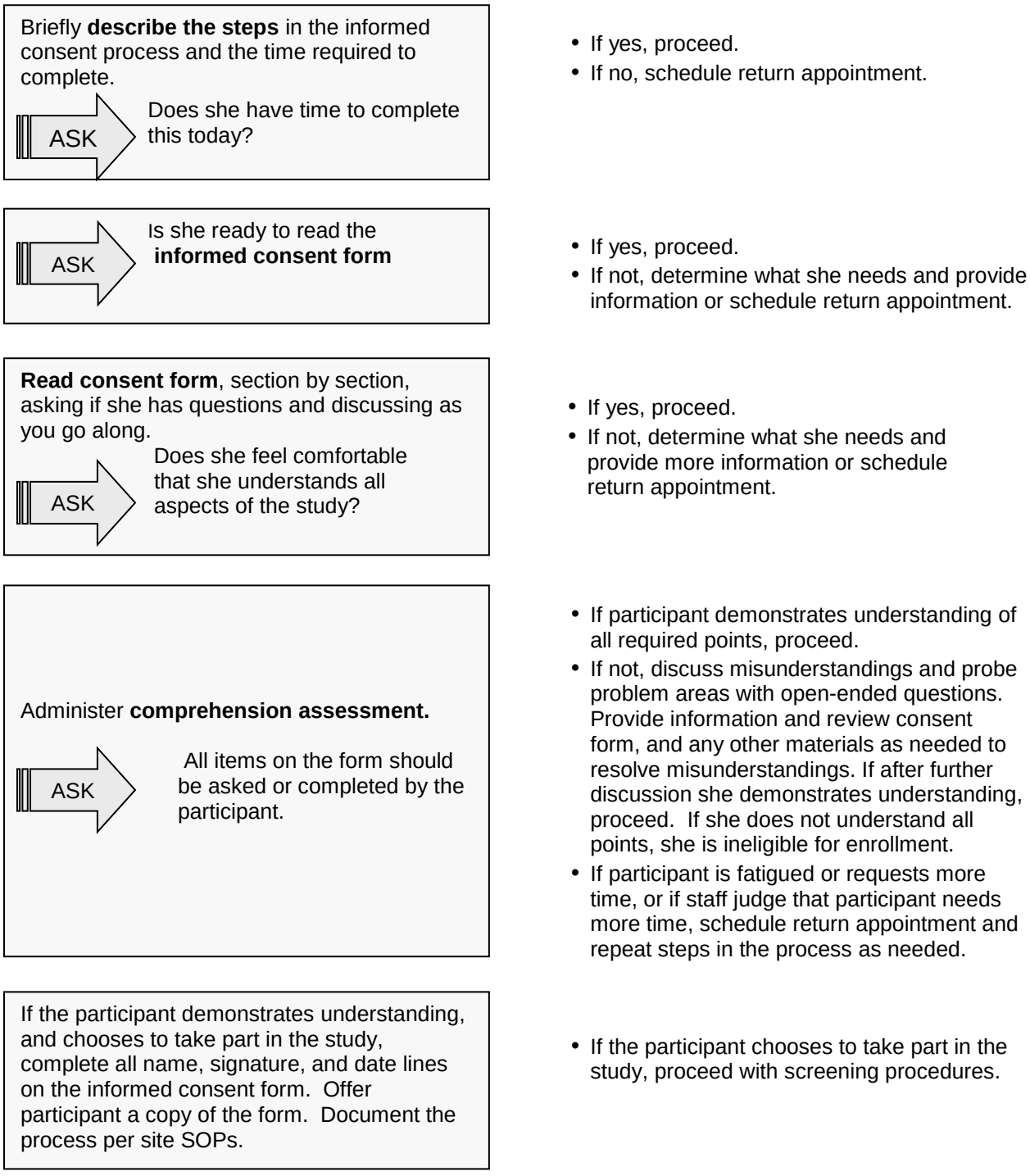
An overview of the standardized approach to the informed consent process is provided in Figure 4-1. Additional details related to key steps in the process are provided in the remainder of this section.

4.4.1 Informed Consent for Specimen Storage and Possible Future Research Testing

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

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

Figure 4-1
Overview of MTN-044/IPM 053/CCN019 Informed Consent Process



4.5 Informed Consent Support Materials

4.5.1 Other Informed Consent Visual Aids

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

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

- Calendar with study visit schedule
- Sample VR
- Urine specimen cup
- Blood collection tubes
- Pelvic model
- VR insertion instructions

4.6 Comprehension Assessment

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

A comprehension assessment should be conducted and documented prior to a participant signing the informed consent form. This assessment should occur after the participant has completed the informed consent discussion described above and before she is asked to sign the informed consent form. It is expected that study staff administering the informed consent and assessing comprehension will be sufficiently knowledgeable about the study to make good judgments about the potential participants' understanding of the required information.

4.6.1 Comprehension Assessment Tools and Scoring System

Templates of assessment tools are available as separate electronic files on the Study Documents section of LiveTrial Home. Sites may use the tools as provided or may choose to adapt for their local use.

True/False Assessment: This assessment tool is structured around questions that correspond with the required elements of informed consent, but uses true/false questions that may be administered either orally or written.

Regardless of the method used to assess comprehension, if the assessment results indicate misunderstanding of any aspect of the study, site staff should review those aspects again until the participant fully understands them. Site staff should ensure and document 100% understanding prior to the participant providing written informed consent.

If, after all possible efforts are exhausted, the participant is not able to demonstrate adequate understanding of the study, do not ask her to sign the informed consent form to screen/enroll in the study. Similarly, if the participant has concerns about possible adverse impacts if they were to take part in the study, or indicates that they may have difficulty adhering to the study requirements, do not ask them to sign the informed consent form to screen/enroll in the study.

4.6.2 Documenting the Comprehension Assessment

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

Comments may be recorded in a designated area on the form (and on the back of the form if additional space is needed) or on an informed consent coversheet (refer to section 4.7 below); however, this is not required. All required points must be satisfactorily addressed by the participant, before proceeding to the final informed consent decision and signing of the informed consent form (s).

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

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

4.7 Documenting the Informed Consent Process

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

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

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

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

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

4.8 Ongoing Assessment of Participant Comprehension

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

Section 5. Study Procedures

Document Revision History

Version	Date	Summary of Changes	Author
V00.01	09 Apr 2018	Initial Draft	Amber Blackmon, Clinical Trial Lead
V00.02	13 Apr 2018	PM Review	Jessica Kappes Clinical Project Manager II
V00.03	13 Apr 2018	Revised based on PM Review	Amber Blackmon, Clinical Trial Lead
V00.04	03 May 2018	Revised based on external review	Jessica Kappes Clinical Project Manager II
V00.05	16 May 2018	Revised based on external review	Amber Blackmon, Clinical Trial Lead
V01.00	31 May 2018	Final Version	Amber Blackmon, Clinical Trial Lead
V01.01	13 Jun 2018	Revised based on external review	Amber Blackmon, Sr. Clinical Trial Lead
V02.00	29 Jun 2018	Final Version	Amber Blackmon, Sr. Clinical Trial Lead
V02.01	27 Dec 2018	Addition of visual ring inspection at enrollment and follow-up visits	Jessica Kappes Clinical Project Manager II
V02.02	08 Jan 2019	Revised based on external review	Jessica Kappes Clinical Project Manager II
V03.00	09 Jan 2019	Final Version	Jessica Kappes Clinical Project Manager II

This section provides information on requirements for study procedures in MTN-044/IPM 053/CCN019, including screening, enrollment and participant follow-up visits.

5.1 Visit Location

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

5.2 Eligibility Determination and SOP

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

- Eligibility determination procedures, including:
  - During-visit eligibility assessment procedures
  - Post-screening visit eligibility assessment and confirmation procedures (i.e., review of laboratory results)
  - Final confirmation and sign-off procedures prior to enrollment
  - 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 Principal Investigator or designee should contact the Protocol Safety Review Team (PSRT).

All eligibility criteria are initially assessed at the Screening visit, and some are reconfirmed on the day of Enrollment (Visit 2). Prior to enrollment, eligibility for study participation must be confirmed and documented on the Eligibility Checklist by designated staff.

In addition to the assessment of eligibility, the study informed consent should be reviewed with the participant to ensure that the participant clearly understands all information and is willing to participate in the study. Review of the informed consent must be documented in the participant's study files. See section 4 of this manual for additional information.

5.3 Screening Visit

The term "screening" refers to all procedures undertaken to determine whether a potential participant is eligible to take part in the 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.

All protocol-specified screening procedures must take place up to 60 days prior to enrollment, beginning on the day the potential participant provides written informed consent. The screening process starts as soon as the participant signs the informed consent form, even if no other screening procedures are conducted on that day.

If all screening and enrollment procedures are not completed within the allowable timeframe after obtaining written informed consent, one additional screening attempt will be allowed, per the discretion of the Principal Investigator or designee. The term "screening attempt" is used to describe each time a participant screens for the study (i.e., each time the participant provides written informed consent for participation in the study). The participant must repeat the entire screening process, beginning with the informed consent process. Note, however, that a new participant identification number (PTID) is not assigned to the participant in this case. Rather, the original PTID assigned at the first screening attempt is used for any repeat screening attempts, as well as future study visits should the participant successfully enroll in the study.

5.3.1 Screening Visit Procedures

Required screening procedures are reflected in Protocol Section 7.2 Table 8. Briefly, after providing informed consent, participants will be assigned a PTID, medical history will be obtained, and will then undergo a series of behavioral eligibility assessments, clinical evaluations, and laboratory tests. Locator and demographic information will be collected. Participants will be reimbursed for their time, and scheduled for their enrollment visit, if presumptively eligible.

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

Clinical screening visit procedures are described in detail in section 7 of this manual and in Protocol Section 7.2, and include:

- Collection of menstrual and medical history, concomitant medications, physical exam, and pelvic exam.
- Evaluation of participant use of prohibited vaginal products and medications, STI/RTI/UTIs, genital signs/symptoms, and overall general health.
- Disclosure of all available test results to the participant, as well as treatment or referrals for UTI/RTI/STIs if indicated.

The HIV testing algorithm for screening is included in Appendix II of the protocol. Details regarding laboratory tests and sample collection at screening are provided in Section 9 of this manual. In summary:

- All participants receive testing for HIV, pregnancy, syphilis, STIs (GC/CT, Trichomonas), CBC with platelets and differential, serum creatinine, and AST/ALT.
- If indicated (see Protocol 7.2 for specific requirements), participants may also have a Pap test, wet prep and vaginal pH, urine dipstick/culture, and/or testing for herpes.
    - Note: A Pap test should be collected if the participant is over 21 and cannot provide documentation of a satisfactory Pap test within the 3 years prior to enrollment. If the Pap test result is not available at the timing of her enrollment visit, then her enrollment visit should be rescheduled.

Per Protocol Section 7.2, multiple screening visits (as part of the same screening attempt) may be conducted if needed, to complete all required procedures. In cases where the Screening visit is conducted over multiple days, all procedures are considered part of the same screening visit/screening attempt. This is distinct from participants who rescreen for the study, in which case all screening procedures, including informed consent, must be repeated (with the exception of PTID assignment – See SSP Section 11 for details on PTID assignment, structure, and further details).

5.3.2 Screening and Enrollment Log

Screening and enrollment logs may be maintained separately or combined into one document. A sample screening and enrollment log suitable for use is available on LiveTrial Home under Study Documents. Study sites are encouraged to reference the eligibility codes listed at the bottom of the sample screening and enrollment log when recording the reason for screening failure/discontinuation.

5.3.3 Participants Found to be Ineligible (Screen Failures)

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

- Completed ICF
- Reason(s) for ineligibility, with date of determination, as per the completed Eligibility Checklist
- Completed Inclusion/Exclusion Criteria CRF

- 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 completed 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.

5.4 Enrollment Visit

A participant's final eligibility status should be determined after completion and final sign off on the Eligibility Checklist. The Principal Investigator (or designee) and a second staff member, per site SOP, should sign and date the Eligibility Checklist to affirm/confirm eligibility. A participant may only be enrolled after the final assessment of eligibility is completed. A participant is considered enrolled in the study only after she has been randomized. All baseline samples, enrollment assessments, and examinations must be collected/completed before a participant is randomized (the definition of enrollment) and the study ring is inserted.

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the Principal Investigator or designee should contact the PSRT immediately for guidance on subsequent action to be taken. PSRT contact details are provided in Section 8 of this manual.

5.4.1 Enrollment Visit Procedures

The Enrollment/Visit 2 serves as the baseline visit for the study and is considered Day 0 of study participation. All procedures for this visit must be conducted on the same day and cannot be split across multiple days. According to Protocol Section 7.3, the participant's menstrual cycle should be considered when scheduling the enrollment visit such that no bleeding occurs during the first 3 days of product use. If a participant is menstruating on the day of enrollment, her entire visit should be rescheduled for after the completion of menses. If the participant is enrolled and subsequently starts her menses during days 1-3, the pelvic exam and sample collection should continue as long as the participant is comfortable doing so.

The Principal Investigator or designated staff will reconfirm and document the criteria specified on the Eligibility Checklist prior to proceeding with enrollment per site SOPs.

On the day of enrollment, before a participant is randomized and can be considered enrolled in the study, site staff must complete the following enrollment visit procedures to confirm her study eligibility:

- Confirm 60-day screening window has not been exceeded
- Update and confirm adequacy of locator information
- Review informed consent and confirm participant is still interested in continued study participation
- Confirm behavioral eligibility criteria. Sites may use the Enrollment Behavioral Eligibility, or other site method, as specified in site SOPs.
- Complete the Baseline Behavioral Assessment.
- Review and update the participant's medical/ menstrual history that was first collected at the screening visit.

- Evaluate participant's use of prohibited vaginal practices, products and medications, assess for STI/RTI/UTIs or reproductive tract signs/symptoms, conduct pregnancy testing, and evaluate overall general health. Document all pre-existing conditions.
- Provide protocol adherence counseling, including vaginal ring use instructions and SMS survey requirements.
    - Note: This may also be conducted after enrollment, but it could be helpful to provide the participant with more information about the study product and SMS requirements prior to her final decision to enroll in the study.
- Prior to ring insertion, collect blood samples for PK testing of DPV and progestogen (including LNG) concentrations, HIV testing, serum creatinine, CBC with platelets and differential, AST/ALT, sex hormone-binding globulin (SHBG) and albumin, serum progesterone and estradiol, and plasma archive.
    - Note: Results of safety laboratory testing (serum creatinine, CBC with platelets and differential, AST/ALT) performed at the Enrollment Visit are expected to be received after the Enrollment Visit and will not be exclusionary. Abnormal results will be noted as baseline medical conditions, and may result in product discontinuation, per Principal Investigator discretion as per Section 9.3 of the protocol.
- Conduct HIV pre- and post-test counseling, and HIV/STI risk reduction counseling in conjunction with HIV testing.
- Conduct a physical exam and pelvic exam. Prior to ring insertion, collect vaginal Gram stain, CVF for DPV and LNG concentrations and microbiota, and CVL for biomarkers and if indicated, perform urine dipstick/culture, GC/CT testing, trichomonas testing, herpes testing, wet prep, and vaginal pH.
- Disclose all available test results to the participant and, if indicated, provide treatment or referrals for STI/RTI/UTIs.
- Offer the participant male condoms.

Once the procedures above and final determination of participant eligibility have been completed by designated site staff, the participant may be randomized to a study arm, at which point she will be considered officially enrolled in the study.

After enrollment, the Principal Investigator or authorized clinician will prescribe study product, and study staff will obtain product from the site pharmacy, review the product use instructions and answer any questions that the participant may have. Prior to dispensing the product, the study staff should visually inspect the ring. If any issues are noted, this needs to be documented on the source documentation and reported to the MTN LOC Pharmacist. The participant may insert the study vaginal ring on her own at the study clinic, or the site clinician may insert it for her. After the vaginal ring is inserted, the clinician will perform a digital exam to check for placement. Study staff will document the date and time of ring insertion on the Ring Insertion and Removal CRF.

The participant will be enrolled into the SMS survey system and trained on its use with the SMS Training Talking Points. She will also be given the SMS Instruction Card to use as reference. Her next visit will be scheduled, and she will be provided with her enrollment visit reimbursement.

Per the inclusion criteria, a potential participant must agree to use an effective method of contraception at enrollment and throughout the duration of her study participation. During the informed consent process, staff should explain which methods are acceptable for study purposes and emphasize that if she cannot commit to using one of these methods during study follow-up, she should not enroll in the study.

Effective methods include:

- Non-hormonal (e.g., copper) intrauterine device (IUD) inserted at least 28 days prior to Enrollment
- Engagement in sex exclusively with women
- Sterilization (of participant or partner)
- Sexual abstinence for the past 90 days (and continuing for the duration of the participant's study participation)
- Consistent and correct male condom use

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. 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. 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 use.

5.5 Follow-up Visits

There are 12 clinic follow-up visits.

- Visit 3 (Day 2)
- Visit 4 (Day 14)
- Visit 5 (Day 28)
- Visit 6 (Day 30)
- Visit 7 (Day 44)
- Visit 8 (Day 58)
- Visit 9 (Day 60)
- Visit 10 (Day 74)
- Visit 11 (Day 90): PUEV/Early Termination Visit Ring Removal
- Visit 12 (Day 91)
- Visit 13 (Day 92)
- Visit 14 (Day 93 or 94)

There are up to 4 phone call follow-up contacts.

- Visit 15 (1 week post ring removal)
- Visit 16 (4 weeks post ring removal)
- Visit 17 (8 weeks post ring removal)
- Visit 18 (12 weeks post ring removal)

NOTE: Menses should not coincide with any follow-up study visit from Visit 2- Enrollment Visit (Day 0) through and including Visit 3 (Day 2). Therefore, a participant's menstrual cycle must be considered when scheduling Visit 2- Enrollment Visit (Day 0). Sites should take into consideration the days of the week when study visits will fall and plan the participants' visit schedule accordingly. Please note: enrollment visits should occur on Mondays, Tuesdays, or Wednesdays in order for follow up visits to occur on a weekday, Monday-Friday.

For example, if a participant is enrolled on May 9, 2018, her clinic visits will be as follows:

May 2018						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1	2	3	4	5
6	7	8	9 **Day 0 (Enrollment)**	10	11 **Day 2 Visit**	12
13	14	15	16	17	18	19
20	21	22	23 **Day 14 Visit**	24	25	26
27	28	29	30	31		

Example: If a participant is enrolled (Day 0) on May 9, 2018, Days 2 and 14 will occur on May 11, 23 respectively.

5.5.1 Target Visit Dates and Visit Windows

Enrolled participants will be scheduled to complete follow-up visits throughout their participation in the study. For each participant, Day 2, 14, and 28 are targeted to take place at specific intervals based on the participant's enrollment (randomization) date. Sites must make every effort to conduct each visit on its target day. When absolutely necessary, visits may be conducted within the short allowable visits windows that are specified in section 11 of this manual. Visits completed on the target date or within the allowable visit window will be considered completed ("retained") visits.

Health Decisions will provide sites with a visit scheduling tool that can be used to generate visit schedules for enrolled participants.

5.5.2 Visits Conducted Over Multiple Days: "Split Visits"

All procedures specified by the protocol to be performed at a particular follow-up visit, ideally, will be completed at a single visit on a single day. In the event that all required follow-up procedures cannot be completed on a single day (e.g., because the participant must leave the study site before all required procedures are performed), the remaining procedures may be completed on a separate day but within the visit window, if at all possible. *Split visits are strongly discouraged and may only occur at the Screening, Day 14, Day 28, Day 44, Day 58, Day 74, Day 90, and Day 93/94 visits*. All other study visits (Enrollment, Day 2, Day 30, Day 60, Day 91 and Day 92) may not be split. As described in section 11 of this manual, all CRFs completed for a split visit are assigned the same visit codes, even though the dates the CRFs are completed will differ.

If study visits must be split, please ensure that:

- All PK specimens (blood and CVF) are collected on the same day of the split visit to avoid complicating interpretability of the data.
- The Ring Insertion and Removal CRF and the Ring Outage SMS CRF are completed on the same day PK specimens are collected during a study follow-up visit, in order to correlate ring use data with PK results.
- If bleeding is reported on the Bleeding SMS CRF, the Vaginal Bleeding Assessment CRF is completed on the same day as the Bleeding SMS CRF.

Any procedures that are not conducted within the visit window will be considered missed. See section 5.5.3 below for guidance on which missed procedures should be made up at an interim visit.

5.5.3 Missed Visits

For participants who do not complete at least part of a scheduled visit within the allowable visit window, the entire visit is considered "missed" and a Missed Visit CRF must be completed to document the missed visit (see the CRF Completion Guidelines for more information on completion of this form).

If visits are missed, sites must make every effort to make up the missed visit and required study procedures (as soon as possible) at an interim visit and retain the participant for her remaining scheduled study follow-up visits. Sites should contact the in-house CRA for additional guidance.

5.5.4 Follow-up Visit Procedures

Required follow-up visit procedures are listed in Protocol Sections 7.4 and Appendix I. As a general guide during follow up:

- Locator information must be obtained/reviewed at every visit.
- Informed consent should be reviewed to confirm participant interest in continued study participation.
- Medical/menstrual history, AE assessment and documentation, assessment of concomitant medications, and provision of any available lab results must be done at all required study visits.
- A pelvic exam is required and should be performed at Visits 4, 6, 7, and 9 – 11 (Days 14, 30, 44, 60, 74 and 90), and other visits if indicated.
- A physical exam must be performed at Visit 11 (Day 90) and a modified physical exam may be performed at any other visit, if indicated. Treatment and referrals for any diagnosed UTI/RTI/STIs will be provided, if indicated.
- CVF samples for PK should be collected within 15 minutes of blood samples for PK. Cervical biopsies should be collected within 30 minutes of blood samples for PK. Cervical biopsies for PK and PD are required at Visits 4, 6 and 11 (Days 14, 30, and 90). For Group 2 participants, PK samples are collected prior to ring removal on Days 28 and 58 and prior to ring insertion on Days 30 and 60.
- Vaginal Gram stain collection is required at Visits 7, 10, and 11 (Days 44, 74, and 90).
- CVF for microbiota and CVL for biomarkers are required at Visits 7 and 10 (Days 44 and 74).
- Pregnancy testing is required at Visits 4, 6, 9, and 11 (Days 14, 30, 60, and 90), and other visits if indicated.
- The VR is collected at Visits 5 and 8 (Days 28 and 58) for Group 2 participants (or, in the event of early product (VR) discontinuation, at the visit when vaginal ring use is

permanently discontinued), and the stored ring is dispensed to the Group 2 participants at Visits 6 and 9 (days 30 and 60).

- A digital exam to check ring placement should be performed at Visits 6 and 9 (Days 30 and 60), and may be done at any visit, if needed.
- For participants in Group 2, the VR should be rinsed and visually inspected when collected at Visits 5 and 8 (Days 28 and 58) and inspected again at Visit 6 and 9 (Days 30 and 60) prior to reinsertion. For participants in Group 1, the VR should be removed, rinsed and visually inspected monthly (e.g. at Days 28 and 58) by study staff and immediately re-inserted following inspection. The VR should also be inspected after removal at Visit 11 (Day 90). Any findings should be recorded on source documentation and any product complaints should be reported to the MTN LOC Pharmacist. If discoloration and a concurrent odor emanating from the ring is noted, the PSRT should be notified and use of the ring should be discontinued.
- Behavioral assessments are required as described in section 5.6
- HIV testing, pre-test and post-test counseling and HIV/STI risk reduction counseling are required at Visit 11 (Day 90) and at any other time if clinically indicated.
- Serum creatinine, CBC with platelets and differentials, and AST/ALT are required at Visits 5 and 11 (Days 28 and 90) and are collected on other visits if indicated. Sex hormone binding globulin (SHBG) and albumin is required at Visit 11 (Day 90). Serum progesterone and estradiol are collected at all visits from Visit 2 Enrollment through Visit 11 Day 90.
- Vaginal fluid pH and wet prep, urine dipstick/culture, herpes testing, trichomonas test, GC/CT, and syphilis serology may be performed at any visit, if indicated.
- Protocol adherence counseling is required at Visits 3 – 11 (Days 2 – 90). Contraceptive counseling is required at Visits 3 – 11 (Days 2 – 90) and Visit 14 (Day 93 or 94).
- Condoms can be provided at any visit, if needed.
- Participants will be reimbursed for their time at each visit and scheduled for their next visit as applicable.

5.5.5 Follow-up Phone Calls/Contacts (Visits 15-18)

Required follow-up contacts after the final PK visit post-ring removal are listed in Protocol Sections 7.4.6 and Appendix I. These contacts will occur 1 week, 4 weeks, 8 weeks, and 12 weeks post-ring removal and will be conducted by phone unless an in-person visit is needed for a study-related indication, for example, adverse event evaluation. Visit windows for these contacts are described in SSP section 11.

All participants will be contacted approximately one week (Visit 15) after ring removal to provide updates on bleeding/menses, AEs, concomitant medications and other study measures as described in Protocol Section 7.4.6 Table 16. AEs and concomitant medications will not be collected after Visit 15. However, any ongoing study product-related AEs will be followed until the AE has resolved or stabilized as per SSP section 8.

Participants who are using a non-hormonal method of contraception or no contraception (including those desiring pregnancy) will be followed monthly until return of menses for up to 3 months after stopping study product use. If a participant has not spontaneously menstruated by 3 months after study product discontinuation, she will be referred for appropriate evaluation of amenorrhea. If a participant reports return to menses or begins a hormonal contraceptive method, subsequent phone calls will not need to be conducted. For example, if a participant reports return of menses at Visit 16 (4 weeks after ring removal), Visits 17-18 do not need to be conducted.

The end of study/final visit will be defined by the last phone call conducted for each participant (V15, 16, 17 or 18) and is dependent on initiation of hormonal contraception, return to spontaneous menses or referral for evaluation of secondary amenorrhea.

As a general guide during follow up:

- Locator information must be reviewed/updated at every contact.
- AE assessment and documentation, assessment of concomitant medications, and provision of any available lab results must be done at Visit 15.
- Medical/menstrual history must be updated at every contact.
- Home pregnancy tests should be performed on the day of the follow-up phone calls after ring removal (1, 4, 8, and 12 weeks after ring removal, or Visits 15-18), and results will be reported to study staff at the time of the call.
- Participants will be reimbursed for their time at each contact and scheduled for their next contact as applicable.
- If a participant has not returned to menses at time of Visit 18 (12 weeks after ring removal), she should be referred for evaluation of secondary amenorrhea.

5.6 Behavioral Assessments

The following types of behavioral assessments will be conducted:

- Baseline Behavioral Questionnaire CRF
- PUEV Behavioral Questionnaire CRF
- Daily Short Message Service (SMS) for vaginal bleeding
- Weekly SMS for ring outage
- Ring Outage SMS CRF
- Bleeding SMS CRF
- In-depth interview

Information on the timing of the behavioral questionnaires (CRFs) and SMS is presented below in Table 5-1.

Table 5-1

Timing of Behavioral Questionnaires, SMS, and In-Depth Interviews

Study Visit	**Behavioral Measures**
Visit 2 (Enrollment)	Baseline Behavioral Questionnaire CRF
Daily bleeding SMS and **weekly** ring outage SMS initiated at Visit 2 (Enrollment) through Visit 11 (Day 90)	SMS Questions
Visit 3 (Day 2) **Visit 4** (Day 14) **Visit 5** (Day 28) **Visit 7** (Day 44)	Bleeding SMS CRF

Visit 8 (Day 58) **Visit 10** (Day 74)	
Visit 6 (Day 30) **Visit 9** (Day 60)	Ring Outage SMS CRF Bleeding SMS CRF
Visit 11 (Day 90)	PUEV Behavioral Questionnaire CRF Ring Outage SMS CRF Bleeding SMS CRF In-depth interview
Visit 12 (Day 91) **Visit 13** (Day 92) **Visit 14** (Day 93 or 94)	Bleeding SMS CRF

Note: Participants who permanently discontinue study product use early are requested to complete all visit procedures scheduled to occur at the Day 90 Visit/PUEV/Early Termination Visit, including the in-depth interview, at the visit when study product use is permanently discontinued. Behavioral assessment procedures will be discontinued for the remaining study visits that occur after permanent discontinuation. See Protocol Section 7.5.3 for further information.

5.6.1 Behavioral Questionnaires

The Baseline Behavioral Questionnaire CRF will be completed at the Enrollment Visit (Visit 2), and the PUEV Behavioral Questionnaire CRF will be completed at the Day 90 Visit (Visit 11) (or at the visit when product use is permanently discontinued, whichever is earlier). The questionnaires will be administered via face-to-face interview, with responses entered directly into the study database, as specified in the site's study-specific Source Documentation SOP. These interviews should be conducted prior to any protocol or adherence counseling activities.

Participants should be informed that site staff will be talking to her about personal and sensitive topics during the interview. Site staff should read all items to the participant word-for-word. They should avoid re-phrasing items because this can change the meaning of the item, making it inconsistent with other participants' interviews. Site staff should only read response categories aloud if the CRF [and/or CRF Completion Guidelines document (CCG)] specifically instructs them to do so for a given form item. At the end of the interview, while the participant is still present, the interviewer should review the form for accuracy and completeness and make any updates or corrections as appropriate. This review step is important because all interviewer-administered CRFs (paper or electronic, per site Source Documentation SOP) are source documents (with the participant being the source of the data). Changes to the participant's answers cannot be made

once the interview is completed as to avoid socially desirable reporting or participant bias as a result of subsequent participant counseling (risk reduction, protocol and/or product adherence).

5.6.2 Short Message Service (SMS)

SMS will be used to collect information about vaginal bleeding (administered daily) and use of study product (administered weekly) starting at the enrollment visit (Visit 2). Questions about use of study product and the bleeding assessment will end at Visit 11 (Day 90). Information on how to set up SMS interviews, access data, and other technical requirements are included in the SMS Technical Manual. Participants will be enrolled in the SMS system during Visit 2, and site staff will give them a brief orientation to the survey procedures using the SMS Training Talking Points. Participants will also receive an SMS Instruction Card to take home for reference. The SMS Technical Manual, SMS Training Talking Points, and SMS Instruction Card will all be available to the site via the Health Decisions LiveTrial Home page.

5.6.3 Entering SMS Data into CRFs

At Visits 3-11, daily SMS data on bleeding will be transcribed from the SMS system onto the Bleeding SMS CRF in the MTN-044/IPM 053/CCN019 Medidata Rave study database. Completion of this CRF is required even if no Bleeding SMS data is available for the participant (i.e. she did not respond to any of the text messages or questions). At Visits 12, 13, and 14, bleeding data will be collected from the participant directly during the visit as described in section 5.6.4.

Staff will transcribe all Bleeding SMS surveys that have been completed *since the last visit*. Special care will be taken to ensure that there is no duplication and that there are no omissions – i.e. all surveys are entered on only one CRF. Responses to each daily SMS survey will be entered on a new log line on the Bleeding SMS CRF, along with the date that the survey was completed. Once all surveys are entered, site staff will summarize the vaginal spotting or bleeding reported via SMS, by counting the number of log lines where “Description of spotting/bleeding” equals Light bleeding/spotting, Moderate bleeding, or Heavy bleeding and will enter the sum in the “On how many days did the participant experience vaginal spotting or bleeding?” field on the CRF (see screenshot below).

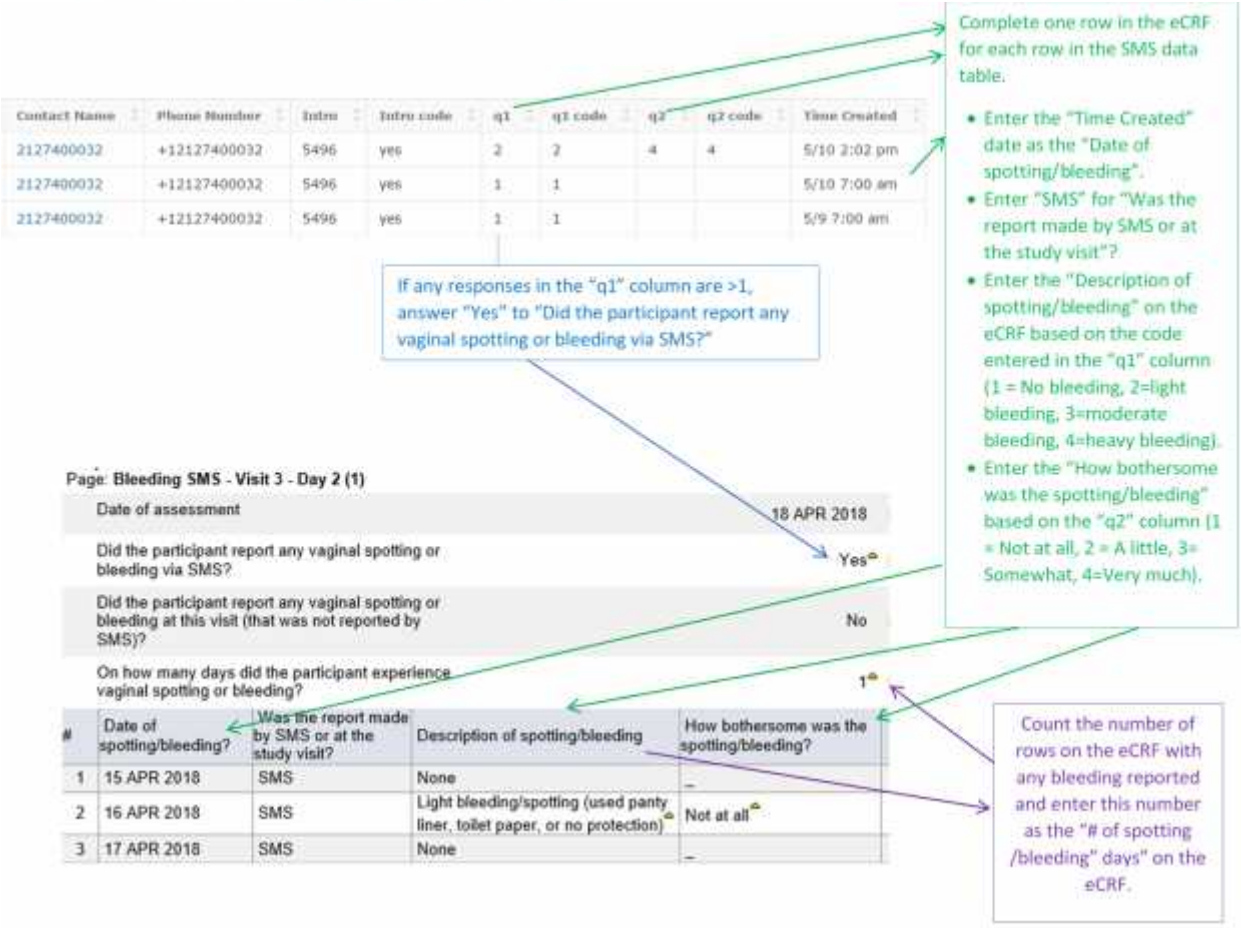


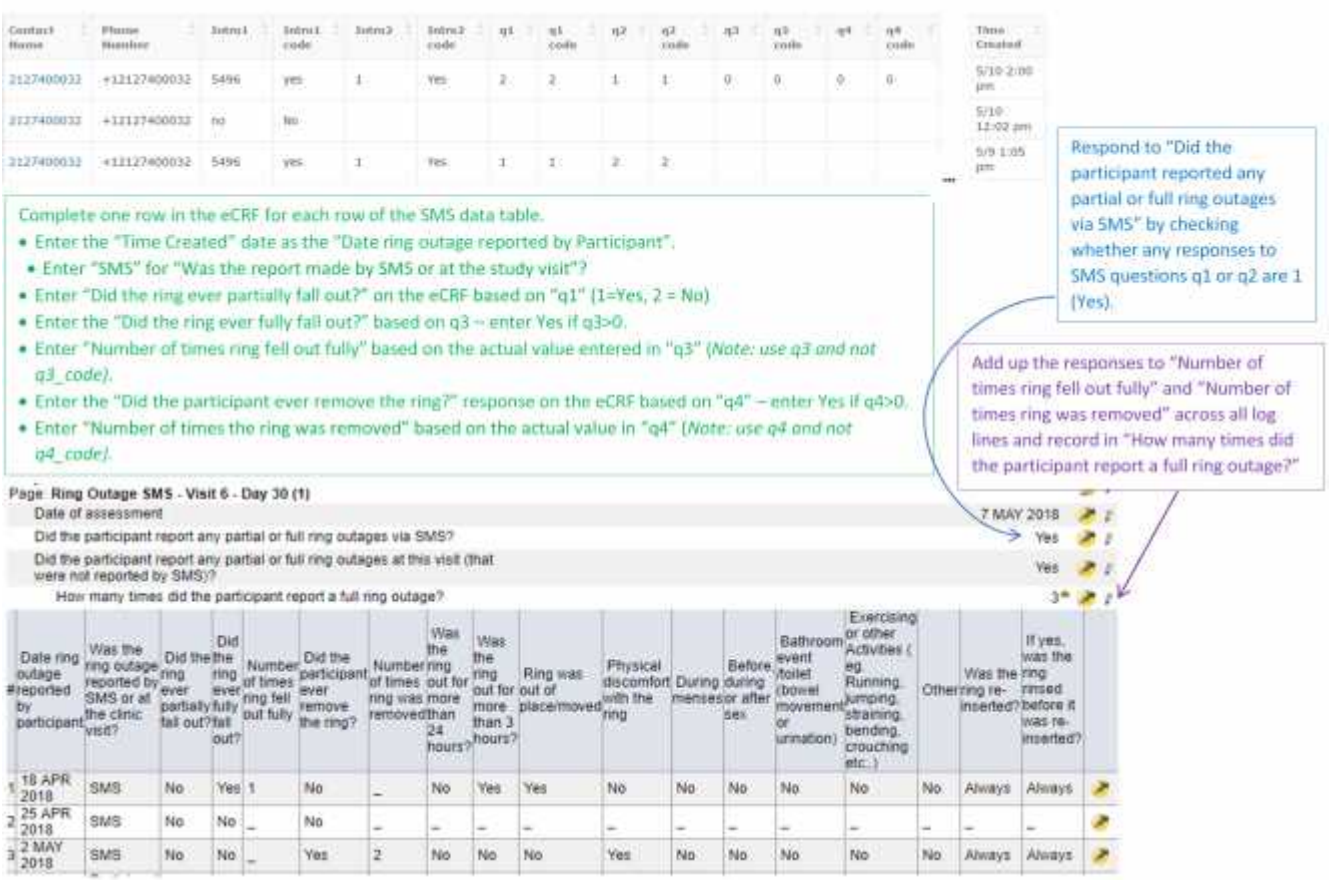
Figure 1: Entry of Bleeding SMS Data onto eCRF

At Visits 6 (Day 30), 9 (Day 60), and 11 (Day 90), weekly SMS data on ring outages will be transcribed from the SMS system onto the Ring Outage SMS CRF in the Medidata Rave study database. As with the Bleeding SMS CRF, completion of this CRF is required even if no Ring Outage SMS data is available for the participant (i.e. she did not respond to any of the text messages or questions).

At the Day 30 visit, staff will transcribe all Ring Outage SMS surveys that have been completed since the Enrollment visit. At the Day 60 visit, staff will transcribe all Ring Outage SMS surveys that have been completed since the Day 30 visit (or Enrollment visit, if the Day 30 visit was missed). At the Day 90 visit, staff will transcribe all Ring Outage SMS surveys that have been completed since the Day 60 visit (or Day 30 visit, if the Day 60 visit was missed). As with the Bleeding SMS CRF, special care will be taken to ensure that there is no duplication and that there are no omissions, i.e. that all surveys are entered on only one CRF.

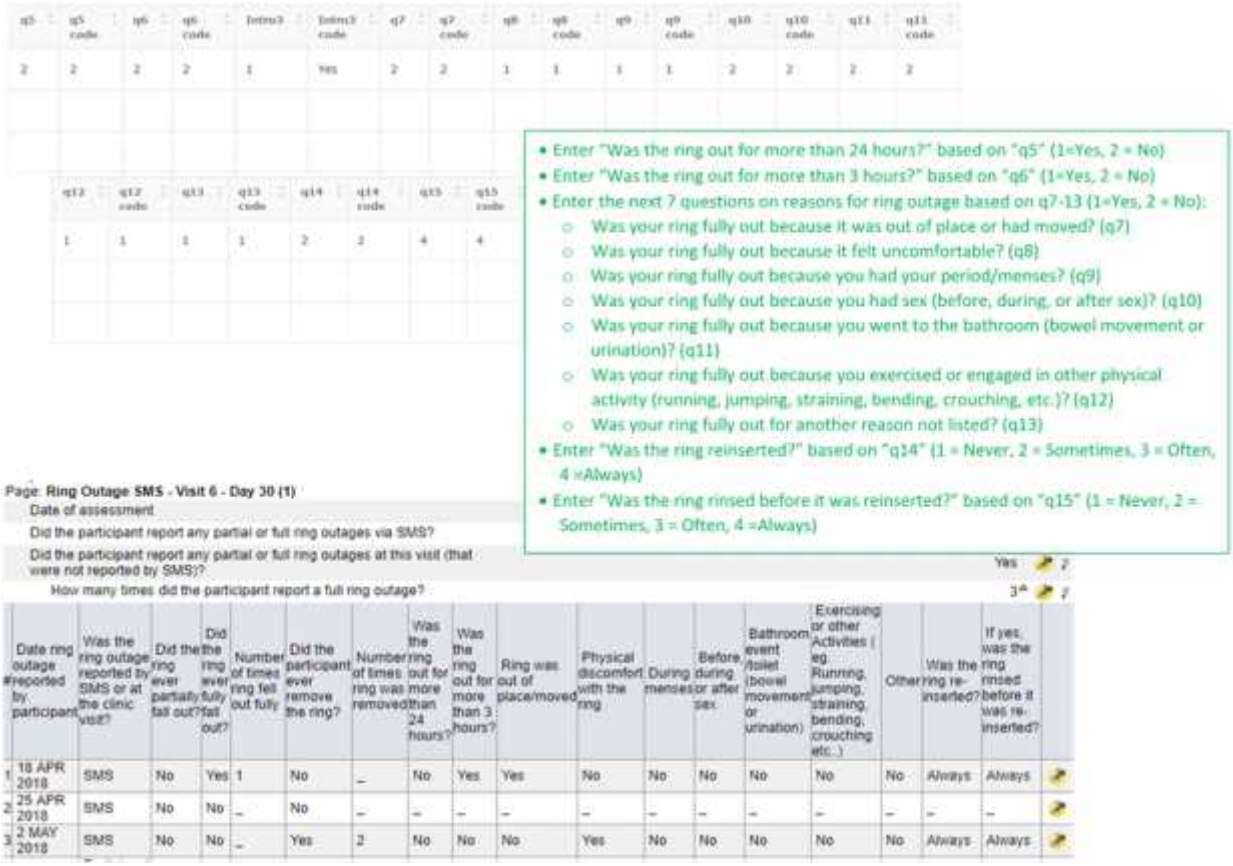
Responses to each weekly Ring Outage SMS survey will be entered on a new log line on the Ring Outage SMS CRF, along with the date that the survey was completed. Once all surveys are entered, site staff will enter data on whether the participant reported *any* partial or full ring outages via SMS by checking whether *any* responses to SMS questions 1 or 2 are 1 (Yes), and will enter the *number of times* that the participant reported a full ring outage by adding the

responses to "Number of times ring fell out fully" and "Number of times ring was removed" across all log lines (see screenshots below).



	Date ring outage reported by participant	Was the ring outage reported by SMS or at the clinic visit?	Did the ring ever partially fall out?	Did the ring ever fully fall out?	Number of times ring fell out fully	Did the participant ever remove the ring?	Number of times ring was removed	Was the ring out for more than 24 hours?	Was the ring out for more than 3 hours?	Ring was out of place/moved	Physical discomfort with the ring	During menses	Before, during or after sex	Bathroom event (toilet movement or urination)	Exercising or other Activities (eg Running, jumping, straining, bending, crouching etc.)	Other	Was the ring re-inserted?	If yes, was the ring rinsed before it was re-inserted?	
1	18 APR 2018	SMS	No	Yes	1	No	_	No	Yes	Yes	No	No	No	No	No	No	Always	Always	
2	25 APR 2018	SMS	No	No	_	No	_	_	_	_	_	_	_	_	_	_	_	_	
3	2 MAY 2018	SMS	No	No	_	Yes	2	No	No	No	Yes	No	No	No	No	No	Always	Always	

Figure 2: Entry of Ring Outage SMS Data onto eCRF (Screenshot 1 of 2)



- Enter "Was the ring out for more than 24 hours?" based on "q5" (1=Yes, 2 = No)
- Enter "Was the ring out for more than 3 hours?" based on "q6" (1=Yes, 2 = No)
- Enter the next 7 questions on reasons for ring outage based on q7-13 (1=Yes, 2 = No):
  - Was your ring fully out because it was out of place or had moved? (q7)
  - Was your ring fully out because it felt uncomfortable? (q8)
  - Was your ring fully out because you had your period/menses? (q9)
  - Was your ring fully out because you had sex (before, during, or after sex)? (q10)
  - Was your ring fully out because you went to the bathroom (bowel movement or urination)? (q11)
  - Was your ring fully out because you exercised or engaged in other physical activity (running, jumping, straining, bending, crouching, etc.)? (q12)
  - Was your ring fully out for another reason not listed? (q13)
- Enter "Was the ring reinserted?" based on "q14" (1 = Never, 2 = Sometimes, 3 = Often, 4 =Always)
- Enter "Was the ring rinsed before it was reinserted?" based on "q15" (1 = Never, 2 = Sometimes, 3 = Often, 4 =Always)

Figure 3: Entry of Ring Outage SMS Data onto eCRF (Screenshot 2 of 2)

See the SMS Technical Manual for information on accessing the SMS data. See the CCG for specific details on form completion, including transcription of the SMS data.

5.6.4 Verifying SMS data with Participants

At visits that require completion of the Bleeding SMS CRF and/or Ring Outage SMS CRF, the site staff should verify the SMS data by reviewing the CRF(s) with the participant.

Site staff will ask the participant to confirm any responses which seem unlikely (e.g., too high) or inconsistent (e.g., the participant reports that the ring was fully out but reports "0" for the number of times it was out). If no discrepancy is noted, site staff will briefly review the SMS data with the participant to verify whether the SMS data are correct. If the discussion reveals an error in the SMS data, the CRF will be updated with the correct information and the site staff should update the response to the question: "Was the report made by SMS or at the clinic visit?" to the "Participant Report at Visit" option and describe the change in chart notes.

In addition, site staff will ask about any bleeding or ring outages for periods in which SMS data is not available. This includes days that the Bleeding SMS survey was not completed and weeks that the Ring Outage SMS survey was not completed, as well as any bleeding or outages that may have occurred since the last survey. At Visits 12, 13, and 14, any bleeding since the previous clinic visit (the day before) will be collected in this manner. Additional reports of bleeding

or ring outages will be added to the respective CRFs on new log lines and site staff will record in the applicable data field that these events were reported at the clinic visit, instead of SMS.

The following updates will be made to the Bleeding SMS CRF or the Ring Outage SMS CRF after any additional log lines are added to enter data reported at the clinic visit:

1. On the Bleeding SMS CRF, enter whether the participant reported any vaginal spotting or bleeding at this visit that was not reported by SMS (yes or no).
    a. If the participant did report additional spotting or bleeding that was not reported by SMS, update the field for total number of days that she experienced vaginal spotting or bleeding.
2. On the Ring Outage SMS CRF, enter whether the participant reported any partial or full ring outages at this visit that were not reported by SMS (yes or no).
    a. If the participant did report additional ring outages that were not reported by SMS, update the field for the total number of times that she reported a full ring outage.

5.6.5 In-Depth Interviews

Overview

During Visit 11, all participants will complete an in-depth interview (IDI). The IDI may also take place at a separately-scheduled time between PUEV and Final Contact Visits to accommodate participants' schedules, or earlier if the participant terminates early from the study. The IDI will address study VR use and acceptability during the study. These IDIs will be conducted by a trained qualitative interviewer and will follow a semi-structured questionnaire guide. They are anticipated to last approximately 45-60 minutes. These IDIs will be conducted over the computer by a non-recorded video. An audio recording will be made with a handheld digital audio recording device that is operated by the qualitative interviewer (off-site at RTI), and a backup recording will be made with audio recording software also operated by the interviewer. In the event of a computer malfunction or lack of internet connectivity, landline telephones will be used for the IDI. The line will be put on speaker and, with the participant's consent, an additional RTI staff member will be present to act as notetaker in case the recording quality is poor.

Participants provide consent to be audio recorded as part of the main study consent, however, they may change their mind and decline to be recorded. The interviewer will ask for the participant's verbal confirmation of consent prior to commencing the interview. For participants who do not agree to be audio recorded, an additional RTI staff member will be present to act as notetaker.

Scheduling the IDI

Study coordinators will notify the off-site qualitative interviewer via email (email: Mtn044interviewer@mtnstopshiv.org) as each Visit 11 (or PUEV, if different than Visit 11) appointment is scheduled so that he/she can prepare for video calls. The qualitative interviewer will confirm the appointment via email to the site coordinator's email (fpr@upmc.edu) with an invitation to the BlueJeans video call for the scheduled date and time. The qualitative interviewer should be notified 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. Contact information for the qualitative interviewer is listed in Appendix 6-1. Any scheduling changes will be confirmed by email. RTI staff will ensure that all participants taking part in IDIs have been scheduled by reviewing a report of PTIDs indicating enrollment dates. This report will be requested from SCHARP on a biweekly basis.

Preparing, initiating, and finishing the IDI

Before the first IDI

Site staff that will be assisting participants with the IDI will be instructed in the use of the BlueJeans 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 BlueJeans 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 AEs that participants may report during the IDI. After the IDI, the interviewer will send a bulleted list of any potential AEs to the clinic staff via email within 24 hours. Clinic staff will be responsible for checking whether any potential AEs have already been documented and for following up with the participant if needed.

Before each IDI

- Ensure there is signage on the door indicating an interview is in progress and the occupant should not be disturbed.
- Ensure the computer with a webcam is available in a private space. Confirm there is a headset with microphone connected to the computer that is operational. If using a laptop, ensure that the laptop is plugged in.
- Ensure the video system is ready and connected to the internet.

Initiating each IDI

- The interviewer will initiate the scheduled meeting in BlueJeans using the meeting ID provided in the interview date email confirmation. The site staff will click on the link in the email 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, then leave the room and close the door.

Finishing each IDI

- Once the interview is done, the interviewer will thank the participant, and ask that s/heshe bring the site staff back into the room. The interviewer will confirm with the site staff that the IDI has been completed and the interviewer will then end the video meeting.

A quick guide for these procedures are contained in Appendix 6-2.

5.7 Study Exit/Termination Considerations

The end of study/final visit will be defined by the last phone call conducted for each participant (V15, 16, 17 or 18) and is dependent on initiation of hormonal contraception, return to

spontaneous menses or referral for evaluation of secondary amenorrhea. Additional contact with the participant may be required for:

- Participants who are pregnant during the study to obtain pregnancy outcome(s)
- Participants with positive or indeterminate HIV test results
- Participants with certain types of AEs that are ongoing at study exit (see detailed guidance in section 8 of this manual).

For each participant, a final contact should be scheduled based on the participant's clinical indication at study exit. Participants should also be contacted post-study to be informed of the study results, if requested by the participant. Participant's preferred method of contact should be determined prior to study termination. Lastly, for participants who study staff may wish to contact regarding participation in future studies, permission for such contact should be sought from the participant, during her termination visit, and documented.

It is recommended that final contact plans, participant preferences for receiving study results and participant permission (or lack thereof) for participation in future studies should be documented in chart notes or on a study exit worksheet or other site-specific tool/document that can be easily accessed by study staff.

All final contacts with study participants must be documented in participant study records. No CRFs are completed for these post-termination contacts (with the exception of the Pregnancy Outcome Log CRF to collect pregnancy outcome data for pregnancies that are ongoing at the time of study termination).

5.7.1 Participants Who Become Infected with HIV

If a participant becomes infected with HIV-1 during her study participation, she will be referred to local care and treatment services and may return to the research clinic for additional counseling and other support services, as needed, per site SOP. Per Protocol Section 7.5.1, once a participant seroconverts, follow-up visits will be discontinued, and the participant will be considered terminated from the study. Participants who seroconvert should be instructed to remove the vaginal ring as soon as possible and return it to the study clinic (permanent study product discontinuation). They may also be offered additional laboratory testing (such as HIV RNA and HIV drug resistance testing), as clinically indicated per site SOP and in consultation with the site Principal Investigator and the PSRT.

5.7.2 Participants Who Become Pregnant

If a participant becomes pregnant during her study participation, follow-up visits and procedures will be discontinued, and the participant will be considered terminated from the study (see Protocol Section 7.5.2). Participants should remove the vaginal ring as soon as possible and return it to the study clinic (permanent study product discontinuation). Pregnant participants will be referred to local health care services and may return to the research clinic for additional counseling, as needed, per site SOP.

Sites should develop a plan with participants to attain pregnancy outcomes for pregnancies that are ongoing at the time of study exit. The study site will make every reasonable effort to contact participants and collect infant outcome at approximately one year after delivery for those pregnancies that result in live birth. For example, site staff could call or e-mail the participant in an attempt to learn the outcome(s) of the pregnancy.

5.7.3 Participants Who Permanently Discontinue Study Product for Other Reasons

Criteria for permanent discontinuation of the VR are listed in Protocol Section 9.3. In the event of early permanent discontinuation of study product use for reasons other than HIV seroconversion or pregnancy, participants will be asked to complete an interim visit where all of the study procedures scheduled to occur at Visit 11-Day 90/PUEV/Early Termination Visit will be conducted.

After consultation with the PSRT and the MTN-044/IPM 053/CCN019 Management Team, these participants may be asked to discontinue study follow-up visits and procedures.

If study follow-up is continued, participants will be asked to continue the visit schedule according to the protocol-specified procedures with the following exceptions (*unless required for AE follow-up), as noted in Protocol Section 7.5.3:

- Pelvic exams*
- Collection of blood for safety assessments*
- Behavioral assessments related to product adherence
- Product use data collection
- Protocol-required counseling will be modified.

*If a participant is permanently discontinued from vaginal ring use early due to an AE, site staff must continue to follow her for clinical management purposes until resolution or stabilization of the AE is documented. If an AE resolves or stabilizes after study exit, updates should be made in the participant's chart notes only (and not on the AE Log CRF).

Note: In consultation with the MTN Pharmacology Core and the MTN-044/IPM 053/CCN019 Management Team, if a participant permanently discontinues vaginal ring use early (i.e., prior to the Day 90 Visit), site staff may ask if her if she is able and willing to return to the clinic one day, two days, and three or four days after ring removal to collect PK specimens. These three visits following ring removal would be considered interim visits.

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

A participant will be put on temporary hold from DPV-LNG VR product use by the Principal Investigator/designee for any of the following reasons:

- Participant reports current or expected continued use of prohibited medications during study participation as listed in Protocol Section 6.8.

The Principal Investigator/designee must consult the PSRT once the temporary hold is initiated. Together, the Principal Investigator/designee and the PSRT will discuss resuming product use, continuing the temporary hold, or progressing to permanent discontinuation.

All protocol-specified study visits and procedures will continue except the following:

- Pelvic exams*
- Collection of PD samples
- Provision of product use/protocol adherence counseling

*Unless required for AE follow-up

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

The MTN-044/IPM 053/CCN019 Management Team, in consultation with the MTN Pharmacology Core, may provide real-time guidance to the sites regarding a modified study visit schedule, in an effort to ensure that PK samples are collected at the appropriate time points. Participants' duration of use and timing of study product permanent discontinuation will be factored into the modified schedule. Site need to immediately e-mail the MTN-044/IPM 053/CCN019 Management Team and PSRT and guidance will be provided on a case by case basis depending on where in follow-up the participant is at the time of discontinuation.

5.7.5 Criteria for Early Termination of Study Participants

Participants may voluntarily withdraw from the study for any reason at any time. The Principal Investigator/designee also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the PSRT. Participants also may be withdrawn if the study is terminated prior to its planned end date.

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

- Ask the participant if she is willing to complete one last visit, during which visit procedures for the Visit 11-Day 90/PUEV/ Early Termination Visit should be completed.
- Record the reason(s) for the termination in participants' study records.
- Print and file consultation with the PSRT regarding investigator decision to conduct an early termination. Note: consultation is not required for voluntary participant withdrawals.
- Update the 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.

Appendix 5-1: CONTACT INFORMATION FOR IN-DEPTH INTERVIEWS

In-Depth Interview
Contact: Mary Kate Shapley-Quinn
Phone: 415 848-1316
Mobile phone (for text messages): 919 260-4144
Email: mshapley@rti.org

Back-up contact: Imogen Hawley
Phone: 415-848-1339
Mobile phone (for text messages): 206-455-1700
Email: ihawley@rti.org

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.

Appendix 5-2: QUICK TIPS FOR IN-DEPTH INTERVIEW

Scheduling

- Notify the off-site qualitative interviewer via email (email: Mtn044interviewer@mtnstopshiv.org) as each Visit 11 (or PUEV, if different than Visit 11) appointment is scheduled
- Interviewer will confirm the appointment via Outlook invite with BlueJeans call information for the time it is scheduled.
- Notify interviewer of all changes or cancellations within 24 hours of the scheduled appointment, if possible.
- 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 a sign reading "Interview in progress, do not interrupt" is available to post on the door when the room is in use.
- Ensure the video system is ready.

Initiating the Video Interview

- Interviewer will initiate the interview in BlueJeans
- Click on the link in the Outlook invite to join the meeting, log into the meeting, 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 site study staff member when the interview is done.
- Interviewer will stop audio recording, disconnect from the meeting, and save audio file to secure HIPAA drive.

Section 6. MTN-044/IPM 053/CCN019 Study Product Considerations for Non-Pharmacy Staff

Document Revision History

Version	Date	Summary of Changes	Author
V00.01	09 Apr 2018	Initial Draft	Amber Blackmon, Clinical Trial Lead
V00.02	13 Apr 2018	PM Review	Jessica Kappes Clinical Project Manager II
V00.03	13 Apr 2018	Revised based on PM Review	Amber Blackmon, Clinical Trial Lead
V00.04	03 May 2018	Revised based on external review	Jessica Kappes Clinical Project Manager II
V00.05	16 May 2018	Revised based on external review	Amber Blackmon, Clinical Trial Lead
V01.00	21 May 2018	Final Version	Amber Blackmon, Clinical Trial Lead
V01.01	21 Jun 2018	Revised based on external review	Amber Blackmon, Sr. Clinical Trial Lead
V02.00	29 Jun 2018	Final Version	Amber Blackmon,

			Sr. Clinical Trial Lead
V02.01	08 Jan 2019	Revisions to section 6.8 (vaginal ring complaints)	Jessica Kappes Clinical Project Manager II
V03.00	09 Jan 2019	Final version	Jessica Kappes Clinical Project Manager II

This section provides information and instructions for non-pharmacy staff related responsibilities for requesting and transporting study product, receiving the vaginal ring (VR) from the site pharmacy, and delivery of the VR to study participants. Record-keeping requirements for non-pharmacy staff also are provided. Associated instructions for pharmacy staff are provided in the MTN-044/IPM 053/CCN019 Pharmacy Study Product Management Procedures Manual, which will be made available to each MTN CRS Pharmacy by the MTN LOC Pharmacist. Please refer to Section 10 of this SSP manual for product use instructions and guidance on study product adherence counseling.

6.1 Randomization Assignment

The MTN Statistical Data Management Center (SDMC) will generate and maintain the study randomization scheme.

Study randomization will occur via the Medidata web-based system, as described in Section 11 (Data Collection) of this manual. Clinic staff will complete a study prescription and send the original, top white portion, to designated site pharmacy staff, as described in section 6.2 below, to notify the site pharmacist that the participant has been randomized and needs to be dispensed a study VR.

6.2 Prescription Completion and Dispensing Study Vaginal Ring at Enrollment

Each enrolled participant is assigned to a regimen for the VR. Participants assigned Regimen A will wear the VR continuously for 90 days. Participants assigned Regimen B will wear the VR cyclically (inserted for 28 days, removed for 2 days) for approximately three cycles.

An MTN-044/IPM 053/CCN019 Prescription will be used by clinic staff to request this study product from the site pharmacy at the participant's Enrollment Visit/Visit 2 (see Appendix 6-1). Prescriptions (Appendix 6-1) will be produced as two-part no carbon required (NCR) forms. A bulk supply of prescriptions and request slips will be provided to the clinic staff by the MTN LOC Pharmacy. The MTN LOC Pharmacist should be contacted if additional supplies of the documents are needed during the study. Each VR will be dispensed directly from the pharmacy to clinic staff on behalf of the participant, upon receipt of an original, written prescription that is signed by an authorized prescriber, as designated in the site's pharmacy study product chain of custody SOP. If staffing issues make it impossible for a clinic staff member to pick up the ring from the pharmacy, a designated transport staff member or runner may pick up the VR and white return bag, and then transfer the VR and bag to a designated clinic staff member who will then provide them to the participant.

Each VR will be dispensed from the pharmacy in its original sealed overwrap – the pharmacist will indicate the PTID and date dispensed on the overwrap label. The pharmacist/designee will also dispense a white VR return bag. The pharmacist/designee will complete the PTID, dispensation

date, and visit number; 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 both the VR and the return bag at the Enrollment Visit/Visit 2. This bag may be used for storage if the used VR is removed or expelled (and not reinserted) prior to the next scheduled visit so that it can be returned to the clinic. Although participants are encouraged not to remove the VR, if they do so, they may place it in this bag for storage and ring return as needed. The VR should always be rinsed with clean water only before reinsertion. If the VR will not be reinserted, it should be patted dry with a paper towel and placed in the white VR return bag and returned to the study clinic at the participant's next visit. Participants may request a new bag at clinic visits as needed if the original bag is used or misplaced.

In Clinic Prescription Procedures (C1-C5):

C1. After the participant is randomized, complete an MTN-044/IPM 053/CCN019 Prescription per instructions on the prescription to indicate PTID, study product regimen, and participant provision of written informed consent for this study. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed and dated informed consent form prior to recording his/her initials on the prescription.

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 Principal Investigator 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 verified that the participant signed the informed consent form and completed the top part of the prescription.

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

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

In Pharmacy Prescription Procedures (P1-P2):

P1. Upon receiving the completed MTN-044/IPM 053/CCN019 Prescription, the pharmacist will review the document for completion and accuracy. In the event that a member of pharmacy staff identifies possible errors on the original prescription, he/she will return the original prescription to clinic staff for clarification(s) or correction(s). 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 the white and yellow sheets. The same corrections and notes should be recorded on both the white original and yellow copy, 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. Following review of the signed MTN-044/IPM 053/CCN019 Prescription, pharmacy staff will dispense the study VR to clinic staff for participant use per instructions in the MTN-044/IPM 053/CCN019 Pharmacy Study Product Management Procedures Manual and in accordance with

the site pharmacy SOP(s).

6.3 Vaginal Ring Request Slip

Once the vaginal ring has been vaginally inserted, the participant should not require additional VRs. Re-supply should be extremely rare – for example, in the event that a clinician/participant drops the ring on a dirty floor prior to insertion, and the pharmacy supplies a new ring. Additionally, in the unusual circumstance that the ring has been removed or expelled during study follow-up and cannot be reinserted, the ring may need to be replaced. In this latter circumstance, the site should consult the MTN-044/IPM 053/CCN019 PSRT with the details of the participant's situation, and in particular when her next in-clinic PK samples are expected to be collected. The MTN-044/IPM 053/CCN019 PSRT will provide guidance on whether or not a VR re-supply should occur. In all cases where VR re-supply is deemed necessary, the MTN-044/IPM 053/CCN019 Vaginal Ring Request Slip should be used (Appendix 6-2). RE-SUPPLY should be marked with the reason for re-supply indicated.

The Vaginal Ring Request Slip can also be used to indicate a clinical (site-initiated) temporary or permanent discontinuation of VR use. Any time a participant is directed by the clinician, outside of the protocol, to remove the ring prior to the Day 90/Visit 11, a Vaginal Ring Request Slip should be completed. Protocol Section 9 (Clinical Management) and SSP Section 7 (Clinical Considerations) specify the circumstances under which use of study product may be temporarily held or permanently discontinued early. For this action, clinic staff should mark the PERMANENT DISCONTINUATION box on the request slip and provide the reason for the study product discontinuation. In the case of a permanent discontinuation no further Vaginal Ring Request Slips will need to be completed for that participant. A Product Discontinuation CRF must also be completed.

For participants who complete the full 90 days of VR use as scheduled, clinic staff should send a request slip marked PRODUCT USE PERIOD COMPLETED to the pharmacy at the Day 90/Visit 11 and no further Vaginal Ring Request Slips will need to be completed. A Product Discontinuation CRF must also be completed.

The Vaginal Ring Request Slip can also be used by clinic staff to communicate to the pharmacy staff any changes in product use status, including a clinical temporary hold of the VR, VR resume (after a temporary hold), and participant-initiated declination of VR use. Any time VR use is to resume, a new request slip must be completed and sent to the pharmacy with the "RESUME" box checked. If a new ring should be dispensed, the appropriate box indicating this to the pharmacist should also be checked.

The request slip will be produced as two-part no carbon required (NCR) sheets. The top white portion is the original (pharmacy), and the bottom portion is the copy (clinic). Bulk supplies of the slips are available from the MTN LOC Pharmacist and will be supplied to clinic staff. Clinic staff will complete the PTID, study product regimen, and specified action. The clinic staff name, signature, and signature date must be completed by a clinic staff member authorized to order study product for participants during follow-up.

Double-check the accuracy of all entries and then separate the two parts of the completed slip. Retain the yellow copy in the participant study notebook and deliver the white original to the pharmacy. If corrections are needed, the same corrections must be made separately on both the white original sheet and the yellow copy. A signed and dated note explaining the corrections also

should be recorded on both sheets. Identical corrections and notes should be recorded on both copies, on the same date, by the same person.

6.4 Vaginal Ring Accountability

The MTN-044/IPM 053/CCN019 Study Product Chain of Custody (Pharmacy) SOP provides documentation regarding who receives the VR from the pharmacist. Responsibilities and procedures from the time of product receipt from the pharmacy until delivery to the participant, including procedures for participant identity verification prior to ring provision, should be outlined in the MTN-044/IPM 053/CCN019 Clinic Study Product Accountability and Destruction SOP. This 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.

Used VRs will be collected by the clinic staff (rather than the pharmacy). Therefore, accommodation must be made to allow for documentation of distribution, collection, and destruction/removal of study product at the site clinic. A sampleClinic-Specific Study Product Accountability Log is available on LiveTrial Home under Study Documents. This log includes tracking the date the ring is distributed to the study participant, the date of return of the used ring 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).

6.4.1 Documentation of Vaginal Ring Provision and Collection

Clinic-Specific Study Product Accountability Log
This log should be maintained and completed for all participants as outlined in the Clinic Study Product Accountability and Destruction SOP. This log should document the initial provision of the ring and final disposition of that ring. For participants who are in Group 2/Regimen B, the two 2-days removals will be documented as outlined below (see 6.4.2). The 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.

Clinic Study Product Destruction Log
This log should be completed to document the destruction of the VR(s) in the specific biohazard waste container/bin. This will be the final documentation required for documenting the accountability of any used VR that is not destined for further testing. If a VR is inserted in the clinic and then removed, during the same visit, due to an adverse event or error subsequently discovered, the VR would be placed in the container for destruction.

Specimen Storage CRF
Site staff must document collection and storage of all returned used vaginal rings *that are intended for remnant content analysis testing* on the Specimen Storage CRF, as well as the Clinic-Specific Study Product Accountability Log.

After documenting return of used rings on the CRF (if intended for remnant content analysis testing) and clinic log, clinic staff should proceed to follow the directions outlined in SSP section 9.7.9. Placement of the used ring in the amber biohazard bag (supplied by MTN Laboratory Center) for storage is documented on the Clinic-Specific Study Product Accountability Log.

In the unusual event that a VR was dispensed but never inserted, the unused vaginal ring must be returned to the clinic and the event documented by study staff on the Clinic-Specific Study Product Accountability Log. The unused vaginal ring should be returned to the pharmacy for quarantine. Only unused vaginal rings (never inserted into the vagina) may be returned to the pharmacy. Clinic staff and pharmacy staff will complete the Pharmacy Record of Return of Clinic-Specific Unused Vaginal Rings.

Clinic Ring Storage Accountability Record
This log should be completed to document the storage and return of the VR(s) for participants in Regimen B (the cyclic use regimen group, see section 6.4.2 for details).

6.4.2 Ring Storage Instructions During 2-Day Ring Removal

During the 2-day ring removal periods for participants randomized to Regimen B, the ring will be removed in the clinic and placed in a white zip storage bag. A supply of these bags will be available in the clinic. The PTID, date, and visit number should be recorded on the bag. The left four columns of the Clinic Ring Storage Accountability Record (see Appendix 6-4) must be completed and then the white zip storage bag should be placed in the clinic designated refrigerator in the biohazard bag marked MTN-044. When the ring is retrieved from the refrigerator to return to the participant, the right four columns of the form must be completed. See Appendix 6-3 for further details.

6.5 Duration of Vaginal Ring Use

Each participant is expected to wear (vaginally inserted) one VR for approximately 90 days. The regimen of VR wear depends upon the randomization of the participants. Participants randomized to Group 1/Regimen A will wear the VR for 90 days continuously. Participants randomized for Group 2/Regimen B will wear the VR for 28 days and removed for 2 days and inserted for two more cycles in a similar fashion. Participants should be counseled to refrain from removing the ring until the applicable clinic visit, unless instructed otherwise by site clinic staff. If a Regimen B participant is unable to complete her Day 28 Visit within the visit window (allowable visit window is study days 27 – 29, per SSP Section 11), site clinic staff will instruct her to remove the vaginal ring on her own (preferably on Day 28) and bring the used ring with her to the site clinic as soon as she is able. Refer to SSP Section 5.5.3 for further guidance on making up missed visit procedures.

6.6 Prohibited and Permissible Medications

Certain medications are prohibited during study participation. Due to potential interactions between levonorgestrel and certain antibiotics and corticosteroids, select antibiotics and corticosteroids are prohibited. Additionally, pre-exposure prophylaxis (PrEP) and post exposure prophylaxis (PEP) regimens are not permitted during trial participation and warrant permanent discontinuation of the study ring. Medications listed in Protocol Section 6.8 result in temporary product hold as per Protocol Section 9.3 and the PSRT must be consulted once the temporary hold is initiated. The PSRT should also be consulted if the Site PI has concerns about extended participant use of any moderate or weak inducers or inhibitors of CYP3A4 as listed in Appendices 6-5 and 6-6. Please refer to Protocol Sections 6.8 and 9.3 and SSP Section 7.1.4 for details.

6.6.1 CYP3A4 Inhibitors and Inducers

Prior to enrollment, participants are prohibited from using CYP3A4 inhibitors and inducers, since both dapivirine and levonorgestrel are CYP3A4 substrates – they are metabolized by CYP3A4. Study staff must promote the avoidance of strong CYP3A4 inhibitors and inducers (prescription medications, over-the-counter medications, herbal supplements, and nutritional supplements) via any route of administration (other than topical) during study participation. If a participant reports current or expected use of a strong CYP3A4 inhibitor or inducer during the study, this will result in a temporary product hold and the PSRT should be consulted.

Appendix 6-5 outlines CYP3A4 inhibitors that participants should avoid using concomitantly in this study. Appendix 6-6 outlines CYP3A4 inducers to be avoided.

Information in Appendices 6-5 and 6-6 is adapted from:
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#4

These lists are for guidance and may not be all inclusive. If drug-drug interaction questions arise during the study that cannot be answered by any of the study-related materials provided (protocol, SSP, SOPs), please contact the PSRT. Medications with unknown interactions will be dealt with on a case-by-case basis with input from the PSRT, as needed.

6.6.2 Permissible Medications

Some medications are permitted to be taken during study participation. All prescription medications, over-the-counter preparations, vitamins, nutritional supplements, and herbal preparations will be recorded as concomitant medications. It is important to note that single dose oral fluconazole for the treatment of vaginal fungal infection is permitted. Short courses of medications that are considered weak or moderate CYP3A4 inhibitors and inducers are permitted during study participation. Topical corticosteroid and antibiotics are permissible. If questions arise about permissible medications that cannot be answered by any of the study-related materials provided (protocol, SSP, SOPs), please contact the MTN-044/IPM 053/CCN019 PSRT. Inquiries will be dealt with on a case-by-case basis with input from the PSRT, as needed.

6.7 Vaginal Ring Retrieval

Protocol Section 6.5.3 specifies the circumstances under which the study vaginal ring must be retrieved from participants. When product retrieval is required, it is expected that the participant will go to the site clinic to return the ring to site clinic staff as instructed. Participants in Regimen A should have the ring retrieved at Day 90/Visit 11. As noted above, participants in Regimen B should have the ring removed and stored in the clinic on Days 28, 58, and 90 (Visits 5, 8, and 11).

The VR must be retrieved and returned to the clinic within 24 hours when study product use has been permanently discontinued due to potential or known HIV infection or pregnancy. The VR must be retrieved within 5 working days following permanent discontinuation of study product use (early or scheduled) from the study for any other reasons, as specified in Protocol Section 9.3. The VR must be retrieved within 7 working days following temporary hold of study product

use with an expected duration of greater than 7 days, as specified in Protocol Section 9.3. If the VR is not returned within these time frames, clinic staff must notify the MTN-044/IPM 053/CCN019 PSRT and complete a Protocol Deviation Log CRF.

The retrieved vaginal ring must be documented by clinic staff on the Specimen Storage CRF and the Clinic-Specific Study Product Accountability Log. If the vaginal ring cannot be retrieved (i.e., participant disposed of it or it was lost after removal), this must be documented on the Protocol Deviation Log CRF and the Clinic-Specific tudy Product Accountability Log. Related details and counseling around the need to ensure return of study product to site should be detailed in the participant's chart notes.

6.8 Vaginal Ring Complaints

During the study, a problem or concern may be observed with a VR. A problem may be noted by the pharmacy staff, clinic staff, or the participant. These complaints may be about the dosage form (vaginal 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 Principal Investigator and the site pharmacist of record (PoR) of the study product complaint. This notification should include as much detail as possible. The following information should be provided in the email: PTID, date of the observed issue, date that the issue was reported, date VR was dispensed, whether an adverse event occurred, description of the nature of the issue, pictures (if relevant), and any other details deemed necessary. If the VR complaint is for odor and the VR is also discolored; the VR will be discontinued and the PSRT will be notified.

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 VR, then the unused VR should be quarantined in the pharmacy. If the complaint/issue is concerning a used VR, then the clinic staff should process/store the VR per SSP Section 9.

Appendix 6-1: MTN-044/IPM 053/CCN019 Prescription

Health Decisions

MTN-044/IPM 053/CCN019 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 and ID:	University of Pittsburgh CRS 1001

Participant ID: ☐☐☐–☐☐☐☐☐☐

Regimen:

_____**continuous** _____**cyclical**

Did the participant provide written informed consent for enrollment into MTN-044/IPM 053/CCN019? YES ☐ NO ☐ Clinic Staff Initials: _____

MTN-044/IPM 053/CCN019 Vaginal Ring
200 mg DPV + 320 mg LNG

Sig: Insert one ring into the vagina.

Quantity: One vaginal ring. May be refilled as needed per request by designated clinic staff on MTN-044/IPM 053/CCN019 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: _____ Date: ☐☐ *dd* – ☐☐☐ *MMM* – ☐☐ *yy*

Version 1.0: 17APR2018 **Pharmacy**

Appendix 6-2: MTN-044/IPM 053/CCN019 Vaginal Ring Request Slip

Health Decisions

MTN-044/IPM 053/CCN019 VAGINAL RING REQUEST SLIP

CRS Name and ID:	University of Pittsburgh CRS 1001

Participant ID: ☐☐☐–☐☐☐☐☐☐

Regimen: _____continuous _____cyclical

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. Deliver the original white copy (labeled "Pharmacy") to the pharmacy. File the yellow copy (labeled "Clinic") in the participant's study notebook.

☐ **RE-SUPPLY** → **Reason:** _____

Pharmacy: Dispense 1 vaginal ring.

☐ **HOLD** → **Reason:** _____

Pharmacy: **Do not** dispense further vaginal rings to the participant until another MTN-044/IPM 053/CCN019 Vaginal Ring Request Slip marked "RESUME" is received.

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

☐ **Do not** dispense a vaginal ring. Participant will continue use of current vaginal ring.

☐ **PARTICIPANT DECLINE**

☐ **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.

Authorized Prescriber Name *(please print)*: _____

Authorized Prescriber Signature: _____

Date: ☐☐ ☐☐☐ ☐☐
dd *MMM* *yy*

Version 2.0: 24APR2018 **Pharmacy**

Appendix 6-3: Clinic Ring Storage Instructions

MTN-044/IPM 053/CCN019

Ring Storage Instructions for Cyclically Used Rings (Regimen B)

Participants assigned to cyclically used ring administration (Regimen B) will return to the clinic at Visit 5 and Visit 8 for ring removal for 2 days. They will return at Visits 6 and 9, respectively, for reinsertion of their ring. These instructions outline the process and documentation for ring accountability and storage these visits.

1. The participant's ring will be removed in the clinic and rinsed with tepid water then blotted dry with a clean paper towel.
2. The ring will be placed in a white zip bag supplied by MTN pharmacists.
3. The participant's PTID, date and visit number will be documented on the label on the bag.
4. The first four columns (Removal and Storage) of the ring storage accountability record will be completed and the ring will be placed in the clear biohazard bag marked MTN-044 (in the clinic refrigerator).
5. When the participant returns for ring reinsertion, the last four columns (Return for Reinsertion) of the accountability record will be completed.
6. The white zip bag can be discarded in a biohazard container.

Appendix 6-4: Clinic Ring Storage Accountability Record

MTN-044/IPM 053 Clinic Ring Storage Accountability Record
(for 2-Day Used Vaginal Ring Removal)

REMOVAL AND STORAGE				RETURN FOR REINSERTION			
Date Stored (dd-MMM-yy)	PTID	Visit#	Clinic Staff Initials	Date Returned to ppt (dd-MMM-yy)	PTID	Visit #	Clinic Staff Initials

Clinic Staff Instructions: Complete one row each time a used VR is removed from the participant and stored in the refrigerator. Complete the "Return for Insertion" columns of that row when the ring is retrieved from the refrigerator and returned to the participant for reinsertion. All entries must be made in dark ink. Corrections may be made by drawing a single line through incorrect entries, entering correct information, and initialing and dating the correction.

Appendix 6-5: CYP3A4 Inhibitors to Avoid

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

Appendix 6-6: CYP3A4 Inducers to Avoid

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

^The effect of echinacea varies widely and is preparation-dependent.

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

Note: This listing is for guidance and may not necessarily be all-inclusive. If drug-drug interaction questions arise during the study that cannot be answered by any of the study-related materials provided (protocol, SSP, SOPs), please contact the MTN-044/IPM 053/CCN019 PSRT (mtn044psrt@mtnstopshiv.org). Medications with unknown interactions will be addressed on a case-by-case basis with input from the PSRT, as needed.

Section 7. Clinical Considerations

Document Revision History

Version	Date	Summary of Changes	Author
V00.01	09 Apr 2018	Initial Draft	Amber Blackmon, Clinical Trial Lead
V00.02	13 Apr 2018	PM Review	Jessica Kappes Clinical Project Manager II
V00.03	01 May 2018	Revised based on external reviews	Amber Blackmon, Clinical Trial Lead
V00.04	16 May 2018	Revised based on external reviews	Amber Blackmon,

			Clinical Trial Lead
V01.00	31 May 2018	Final Version	Amber Blackmon, Clinical Trial Lead
V01.01	27 Jun 2018	Revised based on external review	Amber Blackmon, Sr. Clinical Trial Lead
V02.00	29 Jun 2018	Final Version	Amber Blackmon, Sr. Clinical Trial Lead

This section presents information on the clinical procedures performed in study. 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 9. 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 ongoing 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, advanced practice clinician, 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

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 and documented on the Baseline Medical History Log CRF. ~~Ongoing~~ Medical conditions, problems, signs, symptoms, and findings identified prior to enrollment are considered pre-existing conditions. Pre-existing conditions must be graded and are assigned severity grades in the same way that severity is assessed for AEs. If a pre-existing condition worsens (increases in severity or frequency) after enrollment, the worsened condition is considered an AE and is reportable on the AE Log CRF. If a pre-existing condition resolves after enrollment, but then recurs at a later date, the recurrence is considered an AE. The purpose of having pre-existing conditions documented is to ensure that abnormalities present at baseline and later observed during follow-up, at the same severity and frequency, are not documented as adverse events (see Section 8 for more information).

7.1.2 Participant-Reported Conditions

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

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

To obtain a complete, accurate, and relevant participant self-reported medical history, it will be necessary to ask the participant about her past medical conditions and surgeries, as well as any conditions she is currently experiencing at the time of the Screening and Enrollment visits. It is recommended that sites use the Baseline Medical History Questions sheet (as a source document worksheet) in conjunction with the Baseline Medical History Log CRF and/or chart notes to guide and document medical history taking. Sites may also use a site-specific form per standard site procedure. Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit complete and accurate information from the participant. This is especially important with regard to details about severity and frequency of baseline medical history conditions.

When collecting medical information from the participant, site clinicians should ask probing questions to obtain the most complete and accurate information possible. Details of all relevant conditions identified during the baseline medical history review should be recorded within the Baseline Medical History Log CRF. Relevant conditions include (but are not limited to): hospitalizations; surgeries; allergies; conditions requiring prescription or chronic medication (lasting for more than 2 weeks); and, any condition(s) currently experienced by the participant. The clinician should record as much information as possible about the severity and frequency of any baseline medical condition in the description field within the Baseline Medical History Log CRF to best describe the condition at the time the participant enters the study. In addition to participant-reported conditions, record the following on the Baseline Medical History Log CRF:

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

Generally, it is not expected that conditions less than Grade 1 would be included on the baseline medical history log, unless determined to be relevant by the site clinician.

Clinicians should also assess if the participant meets the exclusion criterion of having any contraindications to a progestin-only contraceptive method, as defined by a category 3 or 4 CDC US Medical Eligibility Criteria for Contraceptive Use (2016) condition (see appendix 7-1). 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.

When collecting medical history, sites should also assess menstrual history and complete the required Screening Menstrual History CRF, at the Screening Visit, and Enrollment Menstrual History CRF, at the Enrollment Visit. Medical history information may be obtained from reviewing the participant's medical records, in accordance with IRB policies.

Sites should complete an entry on the Baseline Medical History Log CRF for any abnormal genital bleeding patterns (per the DAIDS Female Genital Grading Table for Use in Microbicide Studies) reported by the participant. Site staff should carefully consider any abnormal bleeding patterns since participants must have regular menstrual cycles of approximately 21-35 days' duration to be eligible for study participation, and ideally, menses

must not coincide with the first 3 days of product use. Although changes in genital bleeding will not be considered an AE during follow-up (unless also deemed to be an SAE or result in early discontinuation from the study), such changes will be assessed (via SMS and the Vaginal Bleeding Assessment CRF), so it is important to document a participant's baseline abnormal genital bleeding patterns to the extent possible.

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

Information documented on the Baseline Medical History Log 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 and severity grade. Make sure the "Is the condition ongoing?" field is completed/updated for each entry prior to final eligibility confirmation.

Chronic conditions should be marked as "yes" for the question "Is the condition ongoing?" at the Enrollment Visit, even if the participant is not currently experiencing an acute event (e.g., intermittent headaches, seasonal or acute allergies). For severity grading, the highest severity experienced for the condition should be used. In the 'Description of medical history condition/event' item, note the typical severity for outbreaks/acute episodes of the condition, and whether the condition is currently being experienced by the participant, or historical.

During screening, if a participant reports having a history of anaphylactic reactions (such as acute anaphylaxis after eating peanuts), even if it has happened only once before in her lifetime, it is still important for the site clinician to document these events as a pre-existing condition on the Baseline Medical History Log CRF. Per the "acute allergic reaction" row of the DAIDS Toxicity Table, an acute anaphylactic event is considered a severity grade 4 as it is by definition a life-threatening reaction. Record the condition/event as "allergic reaction to peanuts", note types of symptoms (e.g., "throat swelling" or "shortness of breath"), and indicate severity grade 4 in the "Description of medical condition/event" At the Enrollment Visit, check "yes" to the question, "Is the condition ongoing?" and check "no" for the question "Is condition/event gradable?", as the participant was not experiencing an anaphylaxis event at the time of enrollment/randomization. An AE submission for an anaphylactic reaction is required if this same event occurs after enrollment or during study follow-up. Any acute allergic reaction less than a grade 4 should be documented as a chronic condition.

If a pre-existing condition is resolved as of the date of enrollment/randomization, do not make any changes to the severity grade (similar to what is done when resolving adverse events). In this case, the response to the question, "Is the condition ongoing?" must be marked "no." If a pre-existing condition first identified at the Screening Visit is ongoing at the Enrollment Visit, 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 protocol requires documentation of all medications taken by a study participant, beginning at her Screening Visit and continuing throughout her study follow-up period. The Concomitant Medications Log CRF is used to document all concomitant medications used by a given participant during her study participation. 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.

Participants may use concomitant medications during study participation with the exception of medications and products listed as prohibited in protocol section 6.8. Prohibited medications include strong CYP3A inhibitors or inducers. Common examples of medications that are strong, moderate and weak CYP3A4 inhibitors and inducers are provided in SSP Section 6, appendices 6-5, 6-5. Of note, single dose oral fluconazole for the treatment of vaginal fungal infections is permitted. If site staff have questions about a specific medication and whether or not it is prohibited, they should contact the PSRT for guidance.

In addition, per protocol section 5.2, participants must be using an effective form of non-hormonal contraception at the time of enrollment. To be eligible, participants must also state a willingness to refrain from the use of any non-study vaginal products and other devices as per protocol section 6.9 (e.g., spermicides, female condoms, diaphragms, other intravaginal rings, vaginal medications, menstrual cups, cervical caps (or any other vaginally applied barrier method), vaginal douches, lubricants, sex toys etc.) 24 hours prior to enrollment through completion of Visit 15. Participants are also expected to be sexually abstinent i.e., no receptive intercourse (vaginal, oral and finger stimulation) and no tampon use for the 24 hours preceding the Enrollment Visit and clinical visits where samples are taken and for one week following each cervical biopsy.

7.2 Clinical Instructions for Checking Ring Placement

At the Enrollment Visit, following insertion of the vaginal ring, the study clinician or designee should perform a digital exam to check for correct placement of the vaginal ring. The study clinician also may check placement of the ring (via visual or digital inspection, per clinician discretion) at pelvic exams done during follow-up visits, and whenever needed. The following is the procedure that the Principal Investigator or designated clinic staff should use to verify ring placement:

- After ring placement, ask the participant to walk around prior to verification of correct ring placement
- Have the participant lie comfortably on the examination table in supine position (on her back)
- Upon genital inspection, ensure that the ring is not visible on the external genitalia. If the ring is visible, the placement is not correct
- Make sure the ring does not press on the urethra
- On digital or bi-manual examination, ensure ring placement at least 2 cm above the introitus, beyond the levator ani muscle
- If, on inspection, the ring is found to be inserted incorrectly, remove and reinsert the ring correctly.

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 Medical, Menstrual, and Medication History Review at Follow-Up

The Baseline Medical History Log CRF can be updated with new or corrected information during follow-up, but only in instances when new information related to the participant's baseline medical history status is obtained after enrollment/randomization. For example, results of safety laboratory testing performed at the Enrollment Visit are expected to be received after the Enrollment Visit. While abnormal results (i.e., results that are severity Grade 1 and higher) are not considered exclusionary, they should be documented as pre-existing conditions. If information is added to the Baseline Medical History Log CRF after the Enrollment Visit, a chart note explaining the update is required.

7.3.1 Participant-reported Follow-up Medical and Menstrual History

An updated participant self-reported medical and menstrual 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. Any changes are recorded on the AE Log CRF, as appropriate. A second purpose is to determine whether new symptoms, illnesses, conditions, etc., have occurred since the last medical history was performed. The AE Log CRF itself, chart notes, or a site-specific tool, if desired, may serve as the source document. All newly-identified participant-reported symptoms and conditions will be documented on the AE Log CRF (see Section 8 for details regarding AE documentation).

For purposes of this study, "newly-identified" is defined as one of the following conditions:

- not present at baseline (enrollment);
- present at baseline and has increased in DAIDS grading of severity or frequency during follow-up (includes baseline conditions and ongoing adverse events that increase in DAIDS grading of severity or frequency during follow-up);
- present at baseline, resolves during follow-up, and then re-occurs (excludes chronic condition which should be reported in accordance section 7.1.2 above)

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 "recovering/resolving" on an AE Log CRF.

If, during follow-up, a pre-existing condition resolves or increases in DAIDS grading of severity or frequency from baseline, this must be documented, but not on the Baseline Medical History Log CRF, which is meant to remain a snapshot of the participant's medical history at enrollment. Document resolution of a pre-existing condition in chart notes or another site-specific tracker. If the pre-existing condition reoccurs or increases in severity or frequency from baseline, complete an AE Log CRF to document the new AE (i.e., the baseline condition at an increased severity and/or frequency) and leave the condition's status as "ongoing" on the Baseline Medical History Log CRF. The AE Log CRF should have the

"yes" box marked for the question, "Was this AE a worsening of a baseline medical condition?".

7.3.2 Review of Medications History

At each follow up visit through Visit 15 (1 week after ring removal), review the participant's concomitant medications history and document this review by completing the Concomitant Medications Summary and Concomitant Medications Log CRFs. Ask the participant if she has started taking any new medications, and record on the Concomitant Medications Log CRF any new medications she reports having started since her last medications assessment. In addition, review all previous entries that do not have a "Date Stopped" entered and ask the participant whether she is still taking the medication (and at the same dose and frequency). If the participant has stopped taking a medication, enter the last date the participant used the medication in the "Date Stopped" field. If the participant is taking the same medication but at a different dose or frequency, enter in the "Date Stopped" field the date the participant last used the medication at the original dose or frequency, and complete a new Concomitant Medications Log form/entry for the new dose or frequency. Ensure that concomitant medications mentioned in previous parts of the visit are documented correctly and consistently on the Concomitant Medications Log CRF, so that study records are not discrepant.

7.4 Physical Exams

The goal of the physical exam during the Screening and Enrollment Visits is to collect detailed information on baseline conditions, as well as to evaluate eligibility. A complete physical exam will be conducted at the Screening, Enrollment, and Day 90/PUEV visits. Per protocol Section 7.10, the following assessments are required at the Screening, Enrollment, and Day 90/PUEV Visit physical exams:

- General appearance
- Weight (see Section 7.4.1 for further guidance)
- Height (See section 7.4.2 for further guidance)*
- Vital signs:
  - Temperature
  - Pulse
  - Blood pressure (See section 7.4.4 for further guidance)
  - Respirations
- Neck
- Lymph nodes
- Heart
- Lungs
- Breast
- Abdomen
- Extremities
- Skin
- Neurological

** Note: Height is only required at the Screening Visit*

A targeted physical exam is performed if indicated at visits 3 – 10 and 12 – 14. The following assessments are included in the targeted physical exam:

- General appearance
- Vital signs:
    - Pulse
    - Blood pressure

Other components of the physical exam may be conducted at any time for clinical care. At the screening and enrollment physical exams, site staff should assess for any other medical condition that would make participation in the study unsafe or interfere with interpreting the study data or achieving the study objectives. Physical exam assessments should be documented on the Physical Exam and Vital Signs CRFs.

7.4.1 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.

7.4.2 Height

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

7.4.3 Body Mass Index (BMI)

Height and weight measurements must be used to calculate BMI at the Screening Visit. If the participant's BMI is greater than 40 kg/m^2 at Screening, she is ineligible for enrollment. Sites are encouraged to use the BMI calculator, available on LiveTrial Home to calculate BMI. If a site uses this calculator, once the data are entered, site staff should print out a copy for the participant chart.

7.4.4 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.

7.5 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 Pelvic Exam CRF, which may be source documented on the Pelvic Exam Diagrams (non-Medidata form) or another site-specific source document, as specified in the site's Source Documentation SOP.

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 Principal Investigator/designee is not exclusionary.

7.5.1 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, 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 allowable; refer to Section 11 of this manual). If this is not possible conduct the pelvic exam, collect all required pelvic specimens (including PK), and note the bleeding in her chart and on applicable CRFs (i.e., Pelvic Exam CRF, Bleeding SMS CRF, Vaginal Bleeding Assessment CRF). 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.

7.5.2 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 collect the pelvic PK specimens prior to or at time of ring removal at the Days 28 and 58 visits for participants in Group 2/Regimen B. CVF DPV and LNG concentrations and cervical biopsies should be collected prior to ring insertion for participants in Group 2/Regimen B at Days 30 and 60. On Days 14, 44, and 74, the ring may stay in place for the pelvic exam. The ring should stay in place for the specimen collection at Day 90. If the participant is uncomfortable, the clinician may remove the ring temporarily for the speculum exam and then replace the ring once done.

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.
- Note: participant must have intact uterus and at least one ovary to be eligible for the study

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.

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.

Perform Bimanual Exam: If clinically indicated, after completing all the above-listed examinations and specimen collection and removing the speculum, perform a bimanual exam for adnexal or fundal masses and/or tenderness.

7.5.3 PK Cervicovaginal Fluid (CVF) Collection

At Enrollment, Days 2,14, 28, 30, 44, 58, 60, 74, 90, 91, 92, and 93 or 94 visits, cervicovaginal fluid (CVF) for PK will be collected from all participants. Two (2) pre-weighed dacron swabs will be inserted into the upper vagina (approximately 5 cm/2 inches) and held for a slow count to 10 seconds (one swab each for DPV and LNG levels). Collection of CVF swabs should occur within 15 minutes of collection of blood sample for PK and prior to the collection of all other vaginal/cervical specimens, and prior to the insertion of the speculum.

CVF should be collected prior to ring insertion or immediately following ring removal, as applicable.

Refer to section 9.7.3 of this manual for instructions on weighing, processing and storage of the swabs for PK.

7.5.4 Cervical biopsies for PK and PD

At Visit 4/ Day 14, Visit 6/Day 30, and Visit 11/ PUEV (Day 90), cervical biopsies for PK will be collected from all participants. Cervical biopsies should be collected within 30 minutes of blood samples for PK. Collection timepoints are included in the table below.

Study Visit	Timing of Collection
Visit 4/ Day 14	During pelvic exam
Visit 6/ Day 30	During pelvic exam (prior to ring insertion for participants in Group
Visit 11/Day 90 (PUEV)	During pelvic exam (prior to or at the time of ring removal for participants in Group 2

Using forceps, take two samples for PK and one sample for PD, each approximately 3 x 5 mm in size from different locations from the cervix. Biopsy of the cervix does not require an anesthetic; this procedure typically feels like a pinch or a cramp. Bleeding may be controlled through a combination of applied pressure, silver nitrate and/or Monsel's solution. Neither Monsel's nor silver nitrate should be applied prior to obtaining all genital tract specimens unless necessary for participant safety. The minimum amount of silver nitrate and/or Monsel's solution should be used to control bleeding, as excessive use of these agents may impact PK measures. Cervical biopsies should be the last PK specimens collected during the pelvic exam for this reason. Participants should be informed that they may experience a small amount of bleeding from the vagina 1-2 days following the procedure. If bleeding is reported as being heavier than the participants' usual menstrual period or if the participant experiences a foul odor or a heavier vaginal discharge (more than usual), they should be instructed to contact the study clinic right away. There is a small risk of the biopsy area becoming infected or having bleeding that is heavier than spotting.

All participants will be instructed to abstain from receptive vaginal sexual activities for 24 hours prior to each clinic visit and to abstain from vaginal sexual activities for 1 week after the collection of these samples. Participants will also be counseled to refrain from the use of aspirin (greater than 81 mg) and any other drugs that are associated with the increased likelihood of bleeding for 72 hours prior to and following mucosal biopsy collection.

7.5.5 Cervicovaginal Lavage (CVL) Collection

At Visit 2/Enrollment, Visit 7/Day 44, and Visit 10/ Day 74 visits, CVL for biomarkers will be collected from all participants. CVL should be collected after CVF when both specimens are collected at the same timepoint as to not dilute the CVF sample. Collection timepoints are included in the table below. The study VR should remain in place during sample collections at Visits 7 and 10. A speculum should be used when CVL is collected during the pelvic exam.

Study Visit	Timing of Collection
Enrollment	During pelvic exam (prior to VR insertion)
Visits 7 and 10/ Days 44, 74	During pelvic exam (with VR in place)

Suggested Materials

- Drape sheet

- Gloves
- Sterile Normal Saline
- Sterile tubing (4-5 cm in length) (optional)
- Metal specimen rack
- Sterile specimen containers
- Sterile needle-less 30 mL syringe
- Metal speculum
- 2 mL pipette
- 15 mL conical centrifuge tube
- Study source documents
- Clock/timer
- Wet ice or cold packs
- Protective eyewear
- Thermometer

Preparation Notes

✓ Prior to examination, have all necessary materials readily available on exam cart or counter near exam table.
✓ Check expiration of sterile saline prior to use.
✓ A training video is available at: http://www.mtnstopshiv.org/node/773.

Sample Collection and Transport:

- Draw 10 mL of sterile normal saline into the syringe.
  - 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 10 mL of saline onto the cervix, or the vagina if the cervix was removed. Gently tilt speculum if necessary to avoid leakage of saline.
- Place tip of a 2 mL pipette onto posterior blade of the speculum and draw fluid into
- pipette, using care not to touch the vagina or cervix, if applicable.
  - Use the 10 mL of saline to lavage the cervix, fornices and vaginal walls. Be sure to lavage each side wall at least twice. Only use the original 10 mL of saline. Do not use any additional saline to perform lavage.
- The saline must be in contact with the vaginal vault for at least 1 minute.
  - After at least 1 minute of contact, remove lavage fluid with 30 mL syringe and sterile tubing or 2 mL pipette.
- Save lavage fluid for analysis. Transfer fluid to 15 mL conical centrifuge tube.
- Once lavage procedure is complete, visually inspect cervix and/or vagina.
- Verify labeling of all specimens with study identifiers, visit code, date of collection.
- Place specimen in refrigerator or on wet ice or cold packs immediately after collection. See SSP section 9 Lab Considerations for details on specimen storage and transport.

7.5.6 Documentation of Findings

All exam findings (normal and abnormal) should be documented on the site-designated source document, as specified in the site's Source Documentation SOP. All abnormal findings must be thoroughly documented (e.g., to include type, size, anatomical location, and

severity grade) on the Pelvic Exam CRF, and any other relevant source documents as desired, to ensure appropriate assessment can be provided during the next pelvic exam.

All abnormal findings observed during the Screening and Enrollment Visits will be documented on the Pelvic Exam CRF and the Baseline Medical History Log 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 AE Log CRF. The results of site local laboratory test results performed using specimens collected during pelvic exams are recorded on the STI Test Results CRF.

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

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

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 CRF term.

7.6 STI/RTI/UTI

7.6.1 Considerations at Screening/Enrollment

Participants diagnosed during Screening and Enrollment with an RTI or UTI may only enroll in the study following completion of treatment and resolution of all symptoms, provided this occurs within 60 days of obtaining informed consent. See Exclusion Criterion #3 in Protocol Section 5.3. Participants diagnosed with an acute STI requiring treatment per CDC guidelines at Screening or Enrollment are ineligible to enroll. See Exclusion Criterion #4, and the note listed underneath, in Protocol Section 5.3.

7.6.2 STI/RTI/UTI Diagnosis

Clinical and laboratory evaluations for gonorrhea, chlamydia, syphilis, and trichomonas are required at screening, and only conducted if indicated at all other visits. If an STI, RTI, or UTI is identified during follow-up, it should be documented as an AE. 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 based solely on the presence of symptoms indicative of a possible UTI, or other method of diagnosis (i.e., urine culture or dipstick) as per site standard of care. See SSP Section 8 for guidance on documenting UTI AEs based on symptoms or culture.

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

7.6.3 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; however, they will be captured on the STI Test Results CRF and in the source documentation.

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 the study but may be recommended per local guidelines.

7.7 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 of vaginal discharge and may investigate clinical findings of vaginal discharge if a transmissible infection is clinically suspected. Whether to treat the underlying cause of the abnormal vaginal discharge will depend on:

1. The underlying diagnosis, and,
2. The presence or absence of symptoms.

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. Sites should prescribe non-vaginal treatment when possible.

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 not be reported since asymptomatic yeast and bacterial vaginosis are not considered adverse events per protocol, in these instances, the clinician observed vaginal discharge should be noted in the chart notes.

7.8 Genital Bleeding Assessment

At each scheduled follow-up visit, study staff will actively ascertain if there are any updates to the participant's menstrual history and whether any genital bleeding was experienced since her last visit. This information is documented on the Bleeding SMS CRF, which is required at Visits 3 – 14; if any spotting/bleeding is reported, the Vaginal Bleeding Assessment CRF is also required. Bleeding information will also be ascertained by the SMS bleeding questions. These responses will be reported on the Bleeding SMS CRF. 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. Per protocol section 8.3.1, changes in genital bleeding will not be reported as an AE, unless deemed to be a Serious Adverse Event or results in early discontinuation from the study. Incidences of all bleeding, regardless of whether AE/SAE criteria are met, should be documented on the Vaginal Bleeding Assessment and Bleeding SMS CRFs. At Visits 15 – 18, the participant will be asked if she has returned to menses. This will be documented on the Phone Follow-up CRF.

7.9 Management of Laboratory Test Results

Serum creatinine, CBC with platelets and differential, and AST/ALT will be performed at Screening, Enrollment, Day 28, and Day 90. HIV testing will be performed at Screening, Enrollment, and Day 90. Sex hormone-binding globulin (SHBG) and albumin will be tested at enrollment and the Day 90/PUEV/Early Termination Visit. Serum progesterone and estradiol will be tested at Visits 2-11. The SHBG/albumin and progesterone/estradiol tests are for research purposes only, and clinical management of results is not required. The Principal Investigator 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. Results should also be documented on CRFs as follows: serum creatinine, albumin and AST/ALT results on the Local Laboratory Results CRF; CBC with platelets and differentials on the Hematology CRF; HIV test results on the HIV Test Results CRF; and SHBG, serum progesterone and estradiol on the Hormone Tests CRF.

Lab results reported on the Local Laboratory Results and Hematology CRFs should be entered using the units reflected in the DAIDS toxicity table version 2.1. If the units present on the source results report do not match the units on the eCRF and in the DAIDS Toxicity Table, values should be converted before entry into the CRF.

The SCHARP Lab Unit Conversions Tool can be found and accessed at the following ATLAS page:
https://atlas.scharp.org/cpas/project/Collaborators/Lab%20Unit%20Conversion%20Tool/begin.view

This tool will enable sites to convert local lab values and enter them into Medidata Rave using the units reflected in the DAIDS toxicity table. Please note that this tool rounds converted lab values to three (3) digits after the decimal. Site use of this tool is optional, and strongly recommended for sites that must convert local lab values in order to enter them into Medidata Rave for a given study.

In addition to participant-reported conditions, record all abnormal Screening Visit lab values (i.e., severity Grade 1 and higher), regardless of grade, on the Baseline Medical History Log CRF. Abnormal laboratory test results from the Enrollment Visit will not be considered exclusionary but will be documented as pre-existing conditions. These abnormal findings will be graded and may result in product discontinuation as per Protocol Section 9.3.

At a minimum, all test results of severity Grade 3 and higher judged to be related to study product use and all results requiring product discontinuation should be urgently reported to the site's study clinician and the PSRT should be consulted for further decision on product use.

The Principal Investigator or designee should routinely review participant study records to ensure proper monitoring and clinical management of laboratory test results, and documentation thereof. This includes documentation of referrals for abnormal, exclusionary laboratory results that are identified during the screening process.

7.10 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for temporary hold or permanent discontinuation (Section 9.3), guidance on clinical management in response to observed AEs (Section 9.4), management of STI/RTIs (Section 9.5), management of specific genital events (Section 9.6), HIV infection (Section 9.7), pregnancies (Section 9.8), and guidance on early study termination (Section 9.9). Below is a list of conditions that require permanent study product discontinuation:

- Acquisition of HIV infection
- Allergic reaction to the vaginal ring
- Pregnancy
- Breastfeeding
- Reported use of PEP for HIV exposure
- Reported use of PrEP for HIV prevention
- Non-therapeutic injection drug use
- Participant is 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

If a participant reports current or expected continued use of prohibited medications, as listed in Section 7.1.4 and further described in the appendices of Section 6, this will result in temporary product hold.

All specifications in protocol Section 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.

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, communication must be printed and filed in participant study records.

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

Section 8. Adverse Event Reporting and Safety Monitoring

Document Revision History

Version	Date	Summary of Changes	Author
V00.01	09 Apr 2018	Initial Draft	Amber Blackmon, Clinical Trial Lead
V00.02	13 Apr 2018	Revised based on Medical Monitor Review	Amber Blackmon, Clinical Trial Lead
V00.03	01 May 2018	Revised based on external reviews	Amber Blackmon, Clinical Trial Lead
V00.04	16 May 2018	Revised based on external reviews	Amber Blackmon, Clinical Trial Lead
V01.00	31 May 2018	Final Version	Amber Blackmon, Clinical Trial Lead
V01.01	13 Jun 2018	Revised based on SAE Flow updates	Amber Blackmon, Sr. Clinical Trial Lead
V01.02	15 Jun 2018	Revised based on external reviews	Amber Blackmon, Sr. Clinical Trial Lead
V01.03	28 Jun 2018	Revised based on external reviews	Amber Blackmon,

			Sr. Clinical Trial Lead
V02.00	29 Jun 2018	Final Version	Amber Blackmon, Sr. Clinical Trial Lead

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-044/IPM 053/CCN019. 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)
- Investigator's Brochure for Dapivirine-Levonorgestrel Vaginal Ring

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-044/IPM 053/CCN019, this definition applies to each and every participant, beginning at the time of enrollment/randomization through Visit 15.

8.1.2 Reporting Adverse Events

Per Section 8.3 of the protocol, study staff will report on the AE Log CRF all AEs reported by or observed in enrolled study participants regardless of severity, presumed relationship to study product or expectedness. However, changes in genital bleeding during follow-up *will not be* reportable as an AE, unless also deemed to be a Serious Adverse Event (see Section 8.1.3).

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 the data elements on the form.

Documentation of site-specific delegation of duties should designate study staff authorized by the Principal Investigator to complete the AE Log CRF. Regardless of who initially completes the form, 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 have questions about participant safety or reporting clinical events, they should contact the Protocol Safety Review Team (PSRT) at mtn044psrt@mtnstopshiv.org and cc'ing NICHD_CCN019@healthdec.com.

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 (i.e., enrollment for MTN-044/IPM 053/CCN019) 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 a 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, require additional reporting for rapid review and assessment by IPM, the HD Safety Review Team, the PSRT, and NIH Medical Officers.

8.1.4 Reporting Adverse Events in an Expedited Manner (SAE Reporting)

Serious Adverse Events (SAEs) should be reported promptly in accordance with the Food and Drug Administration (FDA) policy. IPM is responsible for complying with the reporting requirements of SAEs to the FDA in accordance with 21 CFR 312.32. Health Decisions will serve as the third-party monitoring body of SAEs.

All SAEs must be reported within 24 hours of identification/awareness of the SAE via the AE Log CRF in the Medidata Rave electronic data capture (EDC) system, regardless of causality or relationship to the study product. The investigator should complete the SAE section of the Adverse Event Log eCRF within the study Electronic Data Capture (EDC) system which will send the appropriate notifications to HD and SCHARP. SCHARP will notify the PSRT, which includes appropriate funding agencies staff (NIH). The site should also complete the IPM SAE form and submit this to IPM via email at safetyreports@ipmglobal.org within 24 hours of identification/awareness of the SAE. Site Investigators should not wait to collect the additional information needed to fully document the event before initial submission of an SAE; this applies to both the AE Log CRF, as well as the IPM SAE form.

IPM will work with the NIH Medical Officers to perform a medical and expedited reporting assessment of SAEs, and will contact site staff as needed for clarification. In addition, HD will perform data reconciliation reviews to look for consistency between data on the AE Log CRF and the IPM SAE form for a given SAE. For any discrepancies that are identified during this review, HD will place data queries in the EDC system, as appropriate, for site resolution.

When completing the AE Log CRF, 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 to the extent possible. If a previously reported SAE resolves and then later recurs at a level requiring expedited reporting, the second occurrence must be reported as a new log line on the AE Log CRF, if not already completed. Any updates required on the IPM SAE form should be updated on the original form with initials of the person completing the form and date. A new cover page should be used when submitting updates to the IPM SAE form.

Any additional SAE supporting documentation should be submitted whenever possible (with subject identification information redacted) to verify the medical diagnosis. This includes hospital discharge summaries, laboratory report, death certificates/autopsy reports (where applicable), surgical procedure summaries, histology reports, and imaging reports. These supporting documents should be uploaded to the EDC system within 3 days of receipt at the site as an attachment to the Adverse Event Log eCRF.
In the event of an EDC system outage or other complication, whereby sites are not able to complete the AE Log eCRF within 24 hours of an SAE, site staff should phone HD at +1 919-967-1111. Immediately following phone communication, the clinical investigator should complete the IPMSAE Report Form and submit it by fax or email to HD at 1-919-967-1145 or NICHD_019@healthdec.com and to IPM at safetyreports@ipmglobal.org to ensure information on the event is received within 24 hours. HD will then notify the PSRT accordingly and appropriate funding agencies staff. The IPM SAE form is available on the HD Study Home page at https://livetrial.healthdec.com/. Once the system outage is resolved, submission of the AE Log eCRF through the EDC system will be required. Site Investigators should not wait to collect the additional information needed to fully document the event before initial submission of an SAE; this applies to both the AE Log CRF, as well as the IPM SAE form.

Sites are required to submit additional information on the AE Log CRF as soon as significant additional information becomes available. An increase in severity must be reported as a new AE on a new log line on the AE Log CRF. If the increased severity meets SAE reporting criteria, the reporting process should begin including sending a new IPM SAE form.

IPM will be responsible for ensuring that each SAE reported to IPM is appropriately recorded, reviewed, and in compliance with regulatory reporting requirements to the FDA. HD will work with sites to ensure the SAE is properly recorded in the clinical database.

8.2 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in MTN-044/IPM 053/CCN019. 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 the AE text description if the AE is related to a procedure (iatrogenic). For example, if a participant experiences dizziness from a blood draw, then “dizziness due to blood draw” should be submitted as an AE.

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 is MedDRA-coded, and thus, how it will appear in safety reports.

When reporting an AE 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 the AE text description. 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 specify in the AE text description if an AE is 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 an AE is **not** due to the act of study ring insertion or removal, do not include mention of the ring in the AE text description.
- If the text present in the “Comments” field indicates that the AE is due to the act of ring insertion or removal, this same text needs to be present in the AE text description for MedDRA coding purposes. If not, this may result in a clinical data query asking that this information be added to the AE text description so that the AE is described completely and accurately.

Sites should include text in the “Comments” field explaining why the AE has been judged “related” to study product use.

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, and Reproductive System AEs

Vaginal Discharge: Vaginal discharge by participant report and vaginal discharge as observed by the clinician should be graded per the appropriate rows in the FGGT (see below). The verbatim term from the FGGT should be used to distinguish if vaginal discharge was first observed by the site clinician or reported by the participant.

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 both reported by a participant and observed during pelvic examination, only report the one with the highest severity grade. If they are the same grade, "vaginal discharge by participant report" should be reported as the AE term. Grade 3 and 4 vaginal discharge are listed as "NA" in the FGGT, and thus are not pictured here.

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. The Bleeding SMS CRF is completed at all scheduled follow-up visits through Visit 14 and the Vaginal Bleeding Assessment CRF is completed at all scheduled follow-up visits through Visit 14 when bleeding is reported. The Bleeding SMS and Vaginal Bleeding Assessment CRFs may also be completed at interim visits if bleeding or spotting is reported by the participant at an interim visit. Both CRFs are necessary to capture all vaginal bleeding events experienced by participants. Genital bleeding events are not reportable as adverse events for MTN-044/IPM 053/CCN019 unless they are also deemed to be SAEs or result in early discontinuation from the study. Vaginal and/or cervical bleeding associated with speculum insertion and/or specimen collection is likewise not considered to be an adverse event.

If bleeding is associated with an observed abnormal pelvic exam finding, sites should document the abnormal exam finding and its anatomical location. 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 site's pelvic exam source document (e.g., Pelvic Exam CRF and/or Pelvic Exam Diagrams), and may also be noted in the comments section of the AE Log CRF.

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 Amsel's 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-044/IPM 053/CCN019, each suspected genital herpes outbreak should be reported as an AE using the term marked on the Pelvic Exam CRF describing the lesion, together with the anatomical location (e.g., “vulvar ulceration”, or “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 new outbreaks of genital warts as AEs, regardless of whether infection with HPV was known to be pre-existing before enrollment. 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, 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 as the AE term (text description) 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 (e.g., “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 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 study CRFs (specifically, the STI Test Results, HIV Test Results, Hormone Tests, Pregnancy Test Results, and Local Laboratory Results CRFs). Sites should document other results if any, in visit chart notes, or in other designated site-specific documents. Throughout a participant’s study follow-up period, lab

abnormalities that meet the criteria for SAE reporting will be reported separately on the AE Log CRF and reported to HD via the reporting system described in Protocol Section 8.4.1.

8.2.5 HIV and AE Reporting

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

If a participant seroconverts and develops one or more signs or symptoms of acute HIV- infection, it is appropriate to report these sign(s)/symptom(s) as a single AE using ONLY the term "seroconversion illness" for the AE term on the AE Log CRF. Use the comments section of the AE Log CRF to describe each HIV-related sign/symptom (e.g., fatigue, pharyngitis) and to note the alternative etiology as due to "acute HIV". To avoid generating a clinical query, please ensure that the term "acute" is included when describing the required alternative etiology in the comment section.

Complete the other items on the AE Log CRF per the general form instructions. The onset date should be completed using the date on which the participant first reported experiencing the first sign/symptom of acute HIV-infection. If there is more than one HIV-related sign/symptom, record the highest severity grade. A seroconversion illness AE is considered 'resolved' when all the associated signs/symptoms have resolved or returned to baseline per participant report, and medications for the symptoms are no longer indicated. Mark any medications indicated and taken for the associated symptoms, if applicable.

If one or more signs/symptoms, reported on separate AE Log entries, are later attributed to acute HIV-infection, update the AE term for the earliest reported sign/symptom AE to the "seroconversion illness" diagnosis and list any other signs or symptoms in the comments section of this AE Log eCRF. Inactivate the applicable AE Log line within Medidata Rave.

8.2.6 Reporting Sexual Assault

Any physical sequelae that result from a sexual assault reported during the study and that meet AE reporting criteria should be reported on a AE log CRF(s). Each physical sequela should be reported as its own AE with the description of the physical sequela as the AE text (i.e., do not mention sexual assault) and with sexual assault (and additional details, if applicable), referenced in the Comments section of the AE log form. Do not complete a separate AE log form for 'sexual assault' as the AE term.

Participants who disclose any form of violence by an intimate partner (or other family member) or sexual assault by any perpetrator should be offered immediate support, care, and referrals according to site-specific SOPs regarding intimate partner violence and sexual assault response. Generally, response to reports of sexual assault should include first line support—listening and offering comfort, help, and information/referrals to connect him/her to services and social support—as well as offering the participant an opportunity to provide a complete history of events, and receive relevant physical evaluations, and treatment and/or referral for any injuries. Emergency contraception and STI prophylaxis/treatment should be offered as clinically indicated. Plans for continued follow-up and care should be outlined to check in on the participant's well-being and uptake of referrals, as appropriate.

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-044/IPM 053/CCN019 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-044/IPM 053/CCN019 will be graded using:

- Addendum 1, DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT) [Dated November 2007]
- If not identified in the FGGT, the DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table), Corrected Version 2.1, dated July 2017

The DAIDS Toxicity Tables can be accessed on the DAIDS RSC web site (http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables).

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, shown below.

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 for Parameters Not Identified in the Grading Table" row of the Toxicity Table (not the "acute systemic allergic reaction" row).
- When grading using the "Estimating Severity Grade for Parameters Not Identified in the Grading Table" row of the Toxicity Table, note that if the condition requires treatment, it must automatically be graded at Grade 2 or higher.
- If urinary tract infections (UTI) are diagnosed on the basis of symptoms alone, they must be graded according to the "Estimating Severity Grade for Parameters Not Identified in the Grading Table" 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. In either case, document the AE using the AE term "Urinary Tract Infection".
- It is preferable that abnormal Pap test findings are reported and graded based on results of a biopsy, using the "Intraepithelial Neoplasia by biopsy" row of the FGGT (below). However, if further evaluation of the Pap test finding is not performed or is scheduled to be performed at a later date, then abnormal Pap test findings should be graded according to the "Pap" row of the FGGT (see below).

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

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 for "related" to be marked. In addition, if the AE is **due to the act** of study ring insertion or removal, then the "related" category should be utilized.

Study staff must 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 product, an alternative etiology, diagnosis, or explanation (e.g., "not biologically plausible") should be provided in the "Comments" field on the AE Log CRF.

- When an AE is assessed as "Related", a rationale (e.g., "due to the act of ring insertion") should be provided in the "Comments" field on the AE Log CRF. Recording "no other cause identified" is not adequate. Although an AE's relationship status defers to clinician discretion, some clinical explanation is helpful in understanding the nature of the adverse event and in determining a more complete safety profile of the study product. Refer to section 8.2 of this SSP manual section for detailed guidance on reporting AEs due to the act of study ring insertion or removal.

If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required. When reporting an AE that is the result of a study-related procedure other than study ring insertion or removal, mark the "Relationship to Study Product" as "Not Related" and explain in the "Comments" field that the event is the result of a study-related procedure (specify).

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

Each AE identified in MTN-044/IPM 053/CCN019 must be followed clinically through study participation until the AE resolves (returns to baseline) or stabilizes.

At each follow-up visit, an authorized study clinician should review each previously identified, ongoing AE and evaluate and document its current status. Outcomes must also be reported on the AE Log CRF. In many cases, the final outcome of an AE will not be available when the AE Log CRF is first completed. In such cases, the outcome should be marked "recovering/resolving" until the outcome becomes available or the participant terminates the study (whichever is earlier), at which point the "Outcome" on the form should be updated.

As noted above, resolution of an AE is generally defined as when the condition returns to its severity grade at baseline (i.e., at the time of enrollment/randomization). 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 stabilizes. 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 (i.e., a new log line in the study database). In this case, the outcome of the first AE will be documented as "recovered/resolved". 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 Visit 15 (or the early termination visit), the status/outcome of the AE should be updated to "not recovered/resolved" on the AE Log CRF. 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. Ongoing AEs that require reassessment after completion of the 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

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.

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 should 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-044/IPM 053/CCN019 PSRT may advise on whether any additional follow-up is indicated on a case by case basis.

For AEs that are re-assessed after Visit 15, 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 AE Log CRFs based on re-assessments that occur after a participant has completed Visit 15.

8.6.1 Reporting Recurrent Adverse Events

If an AE previously reported on an AE Log CRF resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new AE Log CRF (new log line in the study database).

Some participants may have chronic, episodic, pre-existing conditions. In these situations, if the participant experiences an episode of the condition during follow-up that has not increased in severity or frequency from her baseline condition, it would not be considered an AE. For example, if a woman reports that she has three (3) migraines a month before the study, and they continue at the same frequency and severity during the study, these migraines should not be reported as AEs.

An exception to this rule, however, relates to HSV ulcer outbreaks or HPV genital wart outbreaks. Any new outbreak will be considered an AE, even if the participant has a pre-existing herpes or HPV diagnosis/infection. See section 8.2.2 of this SSP manual section for further details.

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 are reported during the study, study staff should fully document in participant chart notes (and/or another designated source 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 that is, in his/her judgment, deemed 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 status.
- 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 HD report it as an SAE. Also, report the issue or problem to all IRBs/ECs responsible for oversight of MTN-044/IPM 053/CCN019, 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 HD

Study sites may receive product- and safety-related information throughout the period of study implementation. This information will be distributed by HD, and may include:

- Updated Investigator's 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-044/IPM 053/CCN019 protocol for a complete description of the participant safety monitoring procedures in place for MTN-044/IPM 053/CCN019. Section 13 of this manual describes the reports prepared by the MTN SDMC in support of MTN-044/IPM 053/CCN019 safety monitoring procedures.

Participant safety is of the utmost importance in MTN-044/IPM 053/CCN019. 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 (SCHARP) and SAE reports to IPM and HD for distribution/reporting to applicable parties, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- Staff at MTN SDMC will review clinic and laboratory data received and apply clinical data queries to data requiring confirmation, clarification, or further follow-up by site staff. These queries will be applied directly in the study database for site staff to resolve (within the Medidata Rave EDC database) on an ongoing basis throughout the period of study implementation. In addition, MTN SDMC staff or an MTN Protocol Safety Physician may contact site staff directly, if needed, for additional clarification of safety data.
- HD will perform a data reconciliation review of data recorded on the IPM SAE Form and the AE Log CRF to ensure consistency. If discrepancies are identified, HD will apply queries directly in the study database as needed for site staff to resolve (within the Medidata Rave EDC database) on an ongoing basis throughout the period of study implementation.
- IPM, along with the NICHD and DAIDS Medical Officers, will review all SAE reports received for MTN-044/IPM 041/CCN019 and follow up on these reports with site staff, the MTN-044/IPM 053/CCN019 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 via monthly conference calls (or on an as needed basis) 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 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-044/IPM 053/CCN019 Protocol Safety Review Team

Roles and Responsibilities of the PSRT

The roles and responsibilities of the MTN-044/IPM 053/CCN019 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports. Once MTN 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 permanent discontinuation of study product use.

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

4. Review SAE data

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

6. Respond to queries regarding study eligibility and/or re-joining a study participant who previously withdrew consent

PSRT Composition

The following individuals comprise the MTN-044/IPM 053/CCN019 PSRT:

- Sharon Achilles, Protocol Chair
- Beatrice Chen, Protocol Co-Chair
- Katie Bunge, MTN Protocol Safety Physician
- Devika Singh, MTN Protocol Safety Physician
- Ken Ho, MTN Protocol Safety Physician
- Jeanna Piper, DAIDS Medical Officer
- Annalene Nel, IPM Medical Officer
- Jill Long, NICHD Medical Officer

Ideally, all members of the PSRT will participate in routine conference calls. At a minimum, the NICHD and DAIDS Medical Officers (or designee if either MO is not available), the Protocol Chair or Protocol Co-Chair, and a MTN Protocol 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.

The SDMC Clinical Safety Associate (CSA) serves as the primary liaison between the PSRT and the SDMC. The CSA will participate in the PSRT calls, and, based on PSRT discussion and request, will place clinical queries in the study database and communicate with sites as needed. The CSA will also bring to the calls for discussion any data trends or issues observed in the context of routine study clinical data reviews.

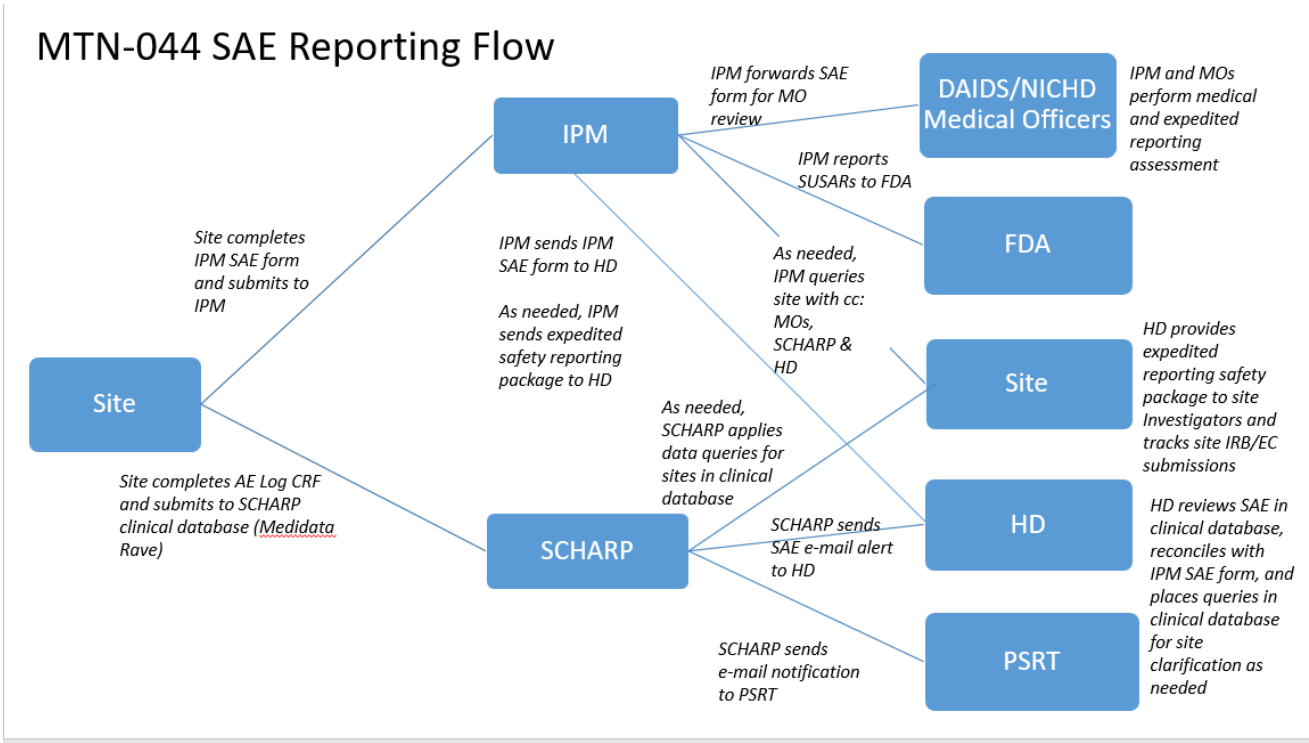
HD Clinical Project Managers, HD Clinical Trial Lead, the MTN SDMC Clinical Data Manager, site investigators and study coordinators may attend PSRT calls as observers and/or discussants.

PSRT Communications

Site consultation with the PSRT will be facilitated using the MTN-044/IPM 053/CCN019 PSRT Query Form, which is available in the Study Implementation Materials section of the MTN-044/IPM 053/CCN019 web page. Site staff will email completed query forms to the MTN Protocol Safety Physicians (mtn044safetymd@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).

Dr. Jill Long is also available to site staff in case of an emergency. Dr. Long's direct telephone number is 301-655-2438 and 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 above-described PSRT query process.

Appendix 8-2: SAE Reporting Flow



Section 9. Laboratory Considerations

Document Revision History

Version	Date	Summary of Changes	Author
V00.01	4-20-18	Initial Draft	May Beamer, MTN Laboratory
V00.02	01 May 2018	Revised based on lab reviews	Amber Blackmon, Clinical Trial Lead

V00.03	16 May 2018	Revised based on external reviews	Amber Blackmon, Clinical Trial Lead
V01.00	31 May 2018	Final Version	Amber Blackmon, Clinical Trial Lead
V01.01	20 Jul 2018	Revised based on Clinic request to exempt collection of blood PK and swab PK samples within 15 minutes for enrollment visit only as previously performed in MTN-030.	May Beamer, MTN LC Michele Austin, MTN LC
V02.00	25 Jul 2018	2nd Final Version	Amber Blackmon, Sr. Clinical Trial Lead

9.1. Overview and General Guidance

As transmission of HIV and other infectious agents can occur through contact with contaminated needles, blood, and blood products, all study staff must take appropriate precautions when collecting and handling biological specimens. Sites must have appropriate written safety procedures in place

Table 9-1. Overview of Laboratory Tests by visit for MTN-044/IPM 053/CCN019

		Visit 1 SCR	**Visit 2** ENR (Day 0)	**Visit 3** (Day 2)	**Visit 4** (Day 14)	**Visit 5** (Day 28)	**Visit 6** (Day 30)	**Visit 7** (Day 44)	**Visit 8** (Day 58)	**Visit 9** (Day 60)	**Visit 10** (Day 74)	**Visit 11** PUEV/Early Termination (Day 90)	**Visit 12-14** (Days 91, 92, & Day 93 or 94)
URINE	Pregnancy test	X	X	*	X	*	X	*	*	X	*	X	
	Urine dipstick/culture	*	*	*	*	*	*	*	*	*	*	*	*
BLOOD	HIV testing	X	X	*	*	*	*	*	*	*	*	X	*
	Plasma for archive		X										
	Serum creatinine	X	X	*	*	X	*	*	*	*	*	X	*
	AST/ALT	X	X	*	*	X	*	*	*	*	*	X	
	CBC with differential and platelets	X	X	*	*	X	*	*	*	*	*	X	*
	Syphilis serology	X	*	*	*	*	*	*	*	*	*	*	*
	DPV concentration		Pre-ring Insertion	X	X	X⌂	X♦	X	X⌂	X♦	X	Pre-ring Removal	X
	Progestogen concentrations including LNG		Pre-ring Insertion	X	X	X⌂	X♦	X	X⌂	X♦	X	Pre-ring Removal	X
	Sex hormone-binding globulin (SHBG) and albumin		X									X	
	Serum progesterone and estradiol		X	X	X	X	X	X	X	X	X	X	
PELVIC	NAAT for GC/CT and trichomonas	X	*	*	*	*	*	*	*	*	*	*	*
	Saline/potassium hydroxide (KOH) wet mount with pH for candidiasis and/or bacterial vaginosis (BV)	*	*	*	*	*	*	*	*	*	*	*	*
	Pap test	^											
	Genital lesion testing for HSV	*	*	*	*	*	*	*	*	*	*	*	*
	Vaginal Gram stain		X					X			X	X	
	CVF DPV concentration		Pre-ring Insertion	X	X	X⌂	X♦	X	X⌂	X♦	X	Pre-ring Removal	X
	CVF LNG concentration		Pre-ring Insertion	X	X	X⌂	X♦	X	X⌂	X♦	X	Pre-ring Removal	X
	Cervical biopsies for DPV concentration and PD				X		X♦					X∞	
	CVF for microbiota		Pre-ring Insertion					X			X		
	CVL for biomarkers		Pre-ring Insertion					X			X		
	Removal and collection of study VR					Group 2 Only			Group 2 Only			X	

X Required; * If indicated and/or per local standard of care; ⌂ To be collected prior to or at the time of ring removal for participants in Group 2;
♦ To be collected prior to ring insertion for participants in Group 2; ∞ To be collected immediately prior to ring removal; ^ If indicated (See section 9.8)

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/.

Table 9-2: Overview of Laboratory Testing Locations, Specimens, and Methods for MTN-044/IPM 053/CCN019

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 Quickvue or SureVue
Urine Dipstick and Culture*	Local lab	Urine	Plastic screw top cup	Siemens Multistix® 10 SG or Uristix 4 or other MTN LC approved method ology
Complete Blood Count with Differential and Platelets	Local Lab	Consult Local Lab Requirements		Local methodology
Chemistries (AST, ALT, Albumin, Creatinine)	Local Lab	Consult Local Lab Requirements		Local methodology
Progesterone & estradiol	Local Lab	Consult Local Lab Requirements		Local methodology
Sex hormone-binding globulin	Local Lab	Consult Local Lab Requirements		Local methodology
Syphilis Serology	Local Lab	Consult Local Lab Requirements		Local methodology
HIV serology	Clinic/Local Lab	Plasma, serum, or whole blood	EDTA or plain, 4-mL	FDA approved tests
Plasma for Archive or Confirmation of Viral Load and HIV Resistance Testing	MTN LC	Plasma	EDTA 10-mL tube	MTN LC Virology procedure
Plasma for Blood PK (DPV & LNG)	JHU CPAL & U-PIT SMBC	Plasma	EDTA 10-mL tube	JHU CPAL collection procedure
Vaginal pH*	In clinic	Vaginal swab	N/A	S/P pH Indicator Strips
Vaginal Saline/KOH Wet Preparation (for BV and/or candidiasis)*	In clinic	Vaginal swab	Tube with 6 drops of saline	MTN LC procedure
Vaginal NAAT for GC/CT	Local Lab	Vaginal swab	Kit specific Transport tube	Cepheid GeneXpert or Gen-Probe Aptima
Vaginal NAAT for *Trichomonas*	Local lab	Vaginal swab	Kit specific Transport tube	Cepheid GeneXpert or Gen-Probe Aptima
Vaginal Swab for PK (DPV and LNG)	JHU CPAL & U-PIT SMBC	Vaginal Swab	2.0-mL Cryovial	JHU CPAL collection procedure
Vaginal Smear for Gram stain	MTN LC	Vaginal Swab	2 Slides	MTN LC procedure
CVF for Microbiota qPCR	MTN LC	Vaginal Swab	2.0-mL Cryovial	MTN LC procedure
CVF for Microbiota: Quantitative Culture	MTN LC	Vaginal Swab	Starplex Starswab	MTN LC procedure
CVL for Biomarkers	MTN LC	Fluid & Pellet	15-mL Conical Tube	MTN LC procedure
Herpes Lesion Testing*	Local lab	Local method	Local method	Local methodology
Cervical Biopsies for PK	JHU CPAL	Tissue	2.0-mL Cryovial	MTN LC collection procedure
Cervical Biopsies for PD	MTN LC	Tissue	2.0-mL Cryovial	MTN LC collection procedure
Pap Test*+	Local Lab	Consult Local Lab Requirements		Local methodology
Used Vaginal Ring (VR) for Remnant Content Analysis	IPM designated lab	Used VR	Biohazard labeled 3”×5” amber Zippit pouch	MTN LC, IPM procedure

*Perform only if clinically indicated per local SOP.
+Perform if participant is over the age of 21 and does not have a documented satisfactory Pap within 3 years prior to Enrollment.

The tests to be performed at each visit during the MTN-044/IPM 053/CCN019 study are listed in Table 9-1. Note that visits 15 – 18 do not involve collection of samples by clinical staff; therefore, these visits are not included in Table 9-1. 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, as shown in Table 9-2.

Table 9-2 also shows where laboratory procedures may be performed: study site clinics or laboratories, approved commercial laboratories, and laboratories within the MTN Laboratory Center (MTN LC), including the MTN Pharmacology Core at Johns Hopkins University Clinical Pharmacology Analytical Laboratory (JHU CPAL) and other testing laboratories, such as University of Pittsburgh Small Molecule Biomarker Core (U-PIT SMBC). Regardless of whether tests are performed in clinic

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

Specimen	Processing	Ship to	Shipping schedule
Plasma for Archive	Prepare as many 1.5-mL aliquots as possible. If sample is collected and held at room temp, aliquot and freeze ≤ -70°C within 4 hours. If refrigerated after collection, aliquot and freeze ≤ -70°C within 24 hours.	MTN LC	Store frozen at site until conclusion of study; however, if plasma for HIV confirmation, ship/deliver immediately to MTN LC Virology Core.
Plasma for Blood PK (DPV & LNG)	Centrifuge and aliquot into two or more cryovials with a minimum of 1.0-mL in each. Freeze within 8 hrs of blood collection.	JHU CPAL: DPV, U-PIT SMBC: LNG	Store frozen at site until conclusion of study.
Vaginal Swab (CVF) for PK (DPV & LNG)	Record Pre- and Post-collection weight of swab. Freeze at ≤ -70°C within 2 hours of collection	JHU CPAL: DPV, U-PIT SMBC: LNG	Store frozen at site until conclusion of study.
Vaginal Smear for Gram stain	Make 2 slides with one vaginal swab. Room temp. Label with LDMS label.	MTN LC	Pair one slide with swab for culture for transport to MTN LC. Store 2nd slide (as backup) at site until all slides from first set are evaluated.
Vaginal Swab for Microbiota: qPCR	2 flocked swabs stored in separate 2-mL cryovials. Freeze at ≤ -70ºC within 2 hrs of collection	MTN LC	Store frozen at site until conclusion of study.
Vaginal Swab for Microbiota: Culture	2 swabs in Starplex transporter. Store at 4ºC if set up after 4 hrs.	MTN LC	Ship/transport on ice packs the day of collection
CVL Supernatant for Biomarker	Centrifuge and aliquot into 6-9 cryovials with ≥1.0-mL in each. Process and freeze ≤ -70ºC within 2 hrs of collection.	MTN LC	Store frozen at site until conclusion of study.
CVL Pellet	Centrifuge, remove residual CVL, then add 0.5-mL normal saline to pellet. Transfer pellet into a single cryovial. Process and freeze ≤ -70ºC within 2 hrs of collection.	MTN LC	Store frozen at site until conclusion of study.
Cervical Biopsies for PK	Collect 2 biopsies, each placed in a 2-mL cryovial. Perform Pre (without biopsy) and Post (with biopsy) weights. Flash-freeze. Store at ≤-70°C.	JHU CPAL	Store frozen at site until conclusion of study.
Cervical Biopsies for PD	Collect 1 biopsy, placed in a cryovial tube containing 1-mL of chilled transport medium.	MTN LC	Deliver to Dezzutti lab immediately. Lab will weigh.
Used Vaginal Ring for Remnant Content Analysis	Rinse in disinfected container and blot dry. Place IVR in amber pouch.	MTN LC	4°C storage at site until conclusion of study.

or laboratory settings, study staff that performs the tests must be trained in properly associated QC procedures prior to performing the tests for study purposes (i.e. training documentation should be available for inspection at any time).

Ideally, one method, type of test kit, and/or combination of test kits will be used for each protocol specified test throughout the duration of the study. If, for any reason, a new or alternative method or kit must be used after study initiation, site laboratory staff must perform a validation study of the new method or test prior to changing methods. The MTN LC must be notified before the change and can provide further guidance on validation requirements.

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

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

9.2. Specimen Labeling

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

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

9.3. Procedures for Specimens that cannot be evaluated

Specimen collection will be repeated (whenever possible) if samples cannot be evaluated per site SOPs. Site clinic and laboratory staff will monitor specimen collection, processing and management as part of ongoing quality assurance (QA) procedures and take action as needed to address any issues or problems.

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

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

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

9.4. Use of LDMS

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

Table 9-4: LDMS Specimen Management Guide to Logging in MTN-044/IPM 053/CCN019 Specimens

Sample	# Tubes, Primary Aliquot ID	Primary Specimen Aliquots	Primary Specimen Unit volume	Primary Aliquot n	Aliquot Sub Additive	Other Spec Derivative	# of additive/		Aliquot unit
Plasma for Archive or Confirmatory Test	1	EA	BLD	EDT	PL1	N/A	CON (follow-up)	2-5	> 1.5	ML
Plasma for PK (LNG and DPV)	1	EA	BLD	EDT	PL1	N/A		2-5	> 1.0	ML
CVF for PK (LNG and DPV)	1	EA	VAG	NON	SWB	N/A	LNG = Heavier swab	1	Net weight	MG
	1	EA	VAG	NON	SWB	N/A	DPV = Other Swab	1	Net weight	MG
Vaginal Smear for Gram Stain	1	EA	VAG	NON	SLD	GRS		2	1	EA
Vaginal Swabs for qPCR	2	EA	VAG	NON	FLS	N/A		2	1	EA
Vaginal Swabs for Culture	1	EA	VAG	CTK	SWB	N/A		1	1	EA
CVL for Biomarkers	1	EA	CVL	NSL	FLD (supernatant)	N/A		6-9	>1.0	ML
					CEN (pellet)	NSL		1	0.5	ML
Cervical Biopsies for PK	2	EA	CVB	NON	BPS	N/A		2	Net weight	MG
Cervical Biopsy for PD	1	EA	CVB	BTM	BPS	N/A		1	1	EA
Used Vaginal Ring for Remnant Content Analysis	1	EA	IVR	NON	IVR	N/A		1	1	EA

*List of Codes and their definitions:

BLD: Whole Blood	**IVR**: Used Intravaginal Ring	**PL1/2**: Single or double spun plasma	**BPS**: Biopsy
VAG: Vaginal Swab	**EDT**: EDTA	**SLD**: Slide	**GRS**: Gram stain slide
CVB: Cervical Biopsy	**NON**: No Additive	**SWB**: Swab	**N/A**: Not Applicable
FLD: Fluid	**CTK:** Culture transporter	**CEN:** Centrifuge	**NSL:** Normal saline
FLS: Flocked Swab	**REC:** rectal		

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

LDMS Help: Questions related to use of LDMS in MTN-044/IPM 053/CCN019 may be directed to MTN LC or LDMS Technical (User) Support. Usual business hours for LDMS User Support are 12:00 am - 6:00 pm (ET) from Monday through Friday. Contact LDMS User Support at:

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

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

Discrepancy Reports: Each site must export its LDMS data to Frontier Science (FSTRF) on a weekly basis. The MTN Statistical and Data Management Center (SDMC) uses exported data to generate a monthly specimen repository report and to reconcile data entered in LDMS with data entered on study case report forms (CRFs). Any discrepancies identified during the reconciliation are included in a

monthly discrepancy report for each site. Sites are expected to resolve all discrepancies within two weeks of receipt of the report. The MTN LC is responsible for reminding sites to adhere to the two-week timeframe and for following up with sites that do not resolve discrepancies within two weeks.

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

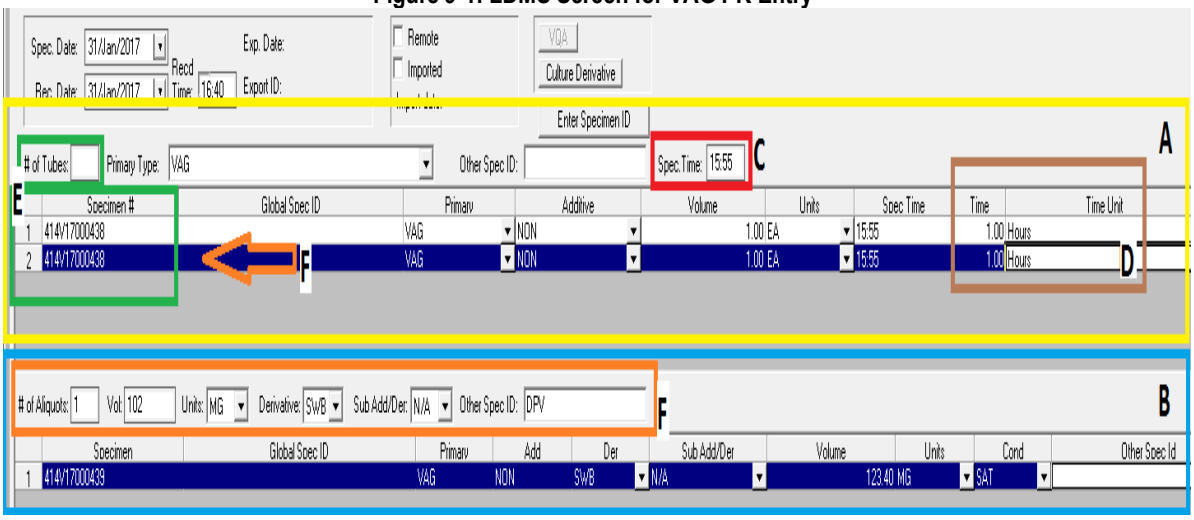
9.4.1. LDMS Codes for Specimen Log In

Table 9-4 should be used as a guide when logging in MTN-044/IPM 053/CCN019 specimens for storage or shipping. Please use the LDMS codes listed above when logging in specimens for each test listed. LDMS tracking sheets can be found in the Study Implementation Materials section on the MTN-044/IPM 053/CCN019 webpage.

9.4.2. Logging in VAG for PK Samples and Time Point for All PK Samples

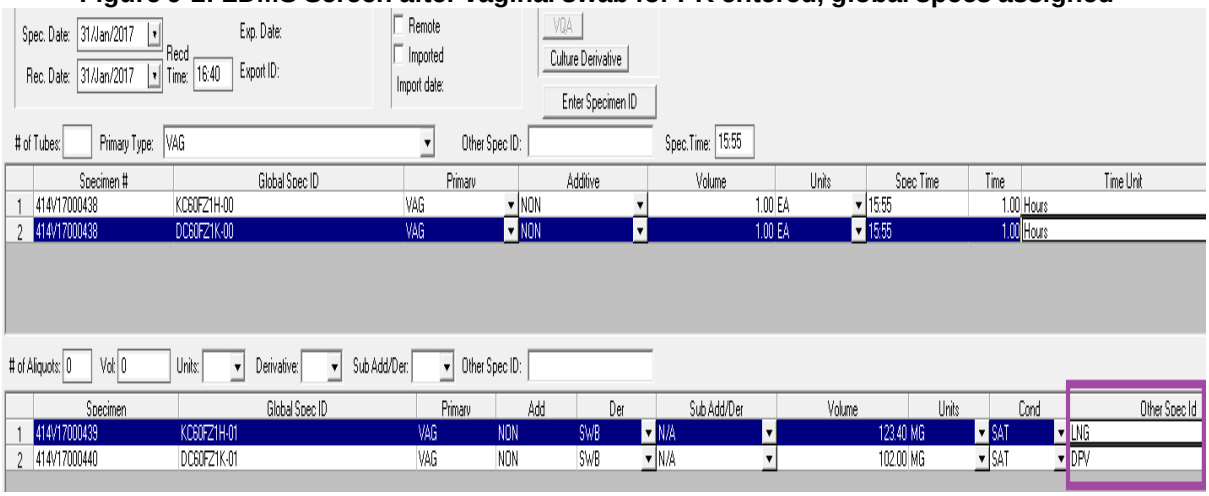
Prior to logging vaginal swabs for PK in LDMS, calculate net weights (post-weight minus pre-weight) in order to designate the heavier swab for LNG testing. In Figure 9-1, the vaginal swabs for PK are entered in the primary area (see yellow rectangle A) as primary VAG sample with 2 tubes, and each tube has an aliquot of weight entered in the lower section for the derivative (see blue rectangle B). The collection time, using the 24-hour clock notation, is entered in the Specimen Time area (see red rectangle C). For this example, it is 15:55.

Figure 9-1: LDMS Screen for VAG PK Entry



After the primary sample is added, two lines corresponding to the # of TUBES appear having the same SPECIMEN # (see green rectangles, E). A unique specimen # and global spec ID will appear after the aliquot information is entered. In this study, there will be no multiple PK time-point visits: therefore no PK time point information is entered in Time and Time Unit area (see brown rectangle D). In Figure 9-1, the aliquot information for the first tube has already been added, and the information in the orange rectangle F corresponds to the second vaginal sample selected (orange arrow F). For MTN-044/IPM 053/CCN019, the OTHER SPEC ID for the aliquot is utilized. The heavier swab will be marked for LNG, and the other swab will be marked as DPV (see Figure 9-2, purple box).

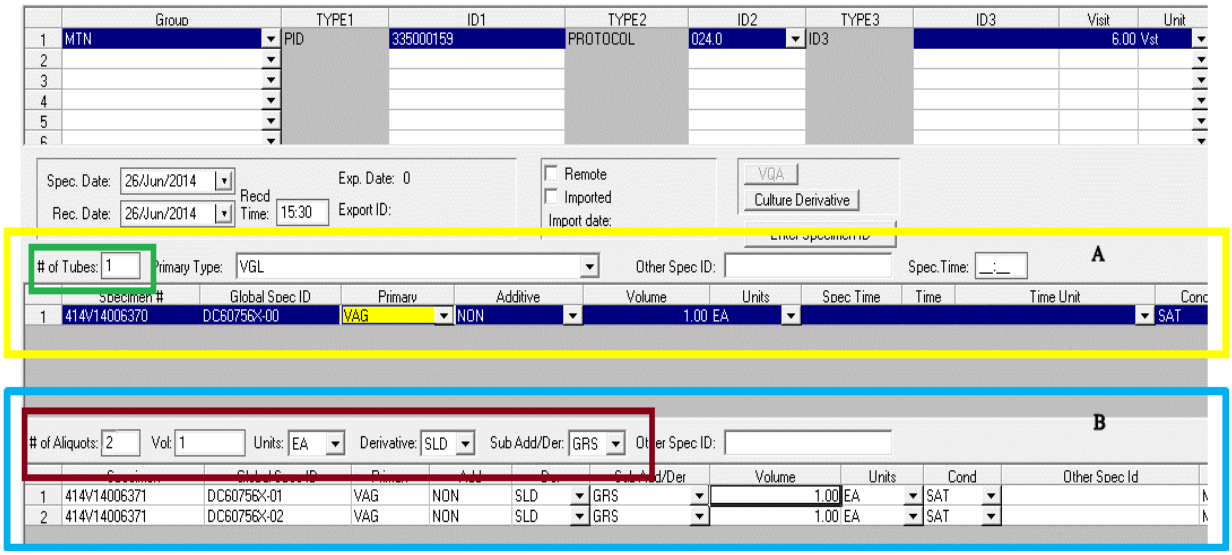
Figure 9-2: LDMS Screen after vaginal swab for PK entered, global specs assigned



9.4.3. LDMS Entry for Vaginal Smear for Gram Stain

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

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



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

9.5.1. Specimen Collection

- The participant should not have urinated within one hour prior to urine collection.

- Provide the participant with a sterile, plastic, preservative-free screw-top urine collection cup labeled with a SCHARP-provided PTID label.
- Instruct the participant to collect the portion of the urine flow that is required by the test
- If the urine is to be used for culture, instruct the participant to clean the labia prior to specimen collection and to collect a midstream urine sample.
- Instruct the participant to screw the lid tightly onto the cup after collection.

9.5.2. Pregnancy Testing

Pregnancy status is a critical participant safety consideration in MTN-044/IPM 053/CCN019. The Quidel QuickVue One-Step hCG urine, Quidel QuickVue Combo hCG urine/serum pregnancy, or Fisher HealthCare Sure-Vue Urine hCG test must be used at all sites. All sites must maintain an adequate inventory of the pregnancy test kits at all times. Inventory should be monitored closely and re-supply orders placed at least 8-12 weeks in advance of actual need (or longer if needed per site procurement policies and procedures). The date and time of pregnancy testing must be documented.

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

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

9.5.3. Urinary Tract Infection

Urine Dipstick and/or Culture: Perform the tests according to the package insert for the dipstick and consult your local SOP for culture.

For initial diagnosis and treatment of a UTI, follow the local standard of care. In the MTN-044/IPM 053/CCN019 SSP, refer to Clinical Considerations Section 7.6 for MTN guidance for UTI diagnosis and treatment and AE Reporting Section 8.3 for additional information on adverse event severity grading.

9.6. Blood Specimens for Chemistry, Hematology, HIV testing, Syphilis, Plasma Archive, Dapivirine (DPV) and Levonorgestrel (LNG) Blood Levels

The blood tests performed at each study visit vary depending on the time point of the visit and potentially the clinical presentation of the participant. Perform all tests according to site SOPs and package inserts. *Note: If locally available tube top colors do not correspond with the tube additives described in this section, use appropriate tubes based on the additives, not the listed tube top colors.*

9.6.1. Specimen Collection and Initial Processing

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

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

9.6.2. Chemistry (Alanine transaminase, Aspartate aminotransferase, Albumin and Creatinine), Hematology (CBC with Diff and Platelets), Sex hormone-binding globulin (SHBG), Progesterone, Estradiol

Testing will be performed per local standard of care.

- Tests performed for Chemistry
  - Albumin
  - Liver Function:
    - Alanine transaminase (ALT),
    - Aspartate aminotransferase (AST).
  - Renal Function:
    - Creatinine
- Hematology tests (Complete blood counts (CBC) with five-part differentials)
  - Hemoglobin,
  - Hematocrit,
  - Platelets,
  - White Blood Cell Count and differential
  - Red Blood Cell Count
- Sex hormone-binding globulin (SHBG)
- Progesterone
- Estradiol

9.6.3. HIV Testing

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

HIV infection status will be assessed using an FDA-approved HIV immunoassay per the HIV testing algorithm (see section appendix 9-1). Rapid tests, such as Oraquick, are considered immunoassays and can be used with whole blood (fingerstick or venipuncture) or plasma. 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 for a second local confirmation test. When sample 2 is drawn, plasma will also be collected for shipment to the MTN Virology Core.

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

9.6.3.1 HIV Test Result Interpretation

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

9.6.3.2 HIV Confirmatory Test for Screening or Enrollment Visit

- Until a participant is randomized/enrolled, treat enrollment testing as part of the screening process to determine participant eligibility.
- If the confirmatory test for SAMPLE 1 is negative, indeterminate or invalid, contact the MTN Virology Core: mtnvirology@mtnstopshiv.org for guidance.
- If the confirmatory test is positive for the screening visit, the participant is considered seropositive and is not eligible for enrollment.

9.6.3.3 HIV Confirmatory Test for Follow-Up Visits

- If, at a follow-up visit, the confirmatory test result on SAMPLE 1 is negative, indeterminate or invalid, contact the MTN Virology Core for guidance:
  - 412-383-8138
  - mtnvirology@mtnstopshiv.org
- If the confirmatory test is positive at a follow-up visit, a second sample of blood (SAMPLE 2 in the algorithm) will be drawn for a second local confirmatory test.
- Plasma is also drawn with sample 2 for shipment to the MTN Virology Core.
  - Draw enough blood to store a total of 5 mL of plasma to send to the virology core. If less than 5 mL of plasma is obtained, contact the MTN Virology Core for guidance.
- Processing of SAMPLE 2 is similar to Plasma for Archive:
  - Log aliquots into LDMS using "Other Spec ID" = CON.
  - Centrifuge per specifications in SSP 9.6.5 and aliquot ≥5 mL plasma into 2-mL cryovials and freeze at <-70ºC.
    - Alert the MTN Virology Core, mtnvirology@mtnstopshiv.org when you are preparing the shipment to ship.
      - The virology core will confirm for you when to ship and will send their current address and other shipping details.
      - The virology core may also request enrollment plasma to be shipped with plasma collected with Sample 2.
- Testing performed at the MTN Virology Core may include repeat confirmation testing, HIV RNA and/or HIV resistance testing.
  - For specific guidance on reporting of HIV results to participants, refer to SSP Section 10.1 HIV pre- and post-test Counseling and HIV/STI Risk Reduction Counseling.

9.6.4. Syphilis Testing

Testing will be performed per local standard of care. Serum is the specimen of choice for treponemal assays (EIA, MHA-TP, TPHA, TPPA, or FTA-ABS) and the non-treponemal VDRL assay. The non-treponemal Rapid Plasma Reagin (RPR) tests may be performed on either serum or plasma. All testing must be done with FDA approved assays and by a CLIA certified laboratory.

Per local standard of care, syphilis testing for MTN-044/IPM 053/CCN019 will be performed using the new Syphilis Total and RPR Assay on the BioPlex 2200 analyzer (BioRad), which provides a reactive/non-reactive result for treponemal IgG/IgM and non-treponemal RPR, and reactive RPR reflexes to titers. Discordant RPR and Syphilis Total results are automatically reflexed to a confirmatory TPPA, in accordance to CDC's forward and reverse testing algorithms.

Questions related to result interpretation concerning eligibility and enrollment in the study should be directed to the MTN-044/IPM 053/CCN019 Protocol Safety Physicians (mtn044safetymd@mtnstopshiv.org).

9.6.5. Plasma Archive

For plasma archive, use collection tubes with EDTA anticoagulant. Aliquot plasma into 2-mL cryovials, store at ≤-70˚C, and batch onsite in storage boxes for MTN-044 Plasma Archive until the MTN LC study team requests shipping and/or testing.

- LDMS will be used to label and track the specimens.
- If sample is collected and held at room temp, aliquot and freeze within 4 hours. If refrigerated or placed on ice after collection, aliquot and freeze within 24 hours.
- Spin blood at room temperature in a centrifuge according to one of these techniques:
    - Single spun: Spin blood at 1300×g for 10 minutes, remove plasma.
    - Double spun: Spin blood at 800×g for 10 minutes, place plasma in a tube to spin again at 800×g for 10 minutes, remove plasma.
- Prepare as many 1.5-mL aliquots as possible, approximately 5-mL total volume.
- If total volume is less than 0.5 mL, redraw as soon as possible.
- If less than 1 mL of plasma is available, store that plasma and inform the MTN LC for instruction.
- If samples are hemolyzed, store the aliquots as per normal and enter comments in LDMS.
- The MTN LC will send instructions to the site when shipping and/or testing is required.

9.6.6. Blood for PK of Dapivirine (DPV) and Levonorgestrel (LNG)

The clinician will collect the vaginal swabs for PK within 15 minutes of the blood draw for PK. *The 15 minute guideline is not applicable for the enrollment visit (to accommodate logistics of sample collection prior to ring insertion).* Cervical biopsies should be collected within 30 minutes of the blood draw. Sites should consider clinic flow when planning for PK draws to ensure sample collection occurs in close succession.

Collect blood into a labeled 10-mL EDTA Vacutainer tube using direct venipuncture.

1. Mix blood sample with the anticoagulant using gentle inversions (8 to 10 times).
2. Centrifuge the sample at approximately 1300×g for 10 minutes. The centrifugation must be completed and sample placed in the freezer within 8 hours of blood collection.
3. Use a pipet to aliquot at least 1.0 mL of the resulting plasma into two 2-mL cryovials (one for DPV and the other for LNG); these will serve as the primary sample. Aliquot the remaining plasma equally into two cryovials; these will serve as a back-up in case the primary samples are accidentally destroyed during shipment.
4. Prepare four storage boxes and label one as “plasma DPV primary samples”, one “plasma LNG primary samples” and the other two boxes “plasma DPV back-up samples” and “plasma LNG back-up samples”. Transfer the tubes from each participant in chronological order into the storage boxes. All samples will be tracked in LDMS.
5. Store the boxes with samples at ≤-70˚C until shipped.
6. See Section 9.9 for shipment to JHU CPAL or delivery to U-PIT SMBC.

9.7. Vaginal Specimens for Herpes Lesion Testing, GC/CT and *Trichomonas* NAAT, Microbiota by qPCR and Culture, Gram Stain, Vaginal Fluid pH and Wet Mount, Vaginal Fluid for PK, and IVR for Remnant Drug Content Analysis

Check for required sequence of specimen collection and diagnostic procedures to be performed during study pelvic exams. The collection order may be described in a pelvic exam checklist or source documents provided by the clinical research site.

9.7.1. Herpes Lesion Testing

Testing will be performed per the local standard of care.

9.7.2. Testing for *GC/CT* and *Trichomonas vaginalis* by NAAT

Testing for chlamydia, gonorrhea and *Trichomonas* is performed at screening and when clinically indicated. Sites can choose to use the Cepheid GeneXpert, 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.

- If using GenProbe Aptima, both GC/CT and *Trichomonas* tests can be performed from one swab. Use only one collection kit.
- If using Cepheid GeneXpert you must use two collection kits, one for GC/CT and the other for *Trichomonas*.
- Use the manufacturer's 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 testing laboratory.

9.7.3. Cervicovaginal Fluid (CVF) for PK of Dapivirine and Levonorgestrel

PK collection times need to be recorded on the LDMS Specimen Tracking Sheet. In addition to sample collection, this section discusses acceptable 'windows' on collection time points and action to be taken if collection falls outside these windows.

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

- When each time-point is due:
  - Blood will be drawn first.
  - Ideally, the clinician will collect the PK swab within 15 minutes of the blood draw and prior to speculum insertion. *The 15 minute guideline is not applicable for the enrollment visit (to accommodate logistics of sample collection prior to ring insertion).*
- Make sure that specimen times are accurate.
- If a collection is missed entirely, notify the MTN-044/IPM 053/CCN019 management team.

In the case that the ring is removed and/or reinserted prior to a visit:

- Vaginal swab for PK should still be collected even if the ring has been out of the vagina for up to 7 days.

Procedure for Vaginal Fluid Sampling for PK assessment and weighing swab

1. On each day of collection of vaginal swabs for PK, QC of the analytical scale is required to ensure accuracy of weighing is within at least 0.1 milligrams. Do not turn off balance until weighing for the day is completed.
2. Materials
   a. Prepare TWO sets of PK swab collection kits at for each participant visit (Suggestion: **Prior to weighing**, use a Sharpie to label the ziplock bag, swab packaging, and tube with a "1" or "2" to keep track of items in each set):
      - Two SCHARP labels with PTID, visit number, visit date, time point, and swab order #.
      - One 2-mL Nalgene cryovial
      - One Pre-packaged Polyester-Tipped (Dacron) Swab (Fisher brand)
      - One Ziplock biohazard sample bag
   b. Urine cup (without lid) or similar lightweight container, placed on middle of scale, to contain items to be weighed. (Some balances have an optional basket.)
   c. A rack that will hold the cryovial
   d. For clinical staff, scissors to cut swab shaft
   e. Calculator
3. Handle items to be weighed with gloves.

4. Place identically-labeled SCHARP label on the cryovial and the biohazard sample ziplock bag.
5. Perform pre-weight.
    a. Zero the urine cup or similar container
    b. Place the labeled 2-mL cryovial in the urine cup.
    c. Place the packaged sterile Dacron swab upright in the urine cup. (Make sure it is not leaning on a part of the scale.)
    d. Record this pre-weight on the LDMS Tracking Sheet.
    e. Place the cryovial and the packaged Dacron swab in the biohazard sample ziplock bag with the matching label to the tube.
    f. If multiple participants on that day, pre-weights for each kit may be obtained, but keep track of labels.
6. Make sure you have the correct participant kit.
    a. In the exam room none of the items in the bag should be thrown into the garbage – only into the ziplock bag.
    b. Prep for the clinician:
        i. Have the rack ready.
        ii. Unscrew the lid of the 2-mL cryovial and place the tube in the rack, the lid in the ziplock bag.
        iii. Start the peel of the packaging of the swab to ensure sufficient separation.
        iv. Peel the packaging and place packaging in the ziplock bag.
        v. The clinician will use the Dacron swab to collect vaginal fluid (slow count to 10).
        vi. Place the swab in the tube.
    c. Cutting or bending to break the swab shaft. (!!!Potential to lose swab shaft!!!)
        i. For the lid to close properly, raise the swab from the bottom of the tube, then cut or bend.
        ii. If cutting the shaft, a suggestion, for leverage, is to not use tip of blades to cut, but make sure shaft of swab is at the pivot point of the scissors, then cut.
        iii. If clinical staff will perform a repeated bend to break the shaft with dominant hand, while doing so, it may be easiest to hold the top of the tube with the forefinger and thumb of the other hand.
    d. Place the cut shaft in the ziplock bag (Suggestion: place the cut shaft in the packaging).
    e. Screw the lid on the cryovial and place sample in the bag with the swab packaging and the swab shaft.
7. Perform Post Weight:
    a. Zero the urine cup or similar lightweight container.
    b. Weigh the capped cryovial containing the absorbed swab tip, the swab packaging and the remainder of the swab shaft (Suggestion: Place the swab shaft into the packaging and have it upright during weighing.)
    c. Make sure that the post-weight is larger than the pre-weight.
    d. Record post-weight on the LDMS Tracking sheet.
    e. Assign the heavier swab of the pair collected at each visit to LNG PK testing.
8. Within 2 hours, place the sample tubes in the freezer at ≤-70˚C.
    a. Series of boxes for MTN-044 VAG SWABS for DPV PK
    b. Series of boxes for MTN-044 VAG SWABS for LNG PK

9. See Section 9.9 for shipment of DPV PK samples to JHU CPAL and delivery of LNG PK samples to U-PIT SMBC.

9.7.4. Vaginal Swabs for Microbiota: qPCR

Vaginal swabs are collected for detection of key microbiota using qPCR at visits 2, 7, and 10. The swabs are stored at <-70ºC and shipped to the LC at the end of the study.

- Label two 2-mL cryovials (Sarstedt) with completed SCHARP labels.
- Collect the specimen by rotating 2 flocked swabs several times over the lateral wall of the vagina. Do not collect swabs in the exact same area that another sample was collected (i.e., collect in a different location in the vagina, preferably closer to the introitus).
- Place the swabs in separate cryovials.
- Break or cut shaft of swab at a minimum of 1-cm beyond the swab and cap the vial.
- Repeat with the second flocked swab as described above.
- Freeze within 2 hours of collection. They can be placed on dry ice at the clinic if transport to the lab is delayed.
- Deliver the tubes with the LDMS Specimen Tracking Sheet to the local LDMS laboratory.
- Log the cryovial into LDMS (Table 9-4) and label each vial with a LDMS label. Avoid covering the entire PTID on the original SCHARP label.
- Freeze at ≤ -70ºC.
- The samples are received by and stored at the MTN LC.

9.7.5. Vaginal Swab for Microbiota: Quantitative Culture

Vaginal swabs are collected for quantitative cultures at visits 2, 7, and 10 and transported to the MTN LC the same day as collection. Delivery instructions follow.

- Use the Starplex Starswab Anaerobic collection and transporter kit. The kit comes with 2 sterile Dacron swabs and a glass transport tube.
- Collect the specimen for culture by rotating 2 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., collect from a different location in the vagina, preferably closer to the introitus). Insert the two swabs into the tube, slowly pushing the swabs half way into the gel, *not to the bottom of the tube*. Break off the shafts of the swabs and secure the cap tightly.
- The specimen may be kept at controlled room temperature for up to 4 hours. After four hours, the specimen must be refrigerated.
- Deliver the Starplex tube with the LDMS specimen tracking sheet to the local LDMS laboratory. The Starplex tube should be accompanied with the vaginal smear for Gram stain.
- NOTE: The LDMS Laboratory for the Pittsburgh CRS is the MTN LC, the testing lab for the specimen.
  - Log the specimen into LDMS (Table 9-4) and affix LDMS label to the Starplex tube.

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

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

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

Wet prep assessments used to diagnose BV and candidiasis are discussed in section 9.7.6.2 and summarized in Table 9-5.

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

- Contact May Beamer (mbeamer@mwri.magee.edu) and Michele Austin (maustin@mwri.magee.edu) of the MTN LC to register names of clinicians who need to take the test.
- The registrants take the test and enter their answers directly on the website.
- The MTN LC sends a report of the results, including any necessary corrective action, to the Laboratory or Clinical Research Site Manager.

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

9.7.6.1 Vaginal Fluid pH, if indicated for BV

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

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

- Obtained by the clinician during the pelvic examination
- Collected by the clinician in a non-speculum exam

Note: a speculum is not required for pH sample collection.

Vaginal Fluid pH Procedure:

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

Table 9-5 Summary of Wet Prep Assessments and Diagnostic Criteria

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

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

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

Preparation and Examination of Wet Prep Slides

Materials:

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

1. Use a pencil to write the PTID and specimen collection date on one side of the frosted end of two microscope slides. Affix a SCHARP-provided PTID label to the other side of the slides (on the frosted end, under the pencil markings)
2. Immediately following collection from the lateral vaginal wall via swab (Dacron or cotton), smear vaginal fluid specimens onto each slide. Alternatively, the swab may be placed in a glass or plastic tube with approximately six drops (100 µL) sterile physiologic saline to allow for non-immediate slide preparation. In this case, vaginal fluid specimens should be smeared onto the two slides upon receipt from the collecting clinician.
3. Apply one drop of 10% KOH to one slide and immediately perform whiff test for a “fishy” amine odor. Then apply cover slip.
4. Apply one drop of sterile physiologic saline to the second slide, emulsify with the vaginal fluid specimen, and then apply cover-slip. Examine immediately at 10X magnification for epithelial cells, budding yeast, and pseudohyphae. Examine at 40X magnification to determine whether observed epithelial cells are clue cells and quantitate the cells. Clue cells are irregularly bordered squamous epithelial cells that are completely covered with bacteria (*Gardnerella vaginalis*). Clue cells must comprise at least 20 percent of the observed epithelial cells in order for the saline prep to be considered positive for clue cells.
5. Examine the KOH slide at both 10X and 40X magnification for yeast and pseudohyphae.

RESULTS:

- If wet prep slides are read in-clinic by clinical staff, results are recorded directly on to source documents and transcribed onto the STI Test Results eCRF.

9.7.7. 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 back-up) will be prepared at each required time point, and both will be logged into LDMS. The primary slide will be delivered to the MTN LC and the back-up will be stored on site or in the LDMS laboratory until written notification is received from SCHARP that the slide may be discarded.

Instructions for preparation of slides

Use a pencil to write the PTID, visit number, and specimen collection date on the frosted end of the slides. The frosted end is the side of the slide that the specimen is to be applied.

1. Immediately following specimen collection from the lateral vaginal wall via swab (Dacron or cotton), roll the swab across each of the two slides.
   - 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.
2. A SCHARP-provided PTID label is placed on the underside of the frosted end of the slide. Write the specimen collection date and visit number in indelible ink (e.g., Sharpie pen) on each label.

3. Allow the specimens to air-dry on the slides. Do not heat-fix.
4. Vaginal smears for Gram stain are logged into LDMS. Place the LDMS label on the frosted end of the slide on top of the pencil markings (same side as sample).

5. The primary slide will be placed in a slide case and transported to the LDMS laboratory.
6. The back-up slide is stored at room temperature at the LDMS laboratory in a slide box for MTN-044 Gram Stain Back-up (in case primary is broken or unreadable).

9.7.8. Cervicovaginal Lavage (CVL) supernatant and pellet for biomarkers

1. 10-mL of normal saline should be used to lavage the cervix, fornices, and vaginal walls. Using a syringe collect all of the CVL and place into a 15-mL conical tube. See MTN044/IPM 053/CCN019 SSP section 7.5 Clinical Considerations for CVL collection.
2. CVL specimens are kept on wet ice or refrigerated and should be processed within 2 hours of collection.
3. At the LDMS Laboratory, the volume of the CVL is estimated for the number of supernatant aliquots. In addition to logging in the cell pellet, this estimated volume is used to log in the number of ≥1-mL aliquots and to create LDMS labels for the cryovials.

4. Centrifuge the 15-mL collection tube of CVL at 800×*g* for 10 minutes.
5. Pipet ≥1-mL aliquots into each supernatant cryovial. Divide among the supernatant cryovials, the final aliquot, which will most likely have volume < 1-mL.
6. Add LDMS label to each cryovial. Without disturbing the cell pellet, pipet as many 1-mL aliquots of supernatant as possible into cryovials.
7. Re-spin the 15-mL conical tube containing cells for 10 minutes at 800×*g*.
8. Without disturbing the cell pellet, pull off additional supernatant and add to a supernatant vial.
9. Resuspend cell pellet in 0.5-mL normal saline and store in a cryovial with an already affixed LDMS label intended for the cell pellet.
10. Freeze all supernatants and cell pellet at ≤-70°C within 2 hours of collection.
11. If < 6 mL total of supernatant recovered, contact the MTN LC.
12. Store one supernatant aliquot in a series of boxes for MTN-044 CVL Supernatant for Biomarker and the remaining aliquots in a series of boxes for MTN-044 CVL Supernatant for back-up.
13. Store the CVL cell pellet in a series of boxes for MTN-044 CVL Pellet.

9.7.9. Testing of Used Vaginal Ring (VR) for Remnant Content Analysis

Used rings will be analyzed for residual levels of DPV and LNG, and will be collected after approximately 90-days of use or early termination visit. The used rings may contain vaginal secretions, and therefore should be treated as a biohazard. The rings will be rinsed then placed and remain in the amber pouch and stored at 4°C until further notice from the MTN LC. Rings that are defective and have been inserted briefly should be photographed and then destroyed at the site via biohazard procedures. Rings that are defective but not inserted should be given to the pharmacist.

Important notes:

- Blood for PK, CVF for PK, and cervical biopsies for PK and PD should first be collected immediately before ring removal for remnant content analysis.
- If the ring is removed by the participant prior to the clinic visit and will not be reinserted, instruct the participant to blot it dry with paper towel/tissue and place it in a ziplock bag/container or the bag provided by pharmacy and store at room temperature. At the clinic, follow the directions below for storage on-site in amber pouch.

Materials:

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

Preparation of used ring for storage on-site:

1. Complete SCHARP label with the participant ID number and visit number and date.
2. Affix the SCHARP label and a biohazard sticker (if one is not already attached to the pouch), making sure not to cover the identifier information.
3. Use PPE when rinsing used VR.
4. The clinician will remove the used VR and place it in a clean container with tap water.
5. Move the VR around in the water or swirl the container to remove vaginal material.
6. Blot the VR dry with paper towels or gauze.
7. The VR should be dry before placing it in the amber pouch.
8. Dispose of cleaning materials and water according to institutional biohazard policy.
9. Site staff will place the ring into the 3”X5” amber Zippit pouch (see figure 9-4)
10. The amber pouch containing the used VR is transported to the LDMS laboratory with the

LDMS tracking sheet for storage at 4°C in appropriate storage container for MTN-044 Used VR for Remnant Content Analysis.

11. At the end of the study, MTN LC will contact IPM-designated testing lab to coordinate shipment.

Figure 9-4: 3"×5" amber Zippit pouch

9.8. Cervical Specimens: Pap Test and Cervical Biopsy Collection for PK and PD

Pap tests are only required if clinically indicated or if a participant is over the age of 21 and has not had a documented normal test within 3 years prior to enrollment. Refer to MTN-044/IPM 053/CCN019 SSP Section 7.5 Clinical Consideration for the collection of two cervical biopsies for PK testing and one for PD testing.

Only the cervical biopsies for PK need to be weighed by the clinical staff. *Cervical biopsy for PD need to be delivered to the MTN LC for immediate processing and weighing of biopsy.*

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

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

9.8.2. Cervical Biopsy for PK

At specified visits, two biopsies will be collected for a tissue PK level.

1. Use gloves to handle cryovials, esp. once weighing begins.
2. Affix completed SCHARP labels onto two 2-mL cryovials (Nunc or Nalgene)
3. Mark the cryovials or the labels with a "1" or "2" to differentiate weights.
    - Also mark one of the lids to prevent mix up.
    - Do not add any additional markings after weights have been recorded.
4. Weigh the labeled cryovials using an analytical scale with a sensitivity rating of 0.1 milligrams or better. Document the pre-weight of the labeled cryovials on the LDMS tracking sheet.
5. Directly transfer the biopsy to a pre-weighed cryovial.
6. Obtain the post-weights for the cryovial containing the biopsy using the same analytical scale in 4 and document on the LDMS tracking sheet.
7. Immediately freeze the cryovials containing the PK biopsies in dry ice ethanol bath (dry ice with enough ethanol to make a slushy consistency).
8. Place the frozen cryovials on dry ice for transport to the LDMS laboratory.
9. The net-weights are calculated on the LDMS tracking sheet, which will accompany the cervical biopsies to the LDMS laboratory.
10. Store the labeled cryovials containing the frozen biopsies at ≤-70˚C within 2 hours in appropriate storage boxes for MTN-044 CX Biopsies for DPV PK.

Cervical biopsies for PK will be shipped to JHU CPAL (see Section 9.9.1).

9.8.3. Cervical Biopsy for PD (ex vivo challenge)

NOTE: MTN LC needs to begin processing biopsy within 30 minutes of collection.

1. If Pitt CRS staff cannot deliver immediately to the Parikh Laboratory, MTN LC, Magee-Womens Research Institute (MWRI), call extension 641-6157 for biopsy pick-up. If there is no answer, call pager#: 412-917-9343.
2. Affix a completed SCHARP label to a 2-mL Corning (orange cap) cryovial containing 1-mL of cold biopsy transport medium, kept at 4°C.
    - Biopsy transport medium will be provided weekly, as needed.
3. One biopsy will be placed immediately into the transport media by gently shaking tube until biopsy is dislodged from forceps.
4. Immediately transport on ice to the Parikh Laboratory, MTN LC, MWRI A540, Craft Ave., Pittsburgh, PA, 15213

9.9. Shipping/Transport of PK Samples

MTN LC will coordinate sample shipments throughout course of study if necessary and at its conclusion. All shipments or deliveries will be on dry ice.

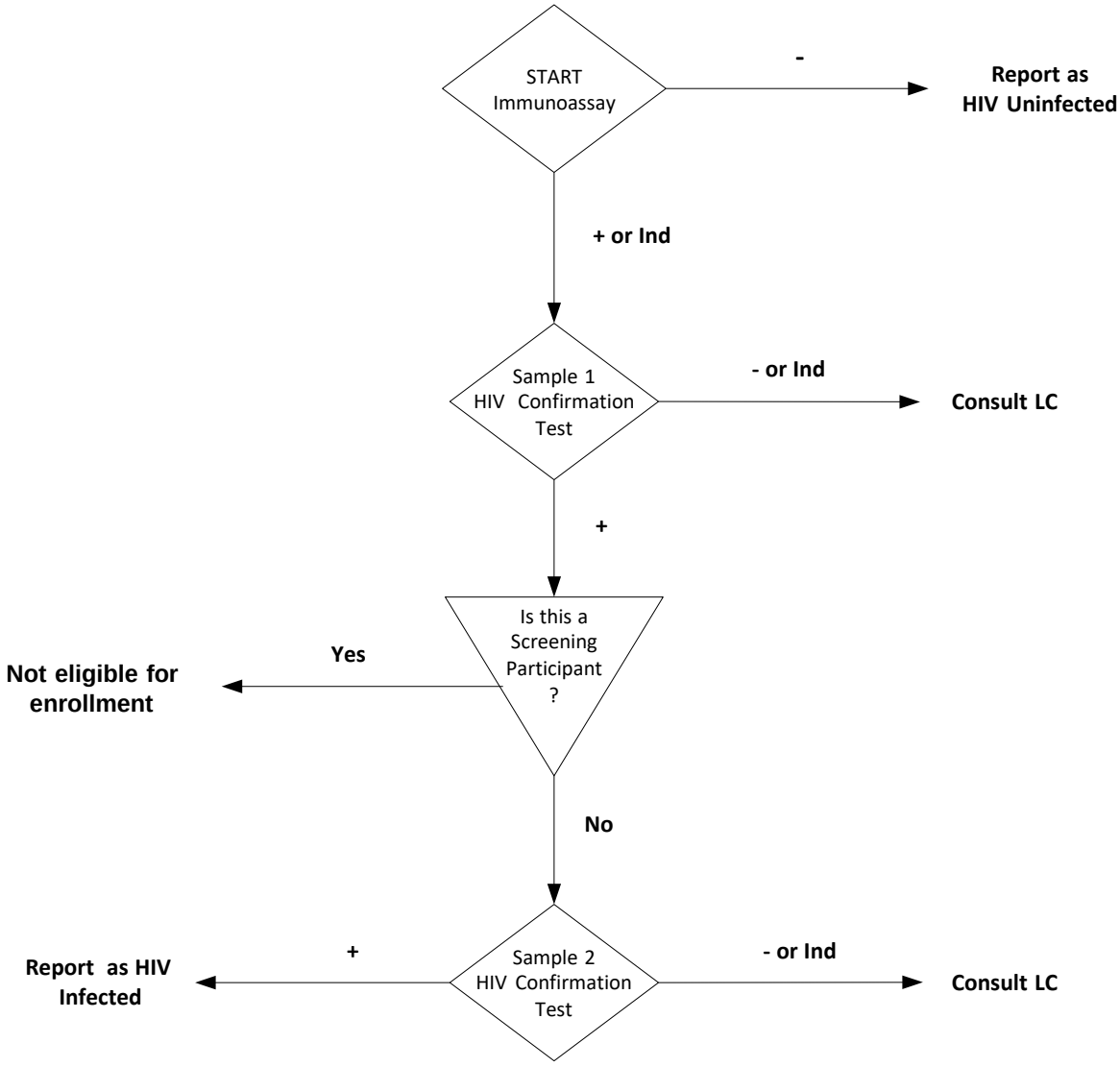
9.9.1. Dapivirine PK Testing: Shipments to JHU CPAL

- Samples for DPV PK Testing:
    a. Primary plasma aliquots for DPV PK
    b. CVF for DPV PK
    c. Cervical biopsies for DPV PK
- All shipments will be on dry ice that will be sufficient for a 24-hour period and can be initiated Monday through Wednesday to ensure that samples arrive in the lab during the work week.
- Ship PK aliquots to JHU CPAL (LDMS Lab 194):
    Attn: Mark Marzinke / James Johnson
    Johns Hopkins School of Medicine
    Clinical Pharmacology Analytical Lab (CPAL) at Bayview
    5200 Eastern Ave
    MFL Center Tower Suite 6000 Rm. 621
    Baltimore, MD 21224
    (410) 550-9703 or (410) 550-9713
    Email: mmarzin1@jhmi.edu and jjohnso6@jhmi.edu
- The back-up samples will be retained at the site until advised by the MTN LC or MTN-044 leadership team. One purpose of the extra aliquots is to be available in case the shipment is not received in the proper condition (e.g. thawing of samples).

9.9.2. Levonorgestrel PK Testing: Deliveries to U-PIT SMBC

- Samples for LNG PK Testing:
    a. Primary plasma aliquots for LNG PK
    b. CVF for LNG PK
- Deliver PK aliquots to SMBC (non-LDMS lab):
    Patrick Oberly / Beth Minnigh
    SMBC Laboratory
    2nd Floor Salk Pavilion, 8D
    335 Sutherland Dr.
    Pittsburgh, PA 15261
    (412) 648-9854
    Email: pjo7@pitt.edu

Appendix 9-1: HIV ANTIBODY TESTING ALGORITHM (See Section 9.6.3)



Ind: Indeterminate test results
LC: Laboratory Center

Section 10. Counseling Procedures

Document Revision History

Version	Date	Summary of Changes	Author
V00.01	09 April 2018	Initial Draft	Amber Blackmon, Clinical Trial Lead
V00.02	13 Apr 2018	PM Review	Jessica Kappes Clinical Project Manager II
V00.03	16 May 2018	Revised based on external reviews	Amber Blackmon, Clinical Trial Lead
V01.00	31 May 2018	Final Version	Amber Blackmon, Clinical Trial Lead
V01.01	15 Jun 2018	Revised based on external reviews	Amber Blackmon, Sr. Clinical Trial Lead
V02.00	29 Jun 2018	Final Version	Amber Blackmon, Sr. Clinical Trial Lead

This section contains guidance on the following types of counseling provided in MTN-044/IPM 053/CCN019: HIV counseling, HIV/STI risk reduction counseling, protocol adherence counseling, and ring use instructions.

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. 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.

10.1 HIV pre- and post-test Counseling, and HIV/ STI Risk Reduction Counseling

HIV testing is required at Screening, Enrollment, and Day 90 visits. 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 10-1 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.

As a component of HIV counseling, 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. Risk reduction counseling should also offer skills-building to the participant when indicated, e.g., how to discuss sensitive issues with partners and other influential persons.

Table 10-1
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.
	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	positive	If **Screening or Enrollment Visit**: HIV-infected; test results indicate that you may be infected with HIV. Counseling and referral for participants with an HIV positive test will occur per local standards. If **Follow-up Visit**: HIV-infected; test results indicate that you may be infected with HIV; however, new blood samples are needed to confirm your status and for additional testing for study purposes.
	negative or indeterminate	HIV status not clear; additional testing is needed to determine your status.
Sample 2 Confirmatory	positive	HIV-infected. Test results have confirmed that you are HIV infected.
	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 counseling worksheet is available for use on the MTN-044/IPM 053/CCN019 LiveTrial Home page. 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.

10.2 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 Visits 2 – 11. Per protocol sections 6.7, 6.8 and 6.9, participants should be counseled accordingly:

- Several concomitant medications/practices will not be permitted. Use of strong CYP3A inhibitors and inducers (as listed in Section 6 of this Manual) or antibiotics and/or corticosteroids that may interact with levonorgestrel are exclusionary. Current or expected continued use of strong CYP3A inhibitors or inducers or other prohibited medications during the study will result in a temporary product hold. These medications are not recommended because LNG and dapivirine are CYP3A substrates.
    - Note: It is important to note that single dose oral fluconazole for the treatment of vaginal fungal infections is permitted.
- Use of heparin, including Lovenox® (enoxaparin sodium), Coumadin® (warfarin), Plavix® (clopidogrel bisulfate), hormone-replacement therapy, and chronic use of non-steroidal anti-inflammatory drugs (NSAIDS) is prohibited during study participation. Participants will be counseled to abstain from using aspirin (greater than 81 mg) and any other drugs (not including acute use of NSAIDS) that are associated with increased likelihood of bleeding for 72 hours before and after the collection of the cervical biopsies.
- Refrain from inserting non-study vaginal products or objects into the vagina, including but not limited to spermicides, female condoms, diaphragms, other intravaginal rings, vaginal medications, menstrual cups, cervical caps, douches, lubricants, and sex toys (e.g. vibrators, dildos, etc.) for **24 hours prior to the Enrollment Visit through completion of Visit 15**.
- Refrain from receptive sexual activity, including penile-vaginal intercourse, receptive oral intercourse, finger stimulation, and tampon use for the **24 hours prior to the Enrollment Visit and clinical visits where samples are taken and for one week following each cervical biopsy**.

If a participant reports a prohibited practice as listed in protocol section 6.7, 6.8 or 6.9, 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 or other site-specific worksheet.

10.3 Ring Use Instructions

Participants will be provided ring use instructions at the Enrollment visit, and at other visits as needed. At enrollment, study participants will be given detailed instructions in the clinic on proper vaginal ring insertion and removal procedures. At follow up visits, these instructions should be referenced as well as exploring the participant's experience with ring use thus far.

In addition to verbal instructions, a copy of the illustrated instructions should be provided to each participant. Vaginal ring insertion instructions are available on LiveTrial Home under Study Documents. 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 and comfort with vaginal ring use.

While reviewing instructions for inserting the ring, it is important to also discuss instructions for ring removal. The participant should be reminded that she should not remove the ring during her 90-day use period unless instructed to do so (e.g. participants in product use Regimen B); however, if ring removal is needed, the below procedures should be followed:

- 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, place the used ring in the bag provided by clinic staff or another suitable container if the provided bag is not available. The participant should contact the study clinic to inform staff the ring was expelled and to receive additional guidance.
- 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 providing product insertion and removal instructions and answering any questions the participant may have, the participant will insert the vaginal ring. She may want to practice removing and inserting the ring herself as well. If she chooses to do so, removal and insertion should be performed in a private space, with study staff standing by in case the participant requests guidance or technical assistance.

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 in chart notes. Clinicians will check for proper ring placement. Instructions to clinicians can be found in SSP Section 7.

Section 11. Data Collection

Document Revision History

Version	Date	Summary of Changes	Author
V00.01	10 April 2018	Initial Draft	Tanya Harrell, SCHARP
V00.02	13 Apr 2018	PM Review	Jessica Kappes, Clinical Project Manager II
V00.03	20 Apr 2018	Revised to incorporate feedback based on group review	Amber Blackmon, Clinical Trial Lead
V00.04	01 May 2018	Revised to incorporate feedback based on group review	Amber Blackmon, Clinical Trial Lead
V00.05	16 May 2018	Revised to incorporate feedback based on group review	Amber Blackmon, Clinical Trial Lead
V01.00	31 May 2018	Final Version	Amber Blackmon, Clinical Trial Lead

V01.01	15 Jun 2018	Revised to correct Randomization Form	Amber Blackmon, Sr. Clinical Trial Lead
V02.00	29 Jun 2018	Final Version	Amber Blackmon, Sr. Clinical Trial Lead

The purpose of this document is to provide site staff with the information they need to successfully complete and submit MTN-044/IPM 053/CCN019 case report forms. For questions about this section or about general data collection policies, procedures, or materials, please contact the SCHARP Clinical Data 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, WA, USA, and is in the US Pacific Time (PT) time zone. The SCHARP MTN-044/IPM 053/CCN019 team members, along with their job role and e-mail address, are listed below.

MTN-044/IPM 053/CCN019 Statistical and Data Management Center (SDMC) Staff

Job Role	Name	Email Address
Protocol Statistician	Barbra Richardson	barbrar@u.washington.edu
Statistical Research Associate	Clifton Kelly	cwkelly@scharp.org
Clinical Data Manager	Tanya Harrell	tharrell@scharp.org
Clinical Programmer	Radhika Etikala	retikala@scharp.org
Clinical Safety Associate	Ning Jiang	njiang2@scharp.org
Laboratory Data Coordinator	Sara Aranda	saranda@scharp.org

11.1 Medidata Rave Overview

Medidata Rave is the data management system used by SCHARP to receive and manage study data collected at study sites. Each site completes study electronic case report forms (eCRFs) by entering data into the Medidata Rave study database. As specified in each site's Source Documentation SOP, data may be entered directly into the study database (i.e., eCRF is source), collected first on paper CRFs and then entered into the study database, and/or entered into the study database based on other non-CRF source documents (e.g., lab reports, testing logs, chart notes, etc.)

The MTN-044/IPM 053/CCN019 study database in Medidata Rave may be accessed at www.imedidata.com.

When using Medidata Rave, the internet browser chosen and connectivity quality will be the most critical factors affecting functionality, as Medidata is accessed via a URL using a web browser. Users using outdated browsers will see a new warning banner on the log-in page of iMedidata. This warning will inform them that their browser does not support security features that are being implemented in future iMedidata releases and to upgrade their browser. Users will see this warning banner if they use any of the following browsers:

- Internet Explorer - Versions older than 8.0
- Chrome - Versions older than 30.0
- Firefox - Versions older than 24.0
- Safari - Versions older than 7.0
- Opera - Versions older than 17.0.

The site's Data Management SOP designates the site staff members responsible for entering data into the study database. SCHARP grants designated site staff access with specific user permissions to the study database. They are required to complete eLearning modules in Medidata, as assigned by SCHARP, before access is granted and data can be entered into the study database. For more detailed information, see the iMedidata Access Guide, posted on the MTN-044/IPM 053/CCN019 Atlas webpage: https://atlas.scharp.org/cpas/project/MTN/044/begin.view.

Detailed guidance on data collection, entry, navigation and general use of Medidata Rave is provided in the Medidata Rave Electronic Data Capture (EDC) Training Manual, which is posted on the MTN-044/IPM 053/CCN019 Atlas web page: https://atlas.scharp.org/cpas/project/MTN/044/begin.view.

Site staff should contact the study Clinical Data Manager with any questions related to study data collection and management. A representative from Medidata Solutions may be contacted (see contact information below) any time a site has technical questions or problems related to access or use of the Medidata Rave software.

For service in English

Toll-free	**Direct number**
1-866-MEDIDATA (633-4328)	1-973-659-6780
Toll-free fax	**Direct fax**
1-877-743-2350	1-973-954-5621

Email

helpdesk@mdsol.com

Hours

24 hours a day, 7 days a week

Data Entry/Quality Control

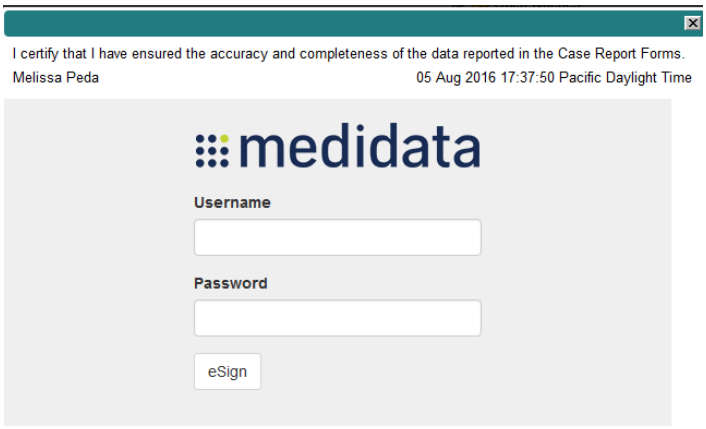
- Once an eCRF is completed and saved in the study database, the following may occur:
  - A system query may be automatically triggered in Medidata Rave (e.g., denoting incomplete or inconsistent data).

- Review may be required for certain forms and/or fields by the SCHARP Clinical Data Manager, and manual data queries may be placed.
- Review may be required for certain forms and/or fields by the site monitor, and data queries may be placed.
- MedDRA coding will be required for AE Log CRFs, and coding queries may be placed.
- WHO coding will be required for Concomitant Medication Log CRF and coding queries may be placed.
- AE-SAE reconciliation will occur, and inconsistency queries may be placed.

- QCs are listed in the Medidata Rave Task Summary on the study home page of designated site users. Designated site staff members are responsible for routinely checking the Task Summary and correcting/updating study data to resolve any outstanding queries.
- When site staff correct/update study data and/or enter a query response to address a manual or coding query, SCHARP staff review the updated data and/or response, and resolve the query or re-query as needed.
- When site staff correct/update study data and/or enter a query response to address a monitoring query, the site monitor (i.e., HD) reviews the updated data and/or response, and resolves the query or re-queries as needed.
- In the rare event that a site utilizes paper CRFs as source documents, any changes to the paper CRFs **must** be entered into the Medidata Rave study database.

Electronic Signatures by Investigators

Each site investigator or designee is expected to complete a single sign-off of a participant's study data (one sign-off for each participant at his/her site) once the participant terminates from the study and site staff have resolved all data queries for the given participant. By completing this participant-level sign-off in the Medidata Rave study database, the investigator or designee attests that the data has been reviewed and is deemed to be accurate. iMedidata users will use their login credentials as their electronic signature (see image below). Please refer to the "Electronic Signature" section of the Medidata Rave Electronic Data Capture (EDC) Training Manual and/or the Investigator e-Learning module for specific instructions.



11.2 CRF Completion

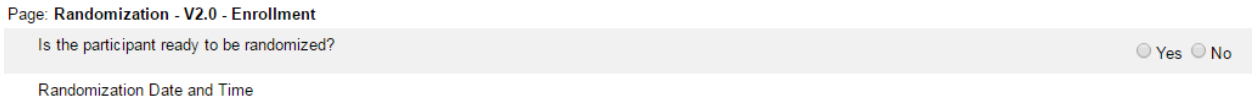
11.2.1 General Guidelines – eCRF Completion

- To the extent possible, site staff should utilize direct data entry into the Medidata Rave study database so that the eCRF serves as the source document. Direct data entry is especially encouraged for data collection based on participant self-report, such as behavioral, bleeding and product (ring) use data.
- When direct data entry is not possible due to the nature of the source data - for example, when the source data is a local lab results report - site staff are encouraged to enter study data into the Medidata Rave study database based on the site-specific source document (in this case, the local lab results report).
    - Site staff are encouraged to avoid paper CRF completion, as it represents an additional, intermediate step of data management and QA/QC review into site data management workflows. In addition, paper CRF completion introduces the risk of data transcription errors and could contribute to database data entry errors.
- When completing an eCRF, refer to the CRF Completion Guidelines (CCG) document, posted on ATLAS, for detailed instructions on data collection pertaining to the given form and fields on that form.
- Complete eCRFs as soon as possible once the data is available and has undergone internal QC review, as applicable. Ideally, completion of all required eCRFs for a given visit will occur within 1–2 business days of the visit, though up to 7 days is acceptable.

11.2.2 Screening and Enrollment/Randomization

- Data entry into the study database begins at the Screening Visit. Queries will fire at the time of data entry.

- For participants who screen but do not enroll in MTN-044/IPM 053/CCN019, data entry is required for the Inclusion Exclusion Criteria eCRF. Other eCRFs that were completed during the failed screening attempt may remain in the study database and will not undergo QC review. Screening form queries will be closed by the SCHARP Data Manager once the Inclusion Exclusion CRF has been completed.
- For participants who enroll in MTN-044/IPM 053/CCN019, enter data for the Inclusion Exclusion Criteria eCRF, along with all required Screening and Enrollment Visit CRFs. Screening form queries will be addressed by the site.
- **Randomization:** Participants will be randomized to a ring use group (continuous or cyclic). Randomization will be done through Medidata. The first step in the ring randomization process is for site staff to complete the Inclusion Exclusion Criteria eCRF with all responses indicating that the participant is eligible for study participation. Once this is done, the Randomization CRF may be completed. To randomize a study participant, site staff mark the "Yes" response box (shown in the image below) for the question "Is the participant ready to be randomized?" on the Randomization eCRF. Once this response is saved, the database (via the Medidata Balance module) will assign the participant to a ring use group and the Randomization Date and Time will appear automatically on the Randomization eCRF. A participant is considered officially enrolled in the study once this step takes place; that is, a randomization assignment is generated for the participant in Medidata Balance, as evidenced by the appearance of a Randomization Date and Time on the Randomization eCRF.



- After a participant is randomized to a treatment arm by Medidata Balance, each participant's ring use group will be provided on the Enrollment eCRF within the participant's RAVE casebook.

11.2.3 Site Data Management SOP

As a condition for study activation, each study site must have a site or study-specific SOP for 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 Data Management SOP outlines site staff responsibilities and contains information on several data topics, including:

- Participant ID (PTID) assignment
- Participant study file organization
- Participant confidentiality
- Site data quality control (QC) processes
- Timing of data entry into the study database
- Data storage

- Data security
- Contingency plans in case of interrupted access to the study database.
- Management of site user account permissions for access to the study database.

11.3 Study-Specific Data Collection Information

11.3.1 Participant Identification Numbers (PTIDs)

As described in each site's Data Management SOP, each participant who provides written informed consent to be screened in MTN-044/IPM 053/CCN019 will be assigned an MTN-044/IPM 053/CCN019 PTID. To do this, site staff will generate in Medidata Rave a participant number (called "Subject ID" in Medidata Rave) within the electronic study and site folder; this number will serve as the participant's PTID. Refer to the "Creating Subjects" section of the Medidata Rave Electronic Data Capture (EDC) Training Manual and the CCG for specific instructions.

Each PTID is unique. It will be assigned to a single participant only at a given site, and not assigned to any other participant at any site or in any study (e.g., MTN, HVTN, HPTN) for which SCHARP is the Statistical and Data Management Center (SDMC).

SCHARP will provide sites with a Microsoft Excel PTID-Name Linkage file and site staff will maintain this document, which will be used to link a participant's name with her assigned PTID. For study purposes, the act of MTN-044/IPM 053/CCN019 PTID assignment is defined as completion of an entry on the MTN-044/IPM 053/CCN019 PTID-Name Linkage Log for a given participant.

The MTN-044/IPM 053/CCN019 PTIDs are nine digits and formatted as "XXXYYYYYZ". The PTID consists of three parts: the site number (XXX), the participant number (YYYYY), and a numerical check digit (Z). The check digit (Z) is a number generated by SCHARP within the participant number and helps ensure that the correct PTID is recorded/entered.

11.3.2 Study Visit Timing

Screening and Enrollment
The initial screening visit is defined as the day the participant provided written informed consent to be screened for the study. The Enrollment Visit will be scheduled to take place within 60 days of the initial Screening Visit. The date the participant is enrolled/randomized is Study Day 0 for the participant. The study Microsoft Excel visit window calendar tool can be used to calculate the allowable window for study enrollment based on the participant's screening date (i.e., date informed consent provided for the current screening attempt). The tool will be posted on the study LiveTrial Home page.

Screening Attempts (Re-screens)
If a participant's first screening attempt is unsuccessful, she may re-screen once if she chooses. If she does re-screen, all screening procedures must be repeated with the exception of PTID assignment. Once a PTID is assigned to a participant, that PTID is used for the re-screening procedures and forms completed for that participant (do not assign a new PTID).

If a participant re-screens and enrolls, all previously completed eCRFs (from the original, failed screening attempt) must be updated to reflect only data from the successful Screening and Enrollment Visit. Note that in this case, the Inclusion/Exclusion Criteria eCRF completed during the failed screening attempt should be updated to reflect the participant's final eligibility status and enrollment into the study.

Follow-Up Visits

For each MTN-044/IPM 053/CCN019 follow-up visit, the visit type, visit code, target visit day, and visit window are listed in Table 11-1. Target days and windows are listed in days, with the day of enrollment/randomization as study day 0.

Target Days and Visit Windows

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

The study Microsoft Excel visit window calendar tool may be used to generate individual participant follow-up visit calendars. The spreadsheet requires that the participant's Enrollment (i.e., randomization) date be entered. Once the enrollment date is entered, the target day and visit window for each of the following required follow-up visits will appear Visit 3 – Day 2, Visit 4 – Day 14, Visit 5 – Day 28, Visit 7 – Day 44, Visit 8 – Day 58, Visit 10 – Day 74, and Visit 11 – Day 90/PUEV. The other target visit dates and windows will populate when actual follow-up visit dates are entered. The target visit dates for Visit 6 – Day 30 and Visit 9 – Day 60 are contingent on the actual visit dates for Visit 5 – Day 28 and Visit 8 – Day 58, respectively. The target visit dates for Visit 12 – Day 91 and Visit 13 – Day 92 are contingent on the actual visit date for Visit 11 – Day 90/PUEV. The target visit date and window for Visit 14 – Day 93/94 are contingent on the actual visit date for Visit 11 – Day 90/PUEV. The actual visit dates and windows for Visit 15 – 1 week post VR removal, Visit 16 – 4 weeks post VR removal, Visit 17 – 8 weeks post VR removal, and Visit 18 – 12 weeks post VR removal, are all contingent on the actual visit date for Visit 11 – Day 90/PUEV. The calendar can be printed, added to the participant's study notebook, and updated as needed.

Split Visits

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 **AND** as long as the visit is Visit 1 – Screening, Visit 4 – Day 14, Visit 5 – Day 28, Visit 7 – Day 44, Visit 8 – Day 58, Visit 10 – Day 74, Visit 11 – Day 90/PUEV, or Visit 14 – Day 93/94. All other study visits may not be split. (Refer to the Study Procedures section of this manual for more information regarding visit procedures and timing). For example, a participant comes in on her Day 14 target day and completes most of the required evaluations. She comes back the next day and completes the remaining required procedures. While not ideal, this is allowed as needed, and is referred to as a "split" visit; meaning, the participant completed all required visit evaluations on two separate days, both days being in the visit window.

Note that for split visits, the "Visit Date" on the Follow-up Visit Summary form within the applicable visit folder is the date of the first part of the split visit. See Section 11.3.3 for more information on assigning visit codes to split visits.

Table 11-1: Visit Timing Requirements

MTN-044/IPM 053/CCN019 Visit Windows
All windows are in days, unless stated otherwise

Visit	Visit Code	Target Day	Window Opens	Window Closes
Visit 1 – Screening	1.0	N/A	N/A	
Visit 2 – Enrollment	2.0	0	Up to 60 days after screening informed consent date	
Visit 3 – Day 2	3.0	2	no window	
Visit 4 – Day 14	4.0	14	13	15
Visit 5 – Day 28	5.0	28	27	29
Visit 6 – Day 30	6.0	30	2 days after Visit 5	
Visit 7 – Day 44	7.0	44	43	45
Visit 8 – Day 58	8.0	58	57	59
Visit 9 – Day 60	9.0	60	2 days after Visit 8	
Visit 10 – Day 74	10.0	74	73	75
Visit 11 – Day 90/PUEV	11.0	90	87	93
Visit 12 – Day 91	12.0	91	1 day after Visit 11	
Visit 13 – Day 92	13.0	92	2 days after Visit 11	
Visit 14 – Day 93/94	14.0	93/94	3 or 4 days after Visit 11	
Visit 15 – 7 days ARR	15.0	97	7 - 14 days after Visit 11	
Visit 16 – 4 weeks ARR	16.0	118	28 - 35 days after Visit 11	
Visit 17 – 8 weeks ARR	17.0	146	56 - 63 days after Visit 11	
Visit 18 – 12 weeks ARR	18.0	174	84 - 91 days after Visit 11	

Missed Visits
In those cases where a participant is not able to complete any part of a required follow-up visit within the visit window, the visit is considered "missed". For example, an enrolled participant does not report to the clinic for her Day 14 visit until 17 days after enrollment. Per Table 11-1, the Day 14 visit has been missed. The missed visit is documented by completion of a Missed Visit CRF.

Interim Visits
An interim visit is a contact with a study participant that meets one of the following criteria:

- Additional study procedures and/or data collection conducted outside of what is specified in the protocol for a required study visit. For example, an interim visit may occur via a phone contact if the participant reports a new AE. Required follow-up visit procedures are not done, either because the required follow-up visit has already been

completed, the participant is in between visit windows, or it is too early in the visit window to complete the required visit.

- Required study visit procedures are conducted outside the visit window, either to make up certain procedures from a missed visit, or to conduct Visit 11 – Day 90/PUEV/Early Termination Visit procedures due to an early product discontinuation (for reasons other than HIV infection or pregnancy). For example, if a participant permanently discontinues study product use at Day 14, she would complete Day 90 visit procedures on Day 14, if she is able and willing.

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 eCRF, the interim visit is assigned an interim visit code (visit number ending in something other than ".0"). All phone contacts that meet interim visit criteria as specified above are also assigned interim visit codes. See section 11.3.3 for information on how to assign visit codes to interim visits.

For MTN-044/IPM 053/CCN019, an Interim Visit Summary CRF is completed for interim visits/contacts as needed.

The following are some examples of interim visits:

1. A participant has a family emergency and is unable to come into the clinic to complete her Day 14 visit until Day 17. Per section 5 of this manual (Study Procedures), an interim visit is conducted on Day 17 to make up certain missed Day 14 visit procedures.

   Why is this an interim visit? The Day 14 visit is considered a missed visit, as the visit window has closed. The visit on Day 17 is being conducted outside of the visit window – that is, between when the Day 14 visit window opened and when the Day 14 visit window closed. The interim visit is assigned an interim visit code as new CRFs will be completed (Interim Visit Summary, Bleeding SMS, Hormone Test Results, Pelvic Exam, Pregnancy Test Results, Specimen Storage, and possibly others, per site consultation with the study management team).

2. A participant completes all required evaluations for her Day 30 visit on the target day. She then returns to the clinic 5 days later to request a new ring.

   Why is this an interim visit? The participant has already completed all Day 30 visit procedures, and it is too early (and not in the visit window) for the Day 44 visit. This is an interim visit, conducted between the Day 30 and Day 44 visits, and is assigned an interim visit code as new CRFs will be completed (Interim Visit Summary, and Ring Insertion and Removal).

3. A participant completes her Day 2 visit as scheduled. Her Day 14 visit window opens on August 15th, and she is scheduled to complete the Day 14 visit on August 16th. The participant reports to the clinic unexpectedly on August 15th to report new genital AE symptoms.

   Why is this an interim visit? The participant is in the Day 14 visit window, but site staff decide not to conduct Day 14 visit procedures for this participant on August 15th (e.g., the participant already has her Day 14 visit scheduled for the next day (on the target date) and has a history of reliably showing up for scheduled study visits, and/or there is limited staff time availability on August 15th). An interim visit code is assigned as new CRFs will be completed (Interim Visit Summary, AE Log, possibly others).

4. A participant completes all required evaluations for the Day 14 visit on the target day, August 15th. She returns to the site complaining of genital symptoms on August 18th. The site clinician decides to do a pelvic exam and observes severe edema of more than 50% of the vulvar surface. Per section 9.6 of the protocol, the study vaginal ring is temporarily held.

   Why is this an interim visit? On August 18th, a pelvic exam is conducted, representing new data collection and the participant is being instructed by study staff to temporarily discontinue use of the study vaginal ring. An interim visit code is assigned, as data collection is occurring between regularly scheduled study visits and outside of the visit windows. The Pelvic Exam CRF and a new Adverse Event Log are completed.

5. A participant completes her Day 74 visit on the target day. The next day, she calls the clinic to report a new mild genital symptom.

   Why is this an interim visit? During the phone contact, the participant reported a new symptom which will result in completion of a new CRF (AE Log). Since new CRFs are completed (AE Log and Interim Visit Summary), an interim visit code is assigned.

11.3.3 Visit Folders and Visit Codes

The eCRFs in the study database are set up within pre-defined study visit folders, so the visit name and visit code automatically appear (and do not need to be entered for required study visits). With the exception of the Medical History Summary and Log eCRFs, which are housed in the Screening Visit folder, all log forms (i.e., AE Summary and Log, Concomitant Medications Summary and Log, Protocol Deviations Summary and Log, and Product Hold Summary and Log) are housed in the "Ongoing Logs" folder within the study database. The Product Discontinuation eCRF and Study Discontinuation eCRF are housed within the "Discontinuations" folder; each of these forms is completed once for each participant to document her permanent product discontinuation and study exit, respectively. The Pregnancy Report eCRF and Pregnancy Outcome eCRF are housed within the "Pregnancy" folder. The Pregnancy Report eCRF is completed if a participant becomes pregnant during the study. The Pregnancy Outcome eCRF is completed once for each pregnancy outcome.

Table 11-2 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 Code
Visit 1 – Screening	1.0
Visit 2 – Enrollment	2.0
Visit 3 – Day 2	3.0
Visit 4 – Day 14	4.0
Visit 5 – Day 28	5.0
Visit 6 – Day 30	6.0
Visit 7 – Day 44	7.0
Visit 8 – Day 58	8.0

Visit 9 – Day 60	9.0
Visit 10 – Day 74	10.0
Visit 11 – Day 90/PUEV	11.0
Visit 12 – Day 91	12.0
Visit 13 – Day 92	13.0
Visit 14 – Day 93/94	14.0
Visit 15 – 7 days ARR	15.0
Visit 16 – 4 weeks ARR	16.0
Visit 17 – 8 weeks ARR	17.0
Visit 18 – 12 weeks ARR	18.0

Visit codes for Split Visits

See Section 11.3.2 for a definition of split visits. When split visits occur, the CRFs completed for the visit are all assigned the same visit code, even though the dates will differ between some of the CRFs. For example, a participant comes in on her Day 14 (Visit 7) target day of 23-JUL-18 and completes all required visit evaluations except pregnancy testing. She returns on 24-JUL-18 (still within the visit window) and provides a urine sample for pregnancy testing. All CRFs dated 23-JUL-18 and 24-JUL-18 are assigned the same visit code of "7.0" and are housed within the Visit 7 – Day 14 visit folder in the study database.

Visit codes for Interim Visits

Note that interim visit codes are not used for visits/contacts between the Screening Visit and Enrollment Visit, as these contacts are considered part of the screening process.

For interim visits occurring after the Enrollment Visit and onwards, interim visit codes are assigned using the following guidelines:

- To the left of the decimal point, record the visit code of 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.*
- To the right of the decimal point:
  - #.1 = the first interim visit after the most recently-required visit,
  - #.2 = the second interim visit after the most recently-required visit,
  - #.3 = the third interim visit after the most recently-required visit, and so on.

Example #1: A participant completes her Day 58 visit (visit code = 8.0) on the target day. She returns to the site one day later to report a new genital symptom. This interim Visit is assigned a visit code of 8.1.

The examples below are from section 11.3.2, where interim visits are defined. These examples now have visit code information added to each example.

1. A participant has a family emergency and is unable to come into the clinic to complete her Day 14 visit until Day 17. Per section 5 of this manual (Study Procedures), an interim visit is conducted on Day 17 to make up certain missed Day 14 visit procedures.

visit code = 4.1

2. A participant completes all required evaluations for her Day 30 visit on the target day. She then returns to the clinic 5 days later to request a new ring.

   visit code = 6.1

3. A participant completes her Day 2 visit as scheduled. Her Day 14 visit window opens on August 15th, and she is scheduled to complete the Day 14 visit on August 16th. The participant reports to the clinic unexpectedly on August 15th to report new genital AE symptoms.

   visit code = 3.1

4. A participant completes all required evaluations for the Day 14 visit on the target day, August 15th. She returns to the site complaining of genital symptoms on August 18th. The site clinician decides to do a pelvic exam and observes severe edema of more than 50% of the vulvar surface. Per section 9.6 of the protocol, the study vaginal ring is temporarily held.

   visit code = 4.1

5. A participant completes her Day 74 visit on the target day. The next day, she calls the clinic to report a new mild genital symptom.

   visit code = 10.1

11.3.4 Form Supply

SCHARP will post a CRF (pdf) file, representing output from the study database eCRFs, on the following MTN-044/IPM 053/CCN019 Atlas web page:

https://atlas.scharp.org/cpas/project/MTN/044/begin.view?

The pdf file represents the complete set of study CRFs and may be used by site staff for local IRB submission as needed, as well as for printing their own paper CRF supplies should they choose to perform paper CRF completion.

11.3.5 Case Report Form Completion Schedule

The SCHARP-provided forms for this study include all forms that are completed and entered into the study database, as well as the Pelvic Exam Diagrams, which is an optional tool sites may use to source document pelvic exam findings for data entry into the Pelvic Exam eCRF.

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. The following table (Table 11-3) lists the forms that are required to be completed at each study visit, as well as the forms that are completed on an “as needed” basis, the ongoing log forms, discontinuation forms, pharmacy form, and pregnancy forms.

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

Visit	Form Name

Visit 1 – Screening Visit (1.0)	Baseline Medical History Y/N, Baseline Medical History Log
	Demographics
	Hematology
	HIV Test Results
	Inclusion/Exclusion Criteria
	Local Laboratory Results
	Pelvic Exam
	Physical Exam
	Pregnancy History
	Pregnancy Test Results
	Screening Date of Visit
	Screening Menstrual History
	STI Test Results
	Vital Signs
	Pelvic Exam Diagrams (non-Medidata Rave)
Visit 2 – Enrollment Visit (2.0)	Baseline Behavioral Questionnaire
	Enrollment
	Enrollment Menstrual History
	Hematology
	HIV Test Results
	Hormone Tests
	Local Laboratory Results
	Pelvic Exam
	Physical Exam
	Pregnancy Test Results
	Randomization
	Ring Insertion and Removal
	Specimen Storage
	Vital Signs
	Pelvic Exam Diagrams (non- Medidata Rave)
Visit 3 – Day 2 (3.0)	Follow-up Visit Y/N, Follow-up Visit Summary
	Bleeding SMS

	Hormone Tests
	Specimen Storage
Visit 4 – Day 14 (4.0)	Follow-up Visit Y/N, Follow-up Visit Summary
	Bleeding SMS
	Hormone Tests
	Pelvic Exam
	Pregnancy Test Results
	Specimen Storage
	Pelvic Exam Diagrams (non-Medidata Rave)
Visit 5 – Day 28 (5.0) Visit 8 – Day 58 (8.0)	Follow-up Visit Y/N, Follow-up Visit Summary
	Bleeding SMS
	Hematology (Visit 5)
	Hormone Test Results
	Local Laboratory Results (Visit 5)
	Ring Insertion and Removal (cyclic group only)
	Specimen Storage
Visit 6 – Day 30 (6.0) Visit 9 – Day 60 (9.0)	Follow-up Visit Y/N, Follow-up Visit Summary
	Bleeding SMS
	Hormone Tests
	Pelvic Exam
	Pregnancy Test Results
	Ring Insertion and Removal (cyclic group only)
	Ring Outage SMS
	Specimen Storage
	Pelvic Exam Diagrams (non-Medidata Rave)
Visit 7 – Day 44 (7.0) Visit 10 – Day 74 (10.0)	Follow-up Visit Y/N, Follow-up Visit Summary
	Bleeding SMS
	Hormone Tests
	Pelvic Exam
	Specimen Storage
Visit 11 – Day 90/PUEV (11.0)	Follow-up Visit Y/N, Follow-up Visit Summary
	Bleeding SMS

	Hematology
	HIV Test Results
	Hormone Tests
	Local Laboratory Results
	Pelvic Exam
	Physical Exam
	Pregnancy Test Results
	PUEV Behavioral Questionnaire
	Ring Insertion and Removal
	Ring Outage SMS
	Specimen Storage
	Vital Signs
	Pelvic Exam Diagrams (non-Medidata Rave)
Visit 12 – Day 91 (12.0) Visit 13 – Day 92 (13.0) Visit 14 – Day 93/94 (14.0)	Follow-up Visit Y/N, Follow-up Visit Summary
	Bleeding SMS
	Specimen Storage
Visit 15 – 7 days ARR (15.0) Visit 16 – 4 weeks ARR (16.0) Visit 17 – 8 weeks ARR (17.0) Visit 18 – 12 weeks ARR (18.0)	Phone Follow-up
As needed	Additional Study Procedures
	Hematology
	HIV Test Results
	Interim Visit Summary
	Local Laboratory Results
	Missed Visit
	Pelvic Exam
	Physical Exam
	Pregnancy Test Results
	Ring Insertion and Removal
	STI Test Results
	Bleeding SMS

	Vaginal Bleeding Assessment
	Vital Signs
	Pelvic Exam Diagrams (non-Medidata Rave)
Ongoing Logs	Adverse Event Log
	Adverse Event Y/N
	Concomitant Medications Log
	Concomitant Medications Y/N
	Protocol Deviations Log
	Protocol Deviations Y/N
	Product Hold Log
	Product Hold Y/N
Discontinuations	Study Discontinuation
	Product Discontinuation
Pharmacy	Pharmacy Dispensation
Interim Visit	Interim Visit
Pregnancy	Pregnancy Report
	Pregnancy Outcome Log

11.3.6 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.

Site staff are encouraged to practice direct data entry when administering the interviewer-administered forms, to the extent possible, so that the eCRFs serve as the source documents. Skip patterns are documented in the CRF Completion Guidelines (CCG) document, which site staff should reference when administering the forms. The CCG will be posted on the Atlas web site along with the complete set of study CRFs (pdf file – see above section 11.3.4). The skip patterns are also programmed into the data checks within the study database, and system queries will be generated in real-time, as data is saved within the database, if required items are missed and/or inconsistent responses are entered. This real-time feedback will allow the interviewer to clarify participant responses and update/correct participant self-reported data during the participant interview, yielding accurate, consistent, and complete study data. Site staff who will conduct the participant interviews and complete the interviewer-administered behavioral and SMS forms are encouraged to practice conducting the interviews,

completing/updating the eCRFs by entering test data, and familiarizing themselves with the eCRF questions, skip patterns, and system queries prior to conducting actual participant interviews.

11.3.7 Site Review (Quality Control) of CRFs

As described in the site's Data Management SOP [and referenced in the site's Clinical Quality Management Plan, (CQMP)], each site must perform Quality Control (QC) review steps, especially for paper CRFs (if used) prior to their data entry into the study database. While paper 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.

11.3.7.1 MTN-044/IPM 053/CCN019 QC Review Step #1 (completed during visit)

- Review visit checklist and pelvic exam checklist (if used) to ensure all required procedures were completed
- Review eligibility checklists/worksheets to ensure completeness and verify participant eligibility
- Review LDMS Specimen Tracking Sheets to ensure completeness and accuracy
- Review completed CRFs based on participant responses to ensure completeness:
    - Screening Visit: Demographics, Baseline Medical History Log, Pregnancy History, Screening Menstrual History, Concomitant Medications Log
    - Enrollment Visit: Baseline Behavioral Questionnaire, Baseline Medical History Log, Enrollment Menstrual History, Concomitant Medications Log
    - Follow-up visits, when present: Bleeding SMS, Ring Outage SMS, Vaginal Bleeding Assessment, PUEV Behavioral Questionnaire, Adverse Event Log, Concomitant Medications Log

11.3.7.2 MTN-044/IPM 053/CCN019 QC Review Step #2 (completed after visit)

General QC #2 procedures for all visits:

- Review visit checklist to ensure all required procedures were completed
- Ensure the PTID is correct, is recorded correctly on all paper source documents (including paper CRFs, if used), and is the same on the paper source documents and the eCRFs for a given participant.
- Ensure that no participant identifiers other than the PTID are present on paper source documents, including paper CRFs (if used).
- Ensure that the assigned visit code is correct, and is consistent between the paper source documents, including paper CRFs (if used), the eCRFs, the LDMS Specimen Tracking Sheet, and LDMS for a given participant visit.

Additional QC #2 procedures for Screening and Enrollment Visit documents:

- Review the Pelvic Exam, Physical Exam, Vital Signs, Local Laboratory Results, Hematology, Pregnancy Test, HIV Tests, STI Tests, and Hormone Tests forms, and ensure that medical conditions are recorded appropriately on the Baseline Medical History Log. Refer to the CCG for further guidance.
- Ensure that all eCRFs used to document lab test results have the correct Specimen Collection Dates entered. If any lab tests were repeated, update the appropriate eCRF(s) to reflect the repeat test result(s).
- If a second (repeat) full pelvic exam is performed during screening, make sure a new pelvic exam source document [e.g., Pelvic Exam Diagrams (non-Medidata Rave)] is completed, and update the Pelvic Exam eCRF in the Screening Visit folder to document the 2nd screening pelvic exam.
- Review the Specimen Storage eCRF and make sure it matches information documented on the visit checklist and Enrollment Visit LDMS Specimen Tracking Sheet (or local lab requisition sheet).
- If a participant screens but does not enroll in the study, make sure the Inclusion Exclusion Criteria eCRF is completed and entered into the study database. Other eCRFs that were completed as part of the failed screening attempt may remain in the study database but will not be QC'd.

Additional QC #2 procedures for follow-up visit documents:

- Concomitant Medications Log CRF: if a medication is taken for an AE, make sure the AE is entered on the Concomitant Medications Log eCRF, and make sure the AE Log CRF for the AE has "Medication" entered for "Other action(s) taken".

QC #2 for Paper CRFs (if used)

This QC review step should occur before forms are data-entered into the study database. 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 Data Management SOP, is to correct data inconsistencies/errors prior to entering data into the study database, so that data is accurate, complete, and available at the time of data entry, thus minimizing the likelihood of data queries.

QC #2 procedures for paper CRFs - all visits:

- Make sure a response has been recorded for each item, as required. Make sure skip patterns have been followed correctly, per instructions in the CRF Completion Guidelines (CCG) document.
- If a response box with "other", "specify", or "describe" line is present, ensure text is present on this line.
- Make sure text responses are clearly recorded.
- For paper CRFs that are not source documents, make sure the data recorded on the paper CRFs matches or is consistent with the source documents.

QC #2 for Electronic CRFs (eCRF)

When data is entered into the study database and an eCRF is saved, system queries are automatically generated in response to inconsistent or incomplete data. Unlike the paper CRFs, which require manual review, eCRFs have the advantage of having the study database itself provide a real-time QC review to ensure data completeness and consistency. In addition, the database design and system queries ensure skip patterns are followed, per instructions in the CCG.

No additional QC #2 review steps are required for eCRFs that are source (i.e., the data is directly entered into the study database, rather than entered based on a separate paper CRF or other paper source document).

Electronic CRFs that are completed based on other source documents (e.g., paper CRFs, SMS data, or lab reports) should be reviewed to ensure that the data entered matches or is consistent with the source documents. The site's Data Management SOP provides additional details and specifies which staff members will perform this review.

11.4 Form-Specific Completion Instructions

Detailed form completion instructions for each form are provided in the CRF Completion Guidelines (CCG) document. The instructions document skip patterns and include guidance on completion of eCRFs in the study database. Some items on forms are straightforward and do not require specific instructions. Therefore, you will not see all form items listed in the CCG, but rather only those items needing detailed explanation.

11.5 Case Report Forms

The current version of the MTN-044/IPM 053/CCN019 case report forms can be found at the MTN-044/IPM 053/CCN019 Atlas web page, link provided below.

https://atlas.scharp.org/cpas/project/MTN/044/begin.view?

Section 12. Data Communiqués

Document Revision History

Version	Date	Summary of Changes	Author
V00.01	09 Apr 2018	Initial Draft	Tanya Harrell, SCHARP
V00.02	13 Apr 2018	PM Review	Jessica Kappes, HD Clinical Project Manager II
V01.00	29 Jun 2018	Final Version	Amber Blackmon, Sr. Clinical Trial Lead

For MTN-044/IPM 053/CCN019, SCHARP will use “Data Communiqués” to document and communicate data decisions and procedures that are made or revised during the study. By using Data Communiqués, SCHARP avoids having to re-distribute a revised version of the Data Collection section of this SSP every time a data collection clarification or revision is made.

Data Communiqués are considered official study documentation. As such, each time a Data Communiqué is sent (via email), please circulate it among relevant staff for their review, print the Data Communiqué, and place it in this section of each MTN-044/IPM 053/CCN019 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 procedures; a Clarification section, used to clarify data collection procedures; and an Updates section, used to communicate when an updated data collection tool or report is being issued or to notify the sites that an updated version of the CRF Completion Guidelines document has been be posted (for example).

Note that a “Data Communiqué” does not request specific actions or corrections to a particular participant’s data - it is a listing of general items to keep in mind when performing data collection for the study.

Section 13 - Study Reporting Plan

Document Revision History

Version	Date	Summary of Changes	Author
V00.01	29 Mar 2018	Initial Draft	Tanya Harrell, SCHARP
V00.02	03 May 20108	External review	Amber Blackmon, Clinical Trial Lead
V01.00	29 Jun 2018	Final Version	Amber Blackmon, Sr. Clinical Trial Lead

The MTN-044/IPM 053/CCN019 Statistical and Data Management Center (SDMC) Staff are listed below.

Job Role	Name	Email Address
Protocol Statistician	Barbra Richardson	barbrar@u.washington.edu
Statistical Research Associate	Clifton Kelly	cwkelly@scharp.org
Clinical Data Manager	Tanya Harrell	tharrell@scharp.org
Clinical Programmer	Radhika Etikala	retikala@scharp.org
Clinical Safety Associate	Ning Jiang	njiang2@scharp.org
Laboratory Data Coordinator	Sara Aranda	saranda@scharp.org

13.1 Purpose of Reporting Plan

The purpose of this reporting plan is to describe the routine reports that the MTN SDMC (SCHARP) plans to generate for MTN-044/IPM 053/CCN019.

The specific purposes of this plan are to:

- Identify the purpose and content of each report;
- Identify those responsible for the preparation and distribution of each report;
- Identify who should review the reports so that follow-up (if necessary) is done.

This reporting plan was prepared by the MTN-044/IPM 053/CCN019 SDMC Clinical Data Manager in collaboration with other MTN-044/IPM 053/CCN019 SDMC staff.

13.2 Study Reports

The reports listed in Table 13-1 are available within the Medidata web-based environment and can be run by designated site users (based on user permissions) at any time to include the most current data available in the Medidata Rave study database.

Table 13-2 lists the reports the SDMC will produce and make available via the MTN-044/IPM

053/CCN019 Atlas web page:

https://atlas.scharp.org/cpas/project/MTN/044/begin.view?

Table 13-3 lists the reports the SDMC will produce and distribute via e-mail.

Following the tables is a description of each report that includes the purpose and components of the report.

Table 13-1: MTN-044/IPM 053/CCN019 SDMC Reports Available in Medidata

Report Title	Permissions List
Site-specific Query Summary	• Site Staff as designated by each site • SDMC Clinical Data Manager
Site-specific Query Details	• Site Staff as designated by each site • SDMC Clinical Data Manager
Site-specific Page Status	• Site Staff as designated by each site • SDMC Clinical Data Manager

Table 13-2: MTN-044/IPM 053/CCN019 SDMC Reports Posted on Atlas

Report Title	Update Frequency	Atlas Viewing Area
Screen Out	Daily	Unsecure
Enrollment	Daily	Unsecure
Retention	Daily	Unsecure
Procedure Completion	Monthly	Unsecure
Data Management Quality	Monthly	Unsecure
Data Summary	Monthly	Unsecure
Missed Visit Listing	Daily	Secure
Missed Visit Summary	Monthly	Secure
Protocol Deviations Listing	Daily	Secure
Protocol Deviations Summary Table	Monthly	Secure
PSRT (Safety)	One week prior to PSRT call	Secure
AE listings	One week prior to PSRT call	Secure
SMC	Approximately every 6 months	Secure

Table 13-3: MTN-044/IPM 053/CCN019 SDMC Reports Distributed via E-mail

Report Title	Distribution Frequency	E-mail Distribution List
LDMS Specimen Monitoring	Monthly	• Site LDMS Laboratory Staff • MTN Laboratory Center Representative(s) • SDMC Clinical Data Managers

1. Data Quality Control (QC Report)

   Purpose: To identify data that is missing, inconsistent, and/or in need of additional clarification
   Components: Data quality control notes and clinical queries

2. Query Summary

   Purpose: To provide data query metrics for a given site
   Components: By site, displays a count of the number of Medidata Rave queries that are generated throughout the study - Open, Answered, Closed, Cancelled, and an overall total grouped by site and role

3. Query Details

   Purpose: To provide detailed information on data queries for a given site
   Components: By site, displays for each data query the query status, query user, marking group, field, form, folder, subject, site group, and site

4. Page Status

   Purpose: To provide the current status of CRFs within a specified study, site, participant, folder, and/or form
   Components: By site, provides current status of CRFs by PTID, by visit folder, and by CRF within a visit folder

5. LDMS Specimen Monitoring

   Purpose: To identify stored specimens whose information in LDMS does not match corresponding information collected per study CRFs
   Components: Listing of those specimens whose LDMS PTID, visit code, and/or collection date information does not match the information recorded on 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

6. Missed Visit Listing

   Purpose: To identify participants who have missed scheduled study visits, to help sites focus retention efforts and prevent participants from becoming chronic defaulters and/or meeting criteria for replacement
   Components: Site-specific listing of cumulative missed visits per the Missed Visit CRF; includes, for each PTID, the enrollment date, visit name, start and end of visit window

7. Missed Visit Summary

   Purpose: To provide a subset of Protocol Team members with a cumulative summary of all missed visits for the study
   Components: Overall and by site, the number and percentages of missed visits

reported for the study

8. Screen Out

   Purpose: To summarize the number of participants screened for the study, the number enrolled, and the reasons participants were not enrolled
   Components: Number screened, number enrolled, number screened out per reason listed on the Inclusion/Exclusion Criteria CRF

9. Enrollment

   Purpose: To report on participant accrual as reflected by data entered into the study database
   Components: By site, activation date, dates 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, and percentage of site target enrolled for the MTN-044/IPM 053/CCN019 study

10. Retention

    Purpose: To report on participant visit retention as reflected by data entered into the study database
    Components: By site and by visit, the number of expected participants who have completed the visit; the number of participants who have not completed the visit; the number of visits missed; the number of participants who missed a visit, but had product available; the number of participants who have terminated early; the number of participants, excluding early terminators, who have completed the visit; and the number of participants not expected

11. Procedure Completion

    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).

12. Data Management Quality Report

    Purpose: To provide information on site performance with regard to key data management and data quality metrics.
    Components: By site and overall data metrics

13. Data Summary Reports

    Purpose: To provide summary information on site performance regarding data management quality, enrollment, retention, and selected procedure completion.
    Components: Cumulative enrollment and retention data, cumulative procedure completion data for selected study procedures, and cumulative and monthly data management quality data

14. Protocol Deviations Listing

Purpose: To provide a subset of Protocol Team members with a cumulative listing of all protocol deviations reported for the study.
Components: Each of the fields/data items as listed on the Protocol Deviations Log CRF.

15. Protocol Deviations Summary Table

    Purpose: To provide a subset of Protocol Team members with a cumulative and past month summary of all protocol deviations for the study
    Components: Overall and by site, the number and percentages of protocol deviations reported for the study

16. PSRT (Safety) Reports

    Purpose: To help the Protocol Safety Review Team (PSRT) monitor participant safety as reflected by adverse events and study product discontinuations reported to the SDMC.
    Components: Cumulative AE and study product discontinuations reported to the SDMC on the AE Log CRF and Treatment Discontinuation CRF.

17. AE Listings

    Purpose: To provide the MTN-044/IPM 053/CCN019 Safety Physicians with a cumulative listing of all adverse events in order to monitor participant safety.
    Components: Cumulative listing of all adverse events reports to the SDMC per the Adverse Event Log CRF

18. Study Monitoring Committee (SMC) Reports

    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