

Section 7. Clinical Considerations

This section presents information on the clinical procedures performed in MTN-024/IPM 031. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 8. Information on performing laboratory procedures is described in Section 10. Instructions for completing data collection forms associated with clinical procedures are provided in Section 11.

The Schedule of Study Visits and Evaluations in Appendix I of the protocol indicates when specific clinical and laboratory assessments are to take place. While the protocol dictates the schedule for data capture, the Investigator of Record or designee should perform the symptom-directed examination at his/her discretion during any visit if s/he determines it to be clinically necessary, particularly if there are any on-going medical or mental health conditions that require closer follow-up. The participant's research record should include documentation of these procedures. Throughout this section the term 'clinician' will refer to a study doctor or a nurse in settings where nursing training, scope of practice, and delegation, permit nurses to perform clinician activities under doctor supervision.

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

7.1.1 Pre-existing Conditions Collection at the Screening Visit

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

7.1.2 Participant-Reported Conditions

Study staff will ask the participant about her past medical conditions as well as any conditions she is currently experiencing at the time of the Screening and Enrollment visits. Because this study is being conducted in post-menopausal women, menstrual history will be obtained only at the Screening Visit.

Per Operational Guidance #02, when obtaining a focused baseline medical history at the Screening Visit, it is not necessary to document the participant's lifetime medical history. Rather, use the following guidance to probe for the most accurate information available from the participant:

- First, focus on conditions (including chronic conditions), changes and/or symptoms that have occurred since the age/onset of the menopause
- Secondly, focus on conditions (including chronic conditions), changes and/or symptoms that have occurred within the 12 months prior to the Screening Visit,
- Lastly, focus on conditions (including chronic conditions), changes and/or symptoms that directly affects eligibility (for example, severe pelvic relaxation or shortening and tightening of the vaginal canal that could make ring use difficult)

Site clinicians should use their best clinical judgment when assessing whether these conditions, changes and/or symptoms should be documented as pre-existing conditions. If any reported conditions, changes and/or symptoms first occurred within the initial few years of transition but have not occurred since, unless it is deemed relevant, it is recommended to document these only in source documents and on the Screening Menstrual History form. Documentation as a pre-existing condition is not necessary. In the event previously experienced conditions, changes and/or symptoms occur during follow up, these conditions may then be documented on the Pre-existing Conditions CRF. If the Pre-existing Conditions CRF is updated after enrollment, site staff should document in a chart note why the update has been made.

Sites should ensure they include a complete history of vaginal dryness and menopausal symptoms when collecting the participant's medical history. Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit the most complete and accurate information from the participant.

To best collect this information, it is recommended that sites use the MTN-024/IPM 031 Baseline Medical History Questions and Screening Menstrual History forms. These tools contain probing questions for capturing medically-relevant symptoms, vaginal bleeding patterns and menopausal history and are available as Word documents on the MTN-024/IPM 031 Study Implementation Materials webpage under Clinical/Safety/Product Use Management: <http://www.mtnstopshiv.org/node/4924>.

Note: Per Operational Guidance #02, age of menopause is defined as the date in which a woman's menses permanently ceases. A woman is considered menopausal once she has gone one year without having a menses. The 'age of menopause' should be documented as the age in which the participant had her last menstrual period (LMP).

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

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

If a pre-existing condition is resolved as of the Enrollment Visit, do not make any changes to the severity grade (similar to what is done when resolving adverse events). If a pre-existing condition first identified at the Screening Visit, is ongoing at Enrollment, assess the severity at the Enrollment Visit and update the severity grade (up or down) as applicable to reflect the severity at the time of enrollment/randomization.

7.1.4 Baseline Medications

The MTN-024/IPM 031 protocol requires documentation of all medications taken by study participants beginning at the Screening Visit and continuing throughout follow-up. The Concomitant Medications Log is used to document all concomitant medications in this study. Medications include the following:

- Prescription and "over-the counter" medications and preparations
- Medications taken for pre-exposure (PrEP) or post-exposure prevention (PEP) of HIV
- Vaccinations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- Recreational drugs

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

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

7.1.4.1 Study-approved Lubricant

The MTN-024/IPM 031 protocol permits the use of an approved personal lubricant (Pre-Seed) to be used as/if needed for the purposes of relieving vaginal dryness or discomfort commonly associated with menopause. Nevertheless, the study approved lubricant is considered a concomitant medication and should be documented as such if use is reported by a study participant. Should a participant report use of the study approved lubricant, site staff should complete an entry on the Concomitant Medications Log at the visit in which use is first reported. If use of study approved lubricant is expected to continue as needed throughout study participation, site staff should complete one entry noting the following: *date started*, *frequency (pr-as needed)* and *dose/units (1-4 grams)*. Note: Vaginal and anal use of the study approved lubricant should be documented as separate entries on the Concomitant Medications Log, specifying the 'route' of administration (e.g. vaginal or rectal) to differentiate use.

Per protocol, participants should be reminded that they are to refrain from inserting anything into their vagina 72 hours prior to each clinic visit. This includes NOT using study-approved lubricant and NOT engaging in vaginal intercourse (See SSP section 9 for further information on protocol adherence counseling requirements). However, if a participant reports using the study-approved lubricant, she should be asked to record how much she used vaginally within the 72 hours prior to her next clinic visit on the Study-approved Lubricant Use Log, which is available on the MTN-024/IPM 031 Study Implementation Materials webpage. Please note use of the study approved lubricant for anal sex should not be recorded on the Study-approved Lubricant Use Log. The participant should be reminded to bring this Log with her to her next study visit. Site staff will transcribe the information from the Log onto the Vaginal Practices CRF.

When providing the Study-approved Lubricant Use Log, site staff should review log instructions in detail to the participant. Participants should be informed that lubricant comes with applicators to apply the lubricant vaginally and each applicator can hold up to 4 grams of lubricant. Participants should try using 1 gram at first, and work up to the right amount for her. For each use, participants should record the date the lubricant was used and mark the applicable "amount used" box (i.e. 1 gram, 2 grams, 3 grams, or 4 grams). If more than one applicator is used on the same day, a separate line should be completed to indicate this since only 4 grams (one full applicator) can be indicated on any line.

7.2 Medical and Medication History Review at Follow-Up

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

7.2.1 Participant-reported Follow-up Medical History

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

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

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

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

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

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

7.2.2. Review of Medications History

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

7.3 Physical Exams

7.3.1 Considerations at Screening and Enrollment

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

- General appearance
- Weight (see Section 7.3.3 for further guidance)
- Vital signs:
 - Temperature
 - Pulse
 - Blood pressure (See section 7.3.5 for further guidance)
 - Respiratory rate
- Abdomen
- Height (at Screening only)
- Lymph nodes*
- Neck*
- Heart*
- Lungs*
- Extremities*
- Skin*
- Neurological*

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

*may be omitted after the Enrollment Visit

7.3.2 Physical Exams Conducted at Follow-up

Physical exams performed during follow-up are documented using the Physical Exam CRF. Abnormal physical exam findings newly-identified during follow-up are recorded and tracked using the Adverse Experience Log (AE-1) CRF. Refer to Section 7.2 for a definition of “newly-reported”. The abbreviated physical exam at follow-up must include the following components:

- General appearance
- Weight (see Section 7.3.3 for further guidance)
- Vital signs:
 - Temperature
 - Pulse
 - Blood pressure (See section 7.3.4 for further guidance)
 - Respiratory rate
- Abdomen

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

7.3.3 Weight

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

7.3.4 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.

7.3.5 Blood Pressure

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

7.4 Pelvic Exam Overview

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

SPECIAL NOTE:

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

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

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

7.4.1 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. At Screening, record the type and size of the speculum used on the Pelvic Exam Diagrams form for reference at subsequent exams.

Exams for Participants with Hysterectomy: Potential participants who have undergone a hysterectomy are still eligible for enrollment into MTN-024/IPM 031. For women who have had a supracervical hysterectomy, all study procedures will be performed. For women who have had a total hysterectomy and no longer have a cervix, the pap smear procedure will be handled slightly differently. Clinicians should collect a vaginal Pap smear when a Pap smear is indicated and note in the comments for the pathologist that the participant is status post hysterectomy. If a vaginal Pap smear is collected, this satisfies the requirement for a "Pap smear."

7.4.2 Detailed Procedural Instructions

Prior to the Exam: Prepare all required equipment, supplies, and paperwork; label specimen collection supplies as needed. Verify that all equipment is in good working order. Review documentation of prior exams and other relevant documentation from the current visit and prior visits. While the participant is clothed, explain the procedure to her and answer any questions she may have. The study clinician should remove the VR just prior to the pelvic exam.

Examine the External Genitalia:

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

Examine the Cervix and Vagina:

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

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

- At Screening and when clinically indicated, collect a vaginal sample to test for **trichomonas** with the rapid test kit.
- At Screening and if clinically indicated at Enrollment, collect a vaginal sample to test for **GC/CT**.

- At Enrollment, 4-Week, 8-Week and 12-Week, collect two vaginal swabs for **quantitative vaginal culture assessment**.
- At Enrollment, 4-Week, 8-Week and 12-Week, collect one vaginal swab for **Gram stain** evaluation.
- At Enrollment, 4-Week, 8-Week and 12-Week, collect one vaginal swab for **pH** assessment.
- At Enrollment, 4-Week and 12-Week, collect one vaginal swab for **biomarker analysis**.
- At Enrollment, 4-Week and 12-Week, collect **cervicovaginal fluid (CVL) for biomarker analysis**. Please refer to section 10.7.1 of this manual for further details regarding preparation, sample collection and processing and storage requirements.
- At Enrollment and 12-Week, collect **cervical cytobrush for flow cytometry**. See section 10 of this manual for details on cytobrush collection procedures (**to be collected on participants with a cervix at select sites*)
- At Screening (if required to confirm eligibility), collect ecto- and endocervical or vaginal cells for **Pap Smear**
- If indicated and per site standard of care, send fluid from a suspicious lesion for additional **herpes testing**.
- If clinically indicated, collect vaginal swab for saline prep and/or KOH wet mount for evaluation of **vaginitis** (yeast or BV).
- **PK Subset only**: at 4-Week, 8-Week and 12-Week, collect vaginal swab for **PK analysis**. See Section 7.4.3 of this manual for further information.
- **Intensive PK Subset**: at 12-Week, collect two cervical biopsies from different areas in the cervix for **PK analysis**. See Section 7.4.3 of this manual for further information.

Removal of Visual Obstruction: After collection of vaginal and endocervical specimens, any obstruction (e.g., mucus, cellular debris) may use 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: After completing all of the above-listed tissue examinations and specimen collection and removing the speculum, perform a bimanual exam for adnexal or fundal masses and/or tenderness.

7.4.3 PK Subset and Intensive PK Subset

7.4.3.1 Vaginal Fluid Collection (PK Subset)

At the 4-Week, 8-Week, and the 12-Week Final Clinic/Early Termination visits, vaginal fluid will be collected from participants who consented to participation in the PK subset. One (1) dacron swab will be collected within one hour of the PK blood draw from the area residing closest to the vaginal ring.

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

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

each cryovial containing the PK swab using an analytical balance, and document the post weight on the LDMS Tracking Sheet.

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

7.4.3.2 Cervical Biopsies Collection (Intensive PK Subset)

The cervical biopsy will always be the last sample collected. Two cervical tissue biopsies will be collected at the 12-Week/Final Clinic Visit from participants who consented to participation in the Intensive PK Subset. Using forceps, cervical biopsies, measuring approximately 3 mm by 5 mm, will be taken from two different areas of the cervix to measure tissue concentration of Dapivirine. Women who have had a total hysterectomy and no longer have a cervix are not eligible for cervical biopsy collection.

Usually, biopsy of the cervix does not require an anesthetic; this procedure typically feels like a sharp pinch or a cramp. Taking a non-steroidal anti-inflammatory drug (NSAID), such as ibuprofen, 20 minutes before the procedure may help relieve any discomfort during the procedure. Post biopsy bleeding may be controlled through a combination of applied pressure, silver nitrate or Monsel's solution.

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

Prior to collecting cervical biopsies for PK assessment, weigh each cryovial and document the pre-collection weight of each labeled cryovial on the LDMS Tracking Sheet.

Following collection of cervical biopsies for PK assessment, transfer each cervical biopsy to its designated pre-weighed cryovial. Obtain the post weight for each cryovial containing a cervical biopsy using an analytical balance and document on the LDMS Tracking Sheet. Immediately freeze the cryovial containing the biopsy in dry ice ethanol bath (dry ice with enough ethanol to make a slushy consistency) or liquid nitrogen.

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

7.4.4 Documentation of Findings

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

All abnormal findings during Screening and Enrollment will be documented on the Pelvic Exam CRF and the Pre-existing Conditions CRF. All abnormal findings identified during follow-up will be documented on the Pelvic Exam CRF. All newly-identified abnormal pelvic exam findings will be documented on an Adverse Experience Log (AE-1) CRF (see Section 7.2 for a definition of "newly-identified"). The results of laboratory test results performed using specimens collected during pelvic exams are recorded on the STI Test Results CRF.

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

- anatomic variants
- gland openings
- Nabothian cysts
- mucus retention cysts
- Gartner's duct cysts
- blood vessel changes other than disruption

- skin tags
- scars

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

Epithelium

Integrity:

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

Color:

- Normal
- Slightly red
- Red
- White
- Other (includes “pale”)

Blood Vessels

Integrity:

- Intact
- Disrupted

Pelvic exam findings should be documented using terminology corresponding to the FGGT and the Pelvic Exam CRF. For findings in which the finding term marked on the Pelvic Exam CRF is more specific than the corresponding term on the FGGT, use the more specific term.

7.5 Genital Bleeding Assessment

Postmenopausal bleeding (PMB) refers to any uterine bleeding in a menopausal woman. Participants will be encouraged to report all occurrences of genital bleeding to study staff. Genital bleeding, no matter how slight or brief in a post-menopausal woman, is abnormal and warrants full clinical evaluation to determine its cause. The only exception to this would be light genital bleeding after study procedures, especially cervical biopsies. Site assessment of unprovoked genital bleeding should include a pelvic examination (that includes a speculum exam) with report of the initial bleeding event. If the bleeding is determined to be secondary to a study procedure or structural abnormality (laceration or abrasion for example), no further evaluation or referral is necessary; however, if there is no identifiable reason for the post-menopausal bleeding, participants should be referred for gynecologic care and the PSRT notified.

Note that each bleeding episode should be captured as an AE. If a participant has an open adverse event for a bleeding adverse event, a pelvic exam is not required each time the participant reports bleeding provided the clinician assesses the bleeding to be consistent with the bleeding captured by the open adverse event. If the AE increases in severity, a new AE Log CRF should be completed to document this change in severity.

Vaginal and/or cervical bleeding associated with study procedures: Vaginal and/or cervical bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the IoR or designee is not considered to be an adverse event. If the bleeding exceeds the amount considered normal by the clinician, it should be considered an AE and should be documented and reported if applicable using the term ‘post procedural bleeding’. The severity of the AE should be graded per the vaginal abrasion row of the FGGT.

Bleeding that is associated with an observed abnormal pelvic exam finding should be considered an AE and should be documented and reported if applicable using the term

associated with the exam finding, with the anatomical location noted. For example, if a vaginal laceration is observed on exam, and there is bleeding attributable to the laceration, the term vaginal laceration should be used to document the AE. The fact that blood or bleeding was present should be documented on the Pelvic Exam Diagrams form and the pelvic exam case report form, and may also be noted in the comments section of the Adverse Experience Log CRF. The term metrorrhagia should not be used to document the AE.

7.6 STI/RTI/UTI

7.6.1 Considerations at Screening/Enrollment

Participants diagnosed during Screening and Enrollment with an STI/RTI/UTI requiring treatment may be enrolled in the study after treatment is complete provided all symptoms have resolved and the screening window is still open. Test of cure for STI/RTI/UTIs after treatment is NOT required before a participant is enrolled. If STI testing is required (based on symptoms) prior to or during the Enrollment visit, the STI-1 CRF completed at the Screening visit should be updated as appropriate with the results of tests conducted.

Syphilis: If a RPR or confirmatory non-treponemal assay is reactive at the Screening visit, appropriate clinical management including referral for care and treatment must take place. Syphilis is not exclusionary but the IoR may decide to not enroll this participant due to the short duration of the study. Refer to section 10.6.4 of this manual for further details regarding Syphilis testing. Please consult the MTN NL with any questions related to Syphilis testing and/or interpretation of unusual test results. Questions related to result interpretation concerning eligibility and enrollment in the study should be directed to the MTN-024 Protocol Safety Physicians (mtn024safety@mtnstopshiv.org). Action required prior to enrollment depends on the current health status of the participant and the availability of medical records documenting her prior infection

Genital warts: Genital warts requiring treatment must be treated prior to enrollment. Genital warts requiring treatment include those that cause an undue burden of discomfort to the participant, e.g., due to bulky size, unacceptable appearance, and/or physical discomfort (equivalent to a Grade 2 or 3 finding on the DAIDS FGGT). Documentation of improved participant symptoms to Grade 1 or 0 must be present before the participant is considered eligible for participation.

Vaginal candidiasis: Chronic (recurrent) vaginal candidiasis is exclusionary for enrollment and is defined by the participant reporting receipt of treatment 4 times or more in the past year. Participants diagnosed with symptomatic vaginal candidiasis during screening are eligible once they have completed treatment and symptoms have resolved.

7.6.2 STI/RTI/UTI Diagnosis

Clinical and laboratory evaluations for STI/RTI/UTIs are only conducted if indicated after Screening. If identified they should be recorded as AEs. Infections should be considered “symptomatic” when a participant self-reports or complains of symptoms associated with the infection. Symptoms should not be confused with “signs” of infection that may be observed during clinical examinations performed by study staff.

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

Urinary tract infections (UTIs): UTIs may be diagnosed in MTN-024/IPM 031 based solely on the presence of symptoms indicative of a possible UTI and graded per the infection row of the DAIDS Toxicity Table. The following symptoms are considered indicative of a possible UTI:

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

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

Incidental findings of STI/RTI on Pap: At some study sites, Pap smear results may include notations of findings associated with certain STIs (e.g., trichomoniasis). Pap smear findings associated with STIs should not be considered diagnostic of any infections. Rather, such findings should be handled as follows:

- Do not consider STI-related notations on Pap smear result reports when assessing participant eligibility or AEs for the study.
- If protocol-specified STI testing was performed on other specimens (i.e., blood, urine, vaginal samples) collected on the same day as specimen collection for Pap smear, the results of the protocol-specified testing overrule STI-related findings noted on the Pap smear result report. Provide treatment as needed based on the results of the protocol-specified tests.
- If protocol-specified testing was not performed on other specimens (i.e., blood, urine, vaginal samples) collected on the same day as specimen collection for the Pap smear, collect specimens for indicated protocol-specified STI testing at the participant's next study visit after receipt of the Pap test result report. Provide treatment as needed based on the results of the protocol-specified tests.

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). Per the MTN-024/IPM 031 protocol, asymptomatic BV and 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.

Current CDC guidelines can be accessed at: <http://www.cdc.gov/std/treatment/>

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

Test of Cure: STI/RTI tests of cure are not required in MTN-024/IPM 031, 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 and/or findings of abnormal vaginal discharge as per their discretion. Per protocol, whether to treat the underlying cause of the abnormal vaginal discharge will depend on:

1. what the underlying diagnosis is and
2. whether the participant is symptomatic.

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

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

7.8 Management of Laboratory Test Results

Hematology, liver function (AST/ALT), and creatinine testing will be performed at Screening and the 12-Week/Final Clinic Visit. For each study participant, the IoR or designee is responsible for monitoring these test results and for ensuring appropriate clinical management of all results. All reviews of laboratory test results should be documented on the lab results report (provided by the lab to the clinic) and/or in chart notes.

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

At a minimum, all test results of severity grade 3 and higher judged to be related and all results requiring product hold, should be considered critical and urgently reported to a study clinician; lower grade results also may be considered critical at the discretion of the IoR.

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

7.9 Pap Smear Results and Management

Women with a documented normal result within the 12 months prior to enrollment need not have a Pap smear during the screening period. However, copies of this Pap result must be obtained and retained on file for purposes of eligibility assessment. If a participant requires Pap specimen collection as part of study screening procedures, and an inadequate specimen is collected, a second (repeat) Pap specimen must be collected and tested prior to Enrollment in order to assess eligibility.

Grade 1 Pap results are not exclusionary, however, if further evaluation is required (i.e. colposcopy and/or biopsy) per site SOPs, enrollment must be delayed until colposcopy and/or biopsy results are available and no treatment is indicated. Biopsies are not considered exclusionary genital/gynecologic procedures under criterion 6i. However, if more invasive procedures are required (i.e. LEEP), the participant cannot be enrolled for 90 days per criterion 6i.

8.0 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for product hold and discontinuation (Section 9.3), guidance on product hold and discontinuation in response to observed AEs (Section 9.4), and management of STI/RTI (Sections 9.5), HIV infection (Sections 9.7), pregnancies (Section 9.8), and early study termination (Section 9.9).

All specifications of protocol Sections 6 and 9 must be followed; IoRs are encouraged to consult the PSRT with any questions related to proper interpretation of the protocol and proper management of study product use in particular.

All clinical and product use management must be fully documented in participant study records. When the PSRT is consulted in relation to clinical and product use management, completed PSRT query forms (including a response from the PSRT) must be printed and filed in participant study records. Product holds and discontinuations must be communicated to site pharmacy staff using the Vaginal Ring Request Slip, as described in Section 6 of this manual. Product holds and discontinuations also must be documented on Product Hold/Discontinuation.