Section 10. Clinical Considerations

This section presents information on the clinical procedures performed in MTN-013/IPM 026. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 11. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 12. Instructions for completing data collection forms associated with clinical procedures are provided in Section 13.

10.1 Baseline Medical, Menstrual, Pregnancy/Contraceptives History and Concomitant Medications

A focused baseline medical/menstrual history is performed during screening. All medications used by the participant also are ascertained at this time. The purpose of obtaining this information during screening is two-fold:

- To assess and document participant eligibility for the study
- To document participants' baseline medical conditions and symptoms, for comparison with conditions and symptoms that may be identified or reported during follow-up

For all abnormal conditions or signs/symptoms, the severity grade of the condition or symptom must be documented, as must onset and resolution dates, when applicable. When a larger diagnosis cannot be made, each sign/symptom contributing to that diagnosis must be documented/listed.

10.1.1 Screening Visit

When obtaining a focused baseline medical history at the Screening Visit, it is not necessary to document the participant's lifetime medical history. Rather, focus on conditions that have occurred in the 12 months prior to the Screening Visit or that affect eligibility, and probe for the most accurate information available from the participant.

Suggested procedures and documents to be used for collecting and documenting baseline medical, menstrual, pregnancy/contraceptive, and concomitant medications are presented below. All documents other than the Concomitant Medications Log will be made available to sites on the MTN-013/IPM 026 Study Implementation Materials web page on the MTN website.

- Complete the **Baseline Medical History Questions** sheet. For any items marked "yes", complete an entry on the **Medical History Log**.
- Complete the **Menstrual History** and **Baseline Pregnancy/Contraceptive History**. Add entries to the **Medical History Log** sheet as needed.
- Add any medical conditions newly-identified during the visit to the **Medical History Log** as needed. This includes signs/symptoms/diagnoses identified as a result of pelvic exam, physical exam, and/or laboratory evaluations.
- Complete **Concomitant Medications Log** case report form.

10.1.2 Enrollment Visit

Suggested procedures for reviewing and updating baseline medical, menstrual, pregnancy/contraceptive, and concomitant medications are presented below. Note that all of the procedures/updates listed below should be completed before the participant is randomized/enrolled.

- Review completed **Baseline Medical History Questions** sheet and update responses as needed. Add entries to the **Medical History Log** as needed.
- Add any medical conditions newly-identified during the visit to the **Medical History Log** as needed. This includes signs/symptoms/diagnoses identified as a result of pelvic exam, physical exam, and/or laboratory evaluations.
- Update previously-recorded entries on the **Baseline Medical History** as needed (i.e. add Outcome Dates as applicable).
- Review all entries of the **Medical History Log(s).** Transcribe each ongoing entry onto the **Pre-existing Conditions** CRF.
- Review/update **Concomitant Medications Log** case report form**.**

10.1.3 Follow-up Visits

An interval (follow-up) medical/menstrual history and review of concomitant medications is required at each scheduled follow-up visit. An interval 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 AEs. The purpose of the interval history is to determine whether previously reported conditions remain ongoing and to determine whether new symptoms, illnesses, conditions, etc., have occurred since the last medical/menstrual history was performed.

Suggested procedures for completing interval medical and menstrual histories during follow-up visits are presented below.

- Review all pages of the **Medical History Log(s)** – review will be documented on the applicable visit checklist. Update "Outcome Date" of previously-recorded entries as needed. Add entries as needed for any newly-identified events (including signs/symptoms/diagnoses).
- Complete and/or update **Adverse Experience Log (AE Log)** case report forms (CRFs) as needed, ensuring data recorded on the **Medical History Log** matches data recorded on the corresponding **AE Log** CRF.
- Review/update **Concomitant Medications Log** CRF.

10.1.4 Ascertainment of Concomitant Medications

The MTN-013/IPM 026 protocol requires documentation of all medications taken by study participants beginning at the Screening visit and continuing throughout follow-up. For purposes of this study, medications include all of the following, regardless of route of administration:

- Prescription and "over-the counter" medications and preparations, including contraceptives
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- Recreational drugs

The Concomitant Medications Log CRF is a recommended source document for recording all medications as listed above.

Study clinicians should ascertain participants' baseline medication information in the context of the baseline medical/menstrual history. In addition to asking open-ended questions to elicit participant report of current medications, use the information obtained in the medical/menstrual history to probe for additional medications that the participant may otherwise forget to report. For example, if the participant reports headaches as part of her medical history, but does not spontaneously list any medications taken for headaches; ask if she takes any medications for headaches. Similarly, if a participant reports taking a medication for a condition that she inadvertently did not report when providing medical history information, add the condition to the baseline medical history source document.

At each visit in which an interval medical/menstrual history is performed, retrieve the participant's previously completed Concomitant Medications Log form, record any new medications, and actively ask the participant whether she is still taking all previously-recorded medications, at the same dose and frequency. Also actively ask whether the participant has taken any new medications since her last medical/menstrual history.

If a participant reports taking a new medication for a condition that she inadvertently did not report when providing interval medical/menstrual history information, add the condition to her Follow-up Medical History Log source document. To help ensure accurate reporting of concomitant medications information, all participants should be encouraged to bring all medications to all study visits.

10.1.5 Pre-Existing Conditions

A key purpose of performing the baseline medical/menstrual history is to document participants' baseline medical conditions, for comparison with conditions that may be identified during follow-up. Abnormal conditions, symptoms, signs, and findings that are ongoing at the time of enrollment/randomization are considered pre-existing conditions. This includes abnormal lab results that are either gradable per the DAIDS Toxicity Table or FGGT, or considered clinically significant by the IoR or designee. All such conditions should be thoroughly source documented and transcribed onto the Pre-existing Conditions CRF.

As described in greater detail in Section 11, the Pre-existing Conditions CRF serves as the "starting point" from which study clinicians must determine whether abnormal conditions, symptoms, signs, and findings identified during follow-up are adverse events (AEs). By definition, pre-existing conditions are present at enrollment/randomization and therefore are not considered AEs. However, pre-existing conditions that increase in severity or frequency during follow-up are considered AEs. With this in mind, when completing the source documents and case report forms listed above, study clinicians should document as much detail as possible about the baseline (status at enrollment) severity and frequency of each pre-existing condition.

10.2 Physical Exams

Complete physical exams are required at every scheduled visit. At all scheduled time points, physical exams should include the following evaluations at a minimum.

- Vital signs
  - Blood pressure
  - Pulse
  - Temperature
  - Respirations
- Weight
- General appearance

The following assessments may be omitted following the Enrollment Visit: height, abdomen, head, eye, ear, nose and throat (HEENT) examination, lymph nodes, neck, heart, lungs, extremities, skin, and neurological. Additional assessments may be performed at the discretion of the examining clinician in response to signs, symptoms, or other conditions present at the time of the exam.

The Physical Exam (non-DataFax CRF) is a recommended source document for recording physical exam findings.

Physical exams performed at Screening may identify additional baseline medical history information that participants inadvertently do not report in their baseline medical/menstrual history. For example, the clinician may identify a skin condition during the physical exam and upon further inquiry learn that the participant has had the condition since age 15. In such situations, the clinician should add the newly identified information to the baseline medical history and/or menstrual history forms.

10.3 Pelvic Exams

Pelvic exams are performed for purposes of determining eligibility and identifying primary study safety outcomes. As such, they are critical to meeting the study objectives and ensuring the ongoing safety of study participants. Pelvic exams are required at every scheduled visit with the exception of Days 29 and 30 when the exam is performed only when clinically indicated to evaluate genital symptoms and at Days 31, 35, or 42 when the timing of the exam is based on the participants random assignment. Pelvic exams must also be performed before resuming use of vaginal study product after a product hold related to a genital complaint.

Exam procedures must be performed in the order shown on the exam checklists provided in Section 7 of this manual. All procedures listed on the exam checklists should be performed during routinely scheduled exams. When additional unscheduled exams are performed, in general, only clinically indicated procedures should be performed. As indicated in greater detail below, exam findings are reported on the following forms provided by the MTN SDMC:

- Pelvic Exam Diagrams (non-DataFax)
- Pelvic Exam Form

10.3.1 Detailed Overview of Pelvic Exams

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. Make sure everything needed for the procedure is in place before the participant is brought into the room.

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 (non-DataFax CRF) for reference at subsequent exams. The VR should remain in place during the pelvic exams. There may be instances when inserting the speculum with the ring in place causes discomfort; in these instances it is acceptable for the clinician to remove the ring during exams. If applicable, VR removal and re-insertion during pelvic examination should be documented on the Pelvic Exam Ring Assessment CRF.

Note: The speculum may be lubricated with warm water if needed. No other lubricant may be used.

Exams During Menstruation: As much as possible, pelvic exams should not be performed during menses, since the presence of menstrual blood will likely interfere with visualization of the vagina and cervix, elevate the vaginal pH, and complicate interpretation of wet prep findings. Site staff should make every effort to schedule participants for study visits when the participant is not menstruating BUT within the allowable window. If the participant is on her menses and the visit cannot be rescheduled, all PK procedures will be conducted, where applicable. If a participant is menstruating 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. However, if this is not possible the participant should be instructed to return for a pelvic exam as soon as possible after menses.

Removal of Visual Obstruction: During the pelvic exams after assessment of vaginal pH and collection of vaginal swabs, if necessary remove any obstruction (e.g., mucus, cellular debris) 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.

Specimen Collection: Perform specimen collection in the sequence specified on the pelvic exam checklists (see Section 7 of this manual). Refer to Section 12 of this manual for further details on collection, processing, and testing of pelvic specimens.

Vaginal Ring Collection: If possible, during post Enrollment visits leave the vaginal ring in place during the pelvic exams. There will be instances when inserting the speculum with the ring in place causes discomfort; in these instances it is acceptable for the clinician to remove the ring during exams. If the vaginal ring is removed during the pelvic exam, site staff should document removal and re-insertion on the Pelvic Exam Ring Assessment case report form. Immediately following the pelvic exam, the vaginal ring should be rinsed with clean warm water and re-inserted.

10.3.2 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.

Position the Participant: Establish a comfortable examination position that allows for the perineum and vulva to be inspected. Make all necessary adjustments to equipment and room to ensure participants comfort: i.e. adjust stirrups and back elevation as needed, provide socks if the room is cold, provide a fan for the participant's face if the room is warm.

Examination of the External Genitalia:

- Do not insert the speculum before examining the external genitalia.
- Spread 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, perianal area, and the epithelial lining of the introitus.

Naked Eye Examination of the Cervix:

- 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 only if needed) to establish the position of the cervix. Then re-insert the speculum.
- Perform naked eye exam of the cervix and vagina without manipulation.
- Assess cervical ectopy (Enrollment only)
- Assess for abnormal vaginal and/or cervical discharge and/or blood tinged discharge

Specimen Collection:

Collect specimens in the order listed on the pelvic exam checklist which is also reflected below. Collect specimens away from apparent abnormalities and exclude swabbed areas from subsequent examination.

10.3.3 Order of Procedures

- Examination of the external genitalia
- Cervicovaginal fluid (CVF) via tear test strip at the introitus
- Naked eye examination of the cervix and vagina*****
- Swab(s) vaginal fluids for the following:
    - Test for trichomoniasis
    - Test for BV by wet mount
    - Test for candidiasis with a KOH wet mount
    - pH
    - Quantitative vaginal culture assessment
    - Gram stain
    - GC/CT testing†
    - Pap Smear (if indicated)
    - Biomarker and PD Assessment
    - Validation
- Cervicovaginal fluid (CVF) via tear test strip on the surface of the cervix
- Cervical biopsy (2x) for PK assessment
- Cervical biopsy (1x) for PD assessment

****At Day 28, the naked eye examination should be performed before and after the vaginal ring is removed to assess baseline findings prior to removing the ring as well as any findings after the ring is removed.***

†GC/CT testing procedures is site specific. Dependent on whether the local lab uses Gen Probe and ProbeTec Viper for the detection and will determine if either vaginal or cervical specimens are required.

Vaginal fluid may be collected from the lateral vaginal wall or the posterior fornix for the following tests:

- Test for trichomoniasis, using the Dacron cotton swab from an OSOM (Genzyme) Rapid Trichomonas Test kit.
- If symptomatic, test for BV by wet mount.
- If symptomatic, test for candidiasis by KOH wet mount

Vaginal fluid may be collected from the posterior fornix for the following tests:

- PD and Biomarker Assessment
- Validation

Vaginal fluid may be collected from the lateral vaginal wall for the following tests:

- Quantitative culture using Darcon swabs (2 swabs); away from any apparent abnormalities
- Assessment of vaginal pH. Vaginal fluids may be collected via swab and then swabbed onto the pH strip. (**Do not** insert the pH strip into the vagina). Match the resulting color of the pH strip to the color scale provided with the strips to determine the pH value.

- Gram stain evaluation (at the MTN Network Laboratory (NL). Be sure to collect specimen from the opposite vaginal wall used for the wet mount specimen collection. See Section 12 of this manual for detailed gram smear slide preparation and assessment procedures.

When required per protocol and/or when clinically indicated, collect ecto- and endocervical cells for Pap smear. In the event that specimens collected for Pap smear are not evaluable, additional specimens should be collected per local guidance. If inadequate specimens are collected, another screening pelvic exam is required for repeat Pap smear collection and testing. If a second screening pelvic exam is conducted, chart note the exam findings. Do not complete a second Pelvic Exam case report form.

Examine the Vagina: To examine the rest 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. Note all findings on the Pelvic Exam Diagrams form. Further document abnormal findings on the appropriate pelvic exam case report form.

Perform Bimanual Exam: Required at Screening and Enrollment and when clinically indicated. After completing all tissue examinations and specimen collection, close the speculum blades, gently remove the speculum, and perform bimanual exam for adnexal or fundal masses and/or tenderness.

10.4 Pharmacokinetics Procedures

Throughout the study, participants will have samples (blood, vaginal fluid and cervical tissue) collected for measurement of Dapivirine and Maraviroc levels. PK procedures may not be split over multiple days, meaning all PK procedures must be completed on the same day. In addition, every effort should be made to schedule these visits when the participant is not experiencing her menses. However, if the participant is on her menses at the time of the visit, all PK procedures will be conducted.

10.4.1 Blood Samples for Dapivirine and Maraviroc Levels

The collection of blood samples will be completed at every scheduled study visit either at a single time point or at multiple time points.

Blood samples obtained at a single timepoint on Days 1, 2, 3, 5, 7, 14, 21, 29, 30, 31, 35, 42 and 52.

Blood samples obtained at multiple time points occur at the following visits:
- Enrollment Visit: Within 15 minutes prior to insertion of the VR (Hour 0) and at 1, 2, 4 and 6 hours following insertion of the VR.
- Day 28: Within 15 minutes prior to removal of the VR (Hour 0) and at 1, 2, 4 and 6 hours following removal of the VR.

At the Enrollment Visit, all participants will provide a blood sample within 15 minutes prior to inserting the VR (0 hour time point). At the Day 28 Visit, all participants will provide a blood sample within 15 minutes prior to removing the VR (0 hour time point). Sites should make every effort to collect the 1, 2, 4 and 6 hours PK blood draws following ring insertion/removal at the protocol defined times. However there is an allowable window of +/- 15 minutes (within 15 minutes prior to and following each designated time point) to allow for flexibility.

For the observation of dosing i.e. VR insertion, each site will determine the most culturally appropriate method for observing. For example, a site may choose to directly observe the product insertion or they may choose to allow the participant to insert the product behind a privacy curtain. Regardless of the method chosen, site staff need to ensure that the product has been inserted correctly and placement is accurate.

10.4.2 Vaginal Samples for Dapivirine and Maraviroc Levels

PK procedures may not be split over multiple days, meaning that all PK procedures most be completed on the same day. In addition, every effort should be made to schedule these visits when the participant is not experiencing her menses. However, if the participant is on her menses at the time of the visit, all PK procedures will be conducted, including collection of test tear strip and vaginal biopsies, if applicable.

10.4.2.1 Cervicovaginal Fluid via Tear Test Strip

Following collection of other protocol required vaginal swabs; cervicovaginal fluids will be collected through the use of tear test strip (Tear Flo™ Diagnostic Test Strips) to capture the rate of Dapivirine and Maraviroc concentration. See the applicable study visit checklist and the pelvic checklist for appropriate order of specimen collection.

At scheduled visits in which a single time-point blood draw is required, the tear test strip specimen should be collected within one hour of PK blood draw.

Prior to collecting cervicovaginal fluid:

- Weigh each glass tube (with screw lid) and unused tear test strip on an analytical balance.
- Document the pre-collection weight of each labeled glass tube on the tear test strip Weights case report form.

Note: Sites must determine whether each tube will be labeled with the appropriate SCHARP provided PTID label prior to or following weighing of glass tube (with screw lid). Date and time of specimen collection must occur after post weights are documented.

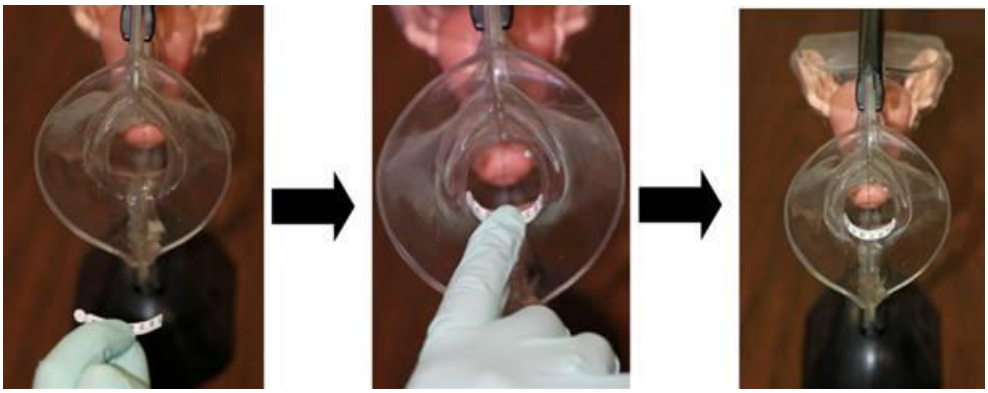
Procedure for Tear Test Strip Collection:

The tear test strips have been supplied in 11 ml (16x100mm) glass tubes and are marked with the locations that sampling should occur. Gently remove the tear test strip from the tube using forceps (ring or sponge forceps work best). Make sure that the vaginal location sampled is the same that is marked on the tube. Insert the strip into the vagina and apply the strip to the epithelial surface of each designated sampling location.

Note: Ensure a new strip and new disposables (gloves, forceps, tweezers, tubes, etc.) are used for each sample.

Location #1: Introitus (Note: this tear test strip is collected prior to insertion of the speculum)

Prior to inserting the speculum, using clean gloved fingers to separate the vulva, position the tear test strip into the introitus circumferentially along the posterior hymenal ring-as shown in the diagram below. The tear test strip should curve in the shape of a semi-circle. Apply pressure to ensure the entire surface of the strip adheres to the posterior vaginal wall. After tear strip is in place, remove gloved fingers allowing vulva to remain closed. Once absorption is complete, remove strip with forceps.



Location #2: Surface of the Cervix

Gently insert an unlubricated speculum into the vagina to separate the walls to dilate it for examination of the vagina and cervix. Position the entire or at least part of the tear strip on the surface of the cervix. Either lateral or vertical positioning (in relationship with the vagina) on the face of the cervix will be acceptable.

Note: If excess mucus or menses clot has accumulated, a large cotton-tipped cotton swab may be used to gently remove this material before inserting the strip.

Each strip should be left in place until the strip becomes partly moist for up to 2 minutes. If absorption is poor (less than 1/3rd of the strip becomes moist) after 2 minutes, reposition the strip to a slightly different location in close proximity to the target location. Lay the entire strip flat onto the tissue for an additional 3 minutes. Optimally, half or larger part of the strip is the desired amount of saturation. Adsorption usually takes approximately two minutes, but may take a little longer. The site clinician should routinely check the absorbance of the strip which varies. The total specimen collection time should not surpass 5 minutes.

Following collection of cervicovaginal fluid:

- Immediately following collection, the strip should be placed back in the glass tube.
- Weigh the glass tube containing the absorbed tear test strip (including the lid) on an analytical balance
- Document the post-collection weight of each labeled glass tube on the Tear Test Strip Weights case report form.

10.4.2.2 Cervical Biopsy

The cervical biopsy will always be the last sample collected. Cervical tissue biopsies (2 for PK and 1 for PD) will be collected at Day 28. Cervical tissue biopsies (2 for PK only) will also be collected on Day 31, 35, or 42 based on the participant's random assignment. 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 and Maraviroc.

Usually, biopsy of the cervix does not require an anesthetic, although 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. Please see section 12.9.1 for further instructions.

Prior to collecting cervical biopsies for PK assessment:

- Each tube should be labeled with the appropriate SCHARP provided PTID label.
- Weigh each plastic cryovial and document the pre-collection weight of each labeled plastic cryovial on the Cervical Biopsy Weights case report form.
- Cool cryovials on ice prior to vaginal biopsy transfer.

Note: Sites must determine whether each tube will be labeled with the appropriate SCHARP provided PTID label prior to or following weighing of glass tube (with screw lid). Date and Time of specimen collection must occur after post weights are documented.

Following collection of cervical biopsies for PK assessment:

- Transfer each cervical biopsy to its designated cool pre-weighed plastic cryovial.
- Obtain the post weight for each plastic cryovial containing a cervical biopsy using an analytical balance and document on the Cervical Biopsy Weights case report form.

10.4.3 Documentation of Pelvic Examination Findings

Document all exam findings — both normal and abnormal — on the Pelvic Exam Diagrams (non-DataFax) CRF. Additionally, abnormal findings should only be documented on the Pelvic Exam CRF and the Pre-existing Conditions CRF (at Enrollment) or the Medical History Log. Supplemental information may also be recorded in chart notes or on other designated source documents as needed. Source documentation for abnormal findings should include the severity grade of the finding, assessed per the Female Genital Grading Table.

For enrolled participants, (non-exclusionary) abnormal pelvic exam findings identified during screening are recorded on the Pre-existing Conditions CRF. Abnormal exam findings identified during follow-up are documented on the Medical History Log and reported as AEs if applicable.

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

- anatomic variants
- gland openings
- Nabothian cysts
- mucus retention cysts
- Gartner's duct cysts
- atrophic changes
- blood vessel changes other than disruption
- skin tags
- scars
- expected menstrual and non-menstrual bleeding (see Sections 10.6.3-10.6.4)

See Section 10.6 below for further detailed guidance on documentation, reporting, and management of pelvic exam findings involving genital bleeding.

Figure 10-1 below provides further information to guide and standardize terminology used to describe abnormal pelvic exam findings. Specific to MTN-013/IPM 026, pelvic exam findings should be documented using terminology corresponding to the Female Genital Grading Table and the study-specific pelvic exam case report form. For findings in which the finding term marked on the pelvic exam case report form is more specific than the corresponding term on the FGGT, use the more specific term. For example, a pelvic exam finding identified as a vulvar laceration. The term corresponding to this finding on the FGGT is "vulvar lesion" but the term marked on the pelvic exam case report form will be "laceration." Because the term "laceration" is more specific than the term "lesion," the term "vulvar laceration" should be used to document the finding. See Figure 11-4 in Section 11 of this manual for further guidance on reporting pelvic exam findings as AEs.

Figure 10-1
CONRAD/WHO Terminology for Pelvic Exam Findings

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

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

Genital Bleeding Assessment

Genital bleeding other than menstrual bleeding, often referred to as intermenstrual bleeding (IMB), is a common occurrence among reproductive age women, and often is of physiologic or benign etiology. Some women normally experience mid-cycle bleeding or pre-menstrual bleeding. IMB is common in hormonal contraceptive users, particularly new and/or inconsistent users. Use of intrauterine contraceptive devices (IUCDs), smoking, and chlamydia infection have been identified as risk factors for IMB, and IMB may be associated with genital tract pathology such as cancer or polyps. IMB also may be associated with traumatic injury to the cervicovaginal epithelium (e.g., due to speculum insertion, product insertion, sexual activity).

10.5.1 Participant Reports of Genital Bleeding

Participants will be counseled to report all occurrences of genital bleeding other than usual menstrual bleeding to study staff as soon as possible after identification of the bleeding. Study staff will provide site contact information to each participant upon enrollment. Thereafter, at each study follow-up visit, contact information will be reiterated and active reporting of genital symptoms including unexpected menstrual bleeding and unexpected non-menstrual genital bleeding will be emphasized.

As described in Section 10.2, at each study visit, clinicians will obtain interval medical/menstrual history information from participants, including active ascertainment of whether any genitourinary symptoms including genital bleeding were experienced since the last study visit. Any changes in participants' use of concomitant medications, including contraceptives and topical and intravaginal medications/preparations, also will be actively ascertained.

10.5.2 Clinician Assessment and Documentation of Genital Bleeding

Pelvic exams will be performed to evaluate any participant report of unexpected menstrual or otherwise genital bleeding. Pelvic exams are not required to evaluate expected bleeding; however, such exams may be performed at the discretion of the IoR or designee.

Figures 10-2b and 10-2c outline the genital bleeding assessment and reporting procedures that will be followed at all sites. As shown in the figures, the sequence of procedures will differ depending on whether genital bleeding is first reported by the participant or first observed by a clinician during a pelvic exam. The Genital Bleeding Assessment (non-DataFax) CRF will be used at all sites to guide and document clinician assessment of both participant-reported genital bleeding and clinician-observed genital bleeding when applicable.

The Genital Bleeding Assessment CRF guides clinicians to collect and consider information on the many factors that may contribute to the observation of genital bleeding, to help determine whether the bleeding is expected or unexpected, may be related to study product use, or whether it may be more likely attributable to another cause. These factors include:

- Early onset of menses
- Use of hormonal contraceptive methods
- Use of intrauterine contraceptive devices (IUCDs)
- Missed oral contraceptive pills or injections
- Sexual activity/trauma
- Trauma associated with insertion of study product or other vaginal preparations
- Trauma associated with pelvic exam procedures
- Sexually transmitted or reproductive tract infections/outbreaks
- Epithelial and/or blood vessel disruption observed on pelvic exam, or other pathology observed on pelvic exam (e.g., polyps, carcinoma)

Figure 10-2a
Overview of Assessment and Reporting Procedures for Genital Bleeding in Non-pregnant Participants — Beginning with Participant Report of Bleeding

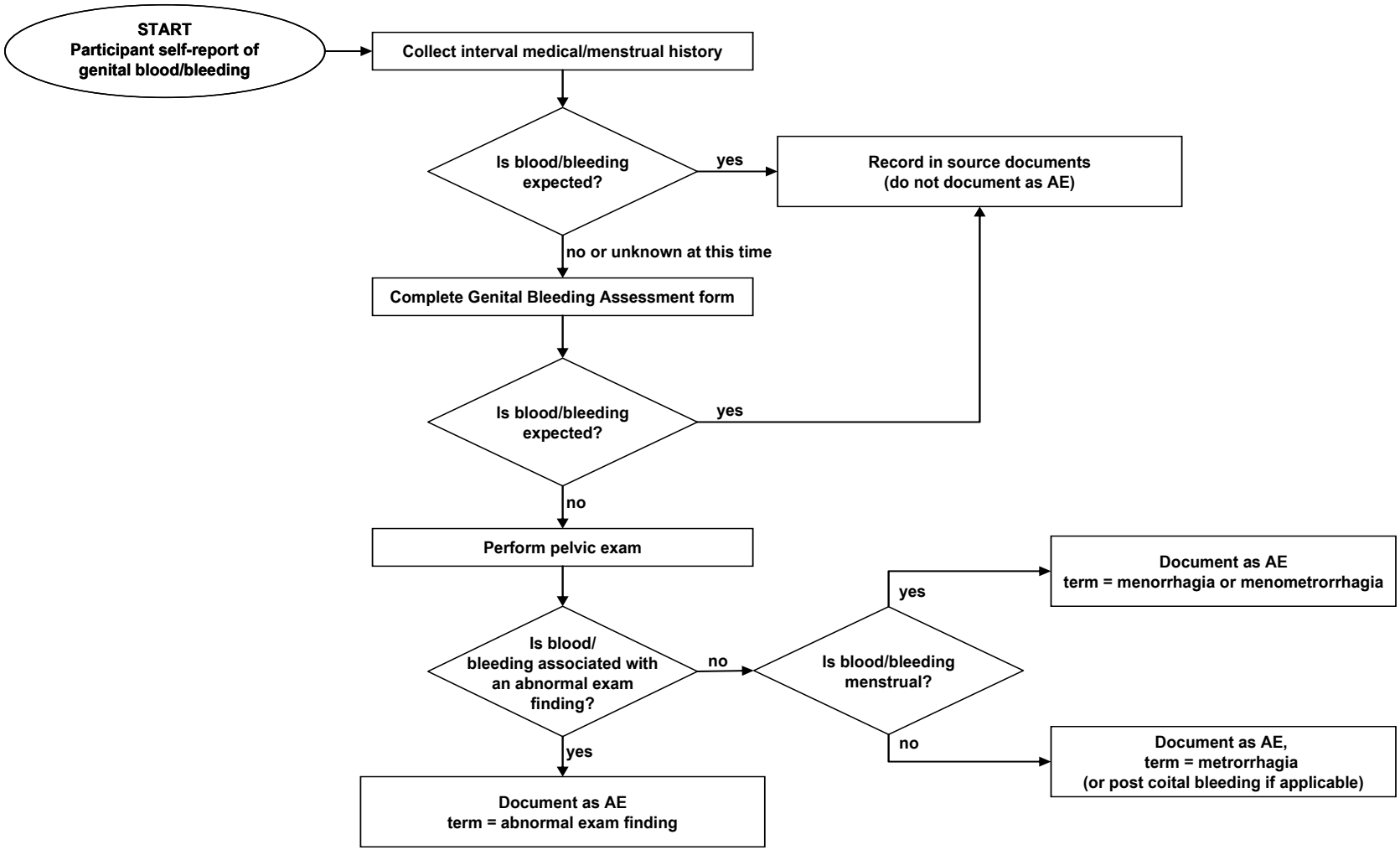
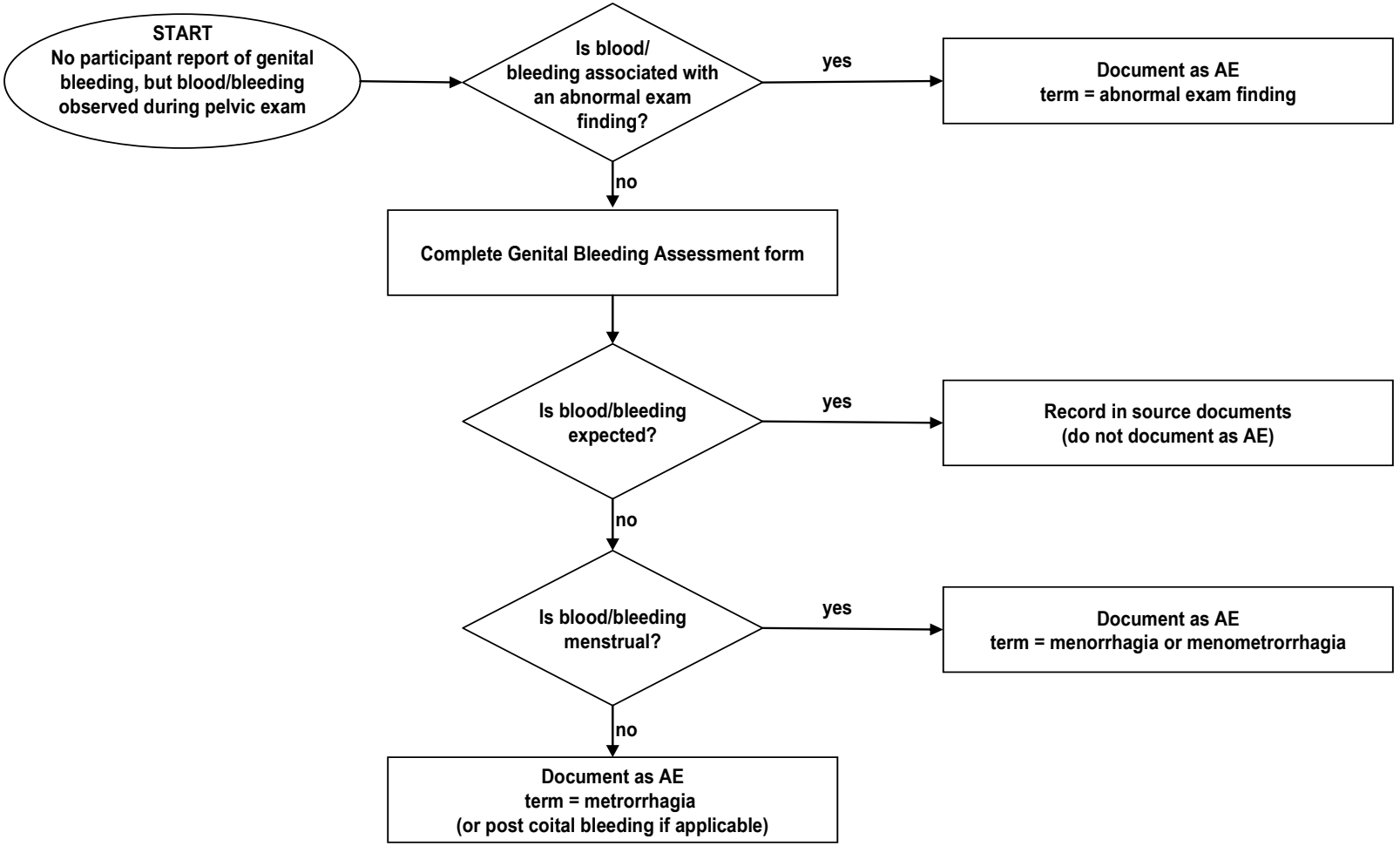


Figure 10-2b
Overview of Assessment and Reporting Procedures for Genital Bleeding in Non-pregnant Participants — Beginning with Clinical Observation of Blood/Bleeding



Assessment of genital bleeding should begin by determining whether the bleeding is expected or unexpected, and then proceed to determining whether the bleeding is menstrual or non-menstrual. Expectedness will be determined based on the participant's baseline medical/menstrual history as well as any other relevant factors such as contraceptive use. If a participant reports bleeding consistent in amount and duration with her baseline medical/menstrual history, or that is consistent with use of her contraceptive method, in the opinion of the IoR or designee, the bleeding should be considered expected. IMB may be expected within the first year after initiating use of an IUCD device or Depo-Provera. IMB may also be expected within the first three months after initiating use of oral contraceptive pills, and after missed pills. Ultimately, however, for each genital bleeding event, the IoR or designee will be required to assess the amount, duration, and pattern of the bleeding, and all other available information, and determine and document whether the bleeding is expected or unexpected and the rationale for the determination.

The Genital Bleeding Assessment form is required to be completed for participants who:

- Self-report genital bleeding that other than their normal menses, unless the bleeding is determined to be expected before completing the form
- Do not self-report genital bleeding, but have genital blood/bleeding observed on pelvic exam that is not expected and not associated with an abnormal exam finding (e.g., laceration).

The Genital Bleeding Assessment form is not required to be completed for participants who:

- Self-report genital bleeding that is determined to be expected prior to completion of the form
- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is associated with an abnormal exam finding.
- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is determined to be expected menstrual bleeding before completing the form.

10.5.3 Genital Bleeding Assessment for Pregnant Participants

If a pregnant participant experiences genital bleeding, study staff will clinically manage the participant per local practice standards for pregnancy. In particular, study staff will refer the participant to a qualified clinician for further evaluation, care, and treatment; pelvic exams may be performed by qualified clinicians unless contraindicated. Study staff will document the bleeding event and all follow-up actions in the participant's study records. Questions about terminology or documentation of genital bleeding in pregnant participants should be referred to the SCHARP or to the MTN-013/IPM 026 Safety Physicians.

10.5.4 Documentation of Genital Bleeding

Participants' prior history of menstrual and non-menstrual genital bleeding will be documented on the Baseline Medical History form and on the Pre-existing Conditions CRF, if applicable.

All clinically observed genital blood/bleeding, whether expected, unexpected, menstrual, or non-menstrual, should be documented on the non-DataFax Pelvic Exam Diagrams (non-DataFax) CRF. The Pelvic Exam CRF should be used to record only abnormal pelvic exam findings. This means that only unexpected menstrual bleeding (excluding early menses) and unexpected non-menstrual bleeding should be recorded on this form. In addition, certain episodes of genital bleeding will be documented on the Genital Bleeding Assessment form, as specified in Section 10.5.3 above.

All episodes of unexpected menstrual bleeding and unexpected non-menstrual genital bleeding — whether participant-reported or clinician-observed or both — will be considered adverse events (AEs) that must be documented on Adverse Experience Log case report forms.

Detailed information on AE reporting is provided in Section 11, however when reporting genital bleeding events, reference also should be made to the nine points below, which standardize the terminology that should be used at all sites when reporting AEs involving genital bleeding.

- Expected menstrual bleeding should not be reported as an AE. "Early menses" also should not be reported as an AE. Although clinical judgment will be required to determine whether any genital bleeding event may be due to early menses, as a general guideline, menses occurring more than two days prior to the participant's usual menstrual cycle should be considered early menses. It is recognized, however, that it may not be possible to make a real-time diagnosis of early menses, based on the information available when first documenting a genital bleeding event. For example, the event could be reported on the first day of bleeding and it may not be known at that time whether a full menstrual period will follow. When information needed for a real time diagnosis of early menses is not available, study clinicians should initially report the event using a term other than "early menses" and then review the event after its final outcome has been ascertained and to determine whether it should be re-categorized as "early menses."

- Unexpected menstrual bleeding (i.e., menstrual bleeding that is heavier in volume or of longer duration than the participant's usual menses), should be reported as an AE using the following AE terms:

  - Menorrhagia: prolonged (more than seven days) or excessive (more than 80 mL) uterine bleeding
  - Menometrorrhagia: prolonged uterine bleeding occurring at irregular intervals

  Grade these AEs per the "Menorrhagia" row of the Female Genital Toxicity Table.

- Expected non-menstrual bleeding should not be reported as an AE. This may include a small amount of cervical bleeding that can occur with speculum insertion or specimen collection, provided the IoR or designee deems the amount of bleeding to be within the range of normal. If the cervical bleeding observed with speculum insertion or specimen collection exceeds that which is expected, in the opinion of the IoR or designee, then the cervical bleeding should be recorded as an AE of "cervical friability", and graded according to the "Cervical edema and friability" row of the Female Genital Toxicity Table.

- Unexpected non-menstrual bleeding that is associated with an observed abnormal pelvic exam finding should be reported as an AE using the term associated with the exam finding, with the anatomical location noted. For example, if a laceration is observed on exam, with blood emanating from the finding, the term "laceration" should be used to describe the AE. The fact that blood or bleeding was present also will be documented on the Pelvic Exam Diagrams form and the Pelvic Exam case report form, and may be noted in the Comments section of the Adverse Experience Log form, but the term "metrorrhagia" ("intermenstrual bleeding") should not be used to describe the AE.

- Unexpected non-menstrual bleeding that is not associated with an observed pelvic exam finding, i.e., for which no abnormal source of blood or bleeding is observed on exam, should be reported as an AE using the term "metrorrhagia." This term refers to bleeding of variable amounts occurring between regular menstrual periods and should be used to report all types of unexpected non-menstrual bleeding such as prolonged or excessive uterine bleeding, spotting between menses, ovulation bleeding, vaginal spotting, and breakthrough bleeding. This term also should be used to report blood-tinged discharge and blood observed in the vagina with no identified source. Grade these AEs per the "Metrorrhagia" row in the Female Genital Toxicity Table.

- In cases with bleeding that qualifies as both menorrhagia and metrorrhagia, it should be labeled menometrorrhagia, but will be graded based on the menorrhagia component. For example, if a participant experiences genital bleeding at irregular intervals that is heavier than her usual menses, you will report the event as "menometrorrhagia" and grade per the "Menorrhagia" row in the Female Genital Toxicity Table.

- If a participant reports genital bleeding after sexual intercourse, you will report this event as "postcoital bleeding" and grade it per the "Postcoital Bleeding" row of the Female Genital Toxicity Table.

- Genital hemorrhage should be reported as an AE; however, the term genital hemorrhage should not be used to describe the AE. When reporting genital hemorrhage, a specific location must be specified. To report uterine hemorrhage, the term menorraghia should be used to describe the AE if it timed at menses and menometrorraghia if the bleeding is in between menses. In the event that a participant experiences a non-uterine genital hemorrhage, the specific location of the hemorrhage needs to be included and the term to be used to describe the AE should be the underlying cause of the condition. For example, if the hemorrhage is caused by trauma in the vagina, then it should be graded per the "Vaginal abrasions or lacerations" row, which is graded by extent of laceration not by degree of bleeding.

10.6 STI/RTI Diagnosis

Clinical and laboratory evaluations may be performed throughout the course of MTN-013/IPM 026 to diagnose the following STIs and RTIs:

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

Genital herpes also may be diagnosed based on clinical presentation, although no laboratory testing will be performed for herpes simplex virus 2 (HSV-2) unless required by local standard of care.

Note: 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.

10.6.1 STI/RTI Treatment

STIs/RTIs will be treated per current CDC guidelines, which can be accessed at:

http://www.cdc.gov/std/treatment/

Should updated guidelines be issued by the CDC during the study, the updated guidelines will then be followed. In day-to-day practice, the CDC guidelines — or local site treatment guidelines based on the CDC guidelines — should be referenced to obtain complete information on treatment regimens, contraindications, etc. To optimize cure rates, directly observed single dose treatment regimens should be provided whenever possible.

Note: Asymptomatic BV and Candida vaginitis do not require treatment per current CDC guidelines. During screening, these asymptomatic infections are not exclusionary and during follow-up these asymptomatic infections are not considered AEs.

Potential study participants diagnosed during screening and /or enrollment with an STI/RTI per CDC guidelines will be offered treatment and may be enrolled after completed treatment and all symptoms have resolved. The only exceptions to this are women with clinical evidence or laboratory evidence of BV or vulvovaginal candidiasis but who are asymptomatic. If the participant is otherwise eligible, she may be enrolled after completing treatment and all symptoms have resolved within 45 days after screening. If symptoms resolve after 45 days, she may be re-screened.

At some study sites, Pap smear results may include notations of findings associated with certain STIs (e.g., trichomoniasis). Because Pap smear methods are not adequately sensitive and specific for STIs, 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. Use only the results of protocol-specified STI tests for purposes of eligibility determination and AE reporting.

- If protocol-specified STI testing was performed on other specimens (i.e., blood, urine, vaginal fluids) 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 fluids) 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.

10.6.2 Adverse Event Reporting Considerations

Any treatable STI/RTI identified during follow-up is considered an AE. Detailed information on AE reporting is provided in Section 11. Any STI/RTI requiring treatment that is identified during follow-up is considered an AE that is recorded on the Follow-up Medical History Log and reported as an AE if applicable.

Genital herpes and genital warts are non-curable STIs and are handled differently from the curable STI/RTIs. Genital herpes and genital warts are associated with chronic viral infections — HSV-1, HSV-2 and HPV — and periodic symptomatic outbreaks — genital ulcers and genital warts. Reporting of these conditions as pre-existing conditions and/or AEs should be handled as follows:

- If infection with HSV-2 or HPV is known to have occurred before randomization, the infection is considered a pre-existing condition: record on the Pre-existing Conditions CRF.

- For HPV, genital warts present at any time before randomization are considered a pre-existing condition; record on the Pre-existing Conditions CRF.

- Any outbreaks that occur after randomization are considered AEs, regardless of whether the viral infection was pre-existing before randomization. Document on the Follow-up Medical History Log and report as an AE as described in Section 11 of this manual.

10.7 Pap Smear Management

A Pap smear is required at the Screening Visit if there is no documentation of a normal result in the form of a written report within the 12 calendar months prior to screening. If no such documentation exists, collect ecto- and endo-cervical cytobrush specimens after completing all naked eye examinations. Participant's results consistent with a Grade 0 according to the FGGT or satisfactory evaluation with no treatment required of Grade 1 or higher Pap result per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines (http://www.asccp.org/) will be presumed eligible.

Pap smear results should be documented in chart notes per the 2001 Bethesda system. The severity of abnormal results should be graded per the "Pap" row of the FGGT only if further evaluation of the Pap smear result is not performed; otherwise, and preferably, severity should be graded based on biopsy results, using the "intraepithelial neoplasia by biopsy" row of the FGGT.

10.8 Urinary Tract Infections

Urinary tract infections (UTIs) will be diagnosed in MTN-013/IPM 026 based on the presence of symptoms indicative of a possible UTI as well as positive dipstick urinalysis results for both nitrites and leukocyte esterase (LE). Dipstick urinalysis for nitrites and LE is required at Screening and when clinically indicated at any other time at Enrollment and during follow-up. The following symptoms are considered indicative of a possible UTI and should prompt dipstick urinalysis for nitrites and LE:

- 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

See Section 12 of this manual for details on urine specimen collection and laboratory testing procedures. Record results on applicable testing log sheets. Additional UTI work-up beyond dipstick urinalysis for nitrites and LE (e.g., urine culture) may be performed if required per site standard of care and documented in chart notes and/or on other site-specific source documents.

All participants diagnosed with UTI based on the presence of symptoms and positive dipstick urinalysis results for both nitrites and LE should be provided treatment per site standard of care and applicable site standard operating procedures (SOPs). Participants diagnosed with UTI during screening may be enrolled in the study after completing treatment and all symptoms have resolved, provided that treatment is completed and symptoms have resolve within 45 days of providing informed consent for screening. For enrolled participants, UTIs diagnosed during follow-up are considered AEs that must be documented and reported if applicable as described in Section 11 of this manual. As explained further in Section 11, the severity of all UTIs should be graded per the "infection (other than HIV infection)" row of the Toxicity Table (not the UTI row of the FGGT).

Participants that present to the study site complaining of UTI symptoms, but are negative for either nitrites or LE, should be clinically managed and treated per standard of care. If a participant develops a presumed UTI during study follow-up but does not meet all of the protocol-specific diagnostic criteria, record each symptom as its own separate AE on a separate AE Log form.

10.9 Clinical and Product Use Management

It is the responsibility and obligation of the IoR and other authorized study clinicians to assess participants' eligibility for continued ring use throughout their participation in the study. Certain product use management decisions and actions must be undertaken, per protocol, under the direction of the study site IoR. Other product use management decisions and actions are undertaken, under the direction of the IoR/designee, in consultation with the MTN-013/IPM 026 PSRT as described in Section 11.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 specific clinical events and STI/RTIs (Sections 9.5), HIV infection (Section 9.6), pregnancy (Section 9.7) and hepatitis B and C infection (Section 9.9). Please refer to Section 9 of this manual for further guidance on product retrieval.

10.9.1 Circumstances In Which Product Use Must Be Permanently Discontinued

- Acquisition of HIV-1 infection; study product should be held beginning immediately upon recognition of the first reactive rapid HIV test
- Pregnancy
- Breastfeeding
- Report of use of post-exposure prophylaxis (PEP) for HIV exposure
- Acquisition of Hepatitis B and/or C infection

10.9.2 Circumstances In Which Product Use May Be Either Temporarily Held or Permanently Discontinued

- Participant reported of use of prohibited medications. Product use may resume only when the participant reports no longer taking the prohibited medication, provided other reasons for temporary product hold/permanent discontinuation do not apply.
- Participants who present with symptoms or signs of clinical hepatitis, the IoR/designee must temporarily hold study product and test the participant for hepatitis (including HBsAg and Anti-HCV plus any other testing indicated by the local standard of care). If hepatitis B or C infection is confirmed, product use must be permanently discontinued.

- Participants who present with symptomatic Candida vaginitis must temporary hold study product and be treated. Product use may resume only following 24 hours after treatment provided other reasons for temporary product hold/permanent discontinuation do not apply.
- 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.
    - The IoR/designee must consult the PSRT on all temporary product holds instituted for this reason for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation.
    - If product use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the IoR/designee should consult the PSRT to resume product use at that time.

10.10 Documentation of Product Use Management

All specifications of protocol Sections 9 must be followed; IoRs are encouraged to consult the PSRT with any questions related to proper interpretation of the protocol and proper management of study product use in particular. All clinical and product use management must be fully documented in participant study records. When the PSRT is consulted in relation to clinical and product use management, completed PSRT query forms (including a response from the PSRT) must be printed and filed in participant study records. Product holds and discontinuations must be communicated to site pharmacy staff using the MTN-013/IPM 026 Vaginal Ring Request Slip. Product holds and discontinuations initiated by study site staff also must be documented on Product Hold/Discontinuation Log case report form. It is expected that signed and dated chart notes, together with correspondence to and from the PSRT, when applicable, will serve as the primary source documentation for these decisions; however other site-specific source documents also may be used.