

Section 7. Clinical Considerations

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This section presents information on the clinical procedures performed in MTN-029/IPM 039. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 8. Information on performing laboratory procedures is described in Section 9. Instructions for completing data collection forms associated with clinical procedures are provided in Section 11.

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

scope of practice, and delegation permit nurses to perform clinician activities under doctor supervision.

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

7.1.1 Pre-existing Conditions Collection at the Screening Visit

To establish each participant's medical status at Enrollment (and also assess medical eligibility), pre-existing conditions will be captured starting at the Screening Visit. The purpose of having pre-existing conditions documented is to ensure that abnormalities 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

To obtain a complete, accurate, and relevant participant self-reported medical history, it will be necessary to ask the participant about her past medical conditions as well as any conditions she is currently experiencing at the time of the Screening and Enrollment visits. It is recommended that sites use the MTN-029/IPM 039 Baseline Medical History Questions sheet; however, sites may use a site-specific form per standard site procedure. When collecting medical history, sites should also assess childbearing and lactation history. This information may be obtained from reviewing the participant's medical records, in accordance with IRB policies.

When collecting medical information from the participant, site clinicians should ask probing questions to obtain the most complete and accurate information possible. This is especially important with regard to severity and frequency of pre-existing conditions. Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit complete and accurate information from the participant.

Sites should also complete an entry on the Pre-existing Conditions CRF for any abnormal bleeding patterns (per the DAIDS Female Genital Grading Table for Use in Microbicide Studies). Site staff should carefully consider whether or not to enroll a woman with abnormal bleeding patterns since menses must not coincide with study visits 2-6 and abnormal patterns may make it difficult to accurately predict when bleeding will occur. Although changes in genital bleeding judged to be related to a participant's contraceptive use, expected irregular bleeding and/or return to menstruation postpartum will not be considered an AE during follow-up, it is important to document her baseline abnormal bleeding patterns to the extent possible.

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.

During screening, if a participant reports having a history of anaphylactic reactions (such as difficulty in breathing or severe hives after eating peanuts), even if it has happened once before in her lifetime, it is still important for the site clinician to document these events as pre-existing conditions on PRE-1 Log CRF. Record the condition in Item 1 as "allergic reaction to peanuts" and note types of symptoms in the comments field including severity grade (per the 'acute allergic reaction' row of the DAIDS toxicity table) when this event occurred. At the Enrollment Visit, check 'yes' for the 'ongoing at enrollment?' box and check 'not gradable' box (as participant was not experiencing an anaphylaxis event at the time of enrollment). An AE submission for an anaphylactic reaction is required if this same event occurs during the study follow-up.

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

Information documented on the Pre-existing Conditions CRF at the Screening Visit must be actively reviewed and updated at the Enrollment Visit, especially for those conditions that

were ongoing at the Screening Visit. This includes a review and update of the condition's description, severity grade, and comments noted for the entry. Make sure the "Ongoing at Enrollment" field is completed for each entry prior to final eligibility confirmation. Chronic conditions should be marked as "ongoing" at Enrollment. For severity grading, the highest severity experienced for the condition should be used. In the comments section, note the typical severity for outbreaks/acute episodes of the condition.

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

7.1.4 Baseline Medications

The MTN-029/IPM 039 protocol requires documentation of all medications taken by study participants beginning at the Screening Visit and continuing throughout follow-up. The Concomitant Medications Log is used to document all concomitant medications in this study. Medications include the following:

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

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

Note that per protocol section 5.2, participants must be using an effective form of contraception at the time of enrollment. To be eligible, participants must also state a willingness to refrain from the use of vaginal products (e.g., spermicides, lubricants, contraceptive VRs, douches, and vaginal medications) for the duration of study participation.

7.2 Clinical Instructions for Checking Ring Placement

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

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

After correct placement is confirmed, the clinician should ask the participant to feel the position of her ring. This will help ensure that she understands what correct placement feels

like, should she need to check this between study visits. This instruction may be repeated at any visit, as needed.

7.3 Medical and Medication History Review at Follow-Up

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

7.3.1 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 one of the following conditions:

- not present at baseline (enrollment);
- 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);
- 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 must 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.

7.3.2 Review of Medications History

At each follow up visit, review the participant's Concomitant Medications Log CRF page(s) and record any new medications the participant reports starting since her last medications assessment. Review all previous entries that are ongoing and ask the participant whether she is still taking the medication (and at the same dose and frequency). It is important to ask whether the participant has taken any new medications 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.

7.4 Physical Exams

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 visit and a targeted (abbreviated) physical exam will

be conducted at the Enrollment visit. Physical exams during follow-up are only conducted if indicated. Per protocol Section 7.9, the following assessments are required at the Screening physical exam:

- General appearance
- Weight (see Section 7.4.3 for further guidance)
- Vital signs:
 - Temperature
 - Pulse
 - Blood pressure (See section 7.4.5 for further guidance)
 - Respirations
- Height (See section 7.4.4 for further guidance)
- Abdomen
- Head, Eye, Ear, Nose and Throat (HEENT)
- Oral mucosa
- Lymph nodes
- Neck
- Heart
- Lungs
- Extremities
- Skin
- Neurological

The following assessments are required at the Enrollment physical exam:

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

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

7.4.1 Weight

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

7.4.2 Height

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

7.4.3 Blood Pressure

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

7.5 Pelvic Exam Overview

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

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.

7.5.1 Pelvic Exam Technique

General Technique: Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to ensure participant comfort and accurate documentation of exam findings. Use clean hand/dirty hand technique, and/or assistants, to avoid contamination. Keep extra gloves available as two hands may be needed at different time points during the exam. Use a speculum of appropriate type and size to permit adequate visualization of the vagina and cervix.

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

7.5.2 Detailed Procedural Instructions

Prior to the Exam: Prepare all required equipment, supplies, and paperwork; label specimen collection supplies as needed. Verify that all equipment is in good working order. Review documentation of prior exams and other relevant documentation from the current visit and prior visits. While the participant is clothed, explain the procedure to her and answer any questions she may have. The study clinician should remove the VR just prior to speculum insertion at the Day 14 visit; however on Days 1 and 7, the ring may stay in place for the pelvic exam. If the participant is uncomfortable, the clinician may remove the ring temporarily for the speculum exam and then replace the ring once done.

Examine the External Genitalia:

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

Examine the Cervix and Vagina:

- The speculum may be lubricated with warm water if needed. No other lubricant may be used. Gently insert the speculum and open it once past the pelvic floor muscles,

using gentle downward pressure, so as to avoid trauma while enabling visualization of the cervical face and upper vagina.

- If the cervix is poorly visualized, to avoid iatrogenic injury, remove the speculum and use a gloved finger (lubricated with warm water if needed) to establish the position of the cervix. Then re-insert the speculum.
- Perform naked eye exam of the cervix, if applicable, and vagina.

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 when clinically indicated, collect a cervical sample to test for **GC/CT** with the Gen-Probe Aptima or Cepheid GeneXpert.
- At Enrollment, Day 14 and Day 16 visits, collect two vaginal swabs for **quantitative vaginal culture assessment**.
- At Enrollment, Days 1, 7, 14, and 16 visits, collect one vaginal swab for **Gram stain** evaluation.
- At Enrollment, Days 1, 7, 14, and 16 visits, collect one vaginal swab for **biomarker analysis**.
- At Enrollment, Days 1, 7, 14, and 16 visits, collect **cervicovaginal fluid (CVF) for DPV levels**. Please refer to sections 7.5.3 and 9.7.8 of this manual for further details regarding sample collection, processing, and storage requirements.
- 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 pH, saline prep and/or KOH wet mount for evaluation of **vaginitis** (yeast or BV).
- At Screening or Enrollment, perform **pap smear**, if the participant is over the age of 21 and she is unable to provide documentation of satisfactory pap smear within 3 years prior to enrollment.

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

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

7.5.3 PK Cervicovaginal Fluid (CVF) Collection

At Enrollment, Days 1, 7, 14, and 16 visits, vaginal fluid for PK (DPV levels) will be collected from participants. One (1) dacron swab will be collected from mid-lateral vaginal wall. Care should be taken to not touch the actual ring with the swab at Enrollment, Days 1 and 7. Care should be taken to not touch the actual ring with the swab at Enrollment, Days 1 and 7. CVF collection should occur at the following time points:

Study Visit	Timing of CVF Collection
Enrollment	Pre-insertion; hour 3 and hour 6 post insertion; as close as possible to collection of other PK/PD samples
Day 1	Approximately 24 hours after ring insertion and as close as possible to collection of other PK/PD samples
Day 7	As close as possible to collection of other PK/PD samples
Day 14	At approximate time of ring removal and as close as possible to collection of other PK/PD samples
Day 16	Approximately 48 hours after ring removal and as close as possible to collection of other PK/PD samples

Weighing vaginal fluid swabs:

- 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).
- 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 9 of this manual for further instructions on processing and storage of the swab for PK.

7.5.4 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. The results of site local laboratory test results performed using specimens collected during pelvic exams are recorded on the STI Test Results CRF.

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

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

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

Epithelium

Integrity:

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

Color:

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

Blood Vessels

Integrity:

- Intact
- Disrupted

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

7.6 Breast Exam and Breast Milk Samples

7.6.1 Breast Exam

A breast exam is required at the Screening visit, Enrollment visit, and Day 16 visit. It may be conducted at any other visit, if indicated. Findings from the exam are documented on the Breast Exam CRF. During the breast exam, site staff will check the participants’ breasts’ appearance. The participant may be asked to raise her arms over her head. The skin covering the breasts should be checked for any rash, dimpling, or other abnormal signs. Site staff will check the entire breast, underarm, and collarbone area for any abnormalities, including any lactation-related abnormalities, such as signs of mastitis. The manual exam is done on one side and then the other. Site staff will also check the lymph nodes near the breast to see if they are enlarged. If a mass or abnormal finding is identified at the Screening or Enrollment visit, the participant should be referred for follow-up evaluation prior to enrollment into the study. If a mass or abnormal finding is identified during follow-up, the participant should be referred for follow-up evaluation and findings should be documented in the participant chart and AE log CRF if applicable.

7.6.2 Breast Milk Collection

Breast milk will be collected at screening and enrollment to ensure the participant has an adequate volume needed for study eligibility purposes. The participant will be requested to express from both breasts until milk stops flowing. Participants must express a minimum of 1 ounce per expression (total for both breasts) in order to be eligible for the study. The participant may choose the method she feels most comfortable using to express milk for the sample, include hand expressing, a manual pump, a personal electric pump, or a hospital-grade pump. At the Enrollment visit, this sample must be collected prior to confirmation of eligibility and study enrollment. The enrollment sample also may be used as the pre-ring insertion sample. Breastmilk collection for eligibility, DVP level, lipids, and anti-viral activity, should occur at the following time points:

Study Visit	Timing of Breastmilk Collection
Screening	Eligibility specimen may be collected at any point in visit, per clinic flow

Enrollment	Pre-ring insertion; hour 3 and hour 6 post ring insertion; as close as possible to collection of other PK/PD samples
Day 1	Approximately 24 hours after ring insertion and as close as possible to collection of other PK/PD samples
Day 7	As close as possible to collection of other PK/PD samples
Day 14	At approximate time of ring removal and as close as possible to collection of other PK/PD samples
Day 16	Approximately 48 hours after ring removal and as close as possible to collection of other PK/PD samples

7.7 STI/RTI/UTI

7.7.1 Considerations at Screening/Enrollment

Participants diagnosed during Screening and Enrollment with an STI, RTI, or UTI may only enroll in the study following treatment and resolution of all symptoms, provided this occurs within 56 days of obtaining informed consent. Please see Exclusion Criteria #6 and #7 in Protocol Section 5.3.

7.7.2 STI/RTI/UTI Diagnosis

Clinical and laboratory evaluations for gonorrhea, chlamydia, and trichomonas are required at screening, and only conducted if indicated at all other visits. Syphilis serology is also done at the Screening visit if the participant does not have a documented result with the past year. If an STI, RTI, or UTI is identified during follow-up, they should be recorded as AEs. Infections should be considered “symptomatic” when a participant self-reports or complains of symptoms associated with the infection. Symptoms should not be confused with “signs” of infection that may be observed during clinical examinations performed by study staff.

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

Urinary tract infections (UTIs): UTIs may be diagnosed in MTN-029/IPM 039 based solely on the presence of symptoms indicative of a possible UTI, or other method of diagnosis (i.e. urine culture or dipstick) as per site standard of care. See SSP Section 8 for guidance on using the DAIDS toxicity tables to grade UTIs. The following symptoms are considered indicative of a possible UTI:

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

7.7.3 STI/RTI/UTI Management

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

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

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

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

Test of Cure: STI/RTI tests of cure are not required in MTN-029/IPM 039, but may be recommended per local guidelines.

7.8 Vaginal Discharge

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

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

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

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

7.9 Genital Bleeding Assessment

At each scheduled follow-up visit, study staff will actively ascertain whether any genital bleeding (menstrual or non-menstrual) was experienced since her last visit. In addition, participants will be counseled to report all occurrences of unusual genital bleeding to study staff as soon as possible after identification of the bleeding. Bleeding that this judged to be related to contraceptive use, return of menstruation postpartum, or judged to be within the range of normally anticipated bleeding for a speculum or specimen collection procedure will not be reported as an AE. Incidences of abnormal bleeding, regardless if considered an AE, should be documented in participant chart notes with a clear rationale and assessment of the cause.

If abnormal bleeding is observed or reported by participants that are not judged to be related to one of the conditions above, sites should note the abnormal bleeding on an AE log CRF. Note that any menorrhagia, metrorrhagia, or menometrorrhagia events ongoing at the time of enrollment are marked as “not gradable” on the PRE. This is because the FGGT grades these events relative to each participant’s baseline bleeding pattern. In the “Comments” field

of the ongoing PRE entry, sites should include text similar to what is in the FGGT row to describe the severity and frequency. For example, for an ongoing event of menorrhagia, mark “not gradable” and in the PRE Comments, record “no interference with participant’s usual activities” (similar to text used to describe Grade 1 severity). Adding such text to the Comments of the PRE entry will help ensure that increases in the severity or frequency of bleeding relative to the participant’s baseline bleeding pattern are identified and reported appropriately. Sites should also document in the comments section if the abnormal bleeding is related to contraceptive use and/or return of menstruation postpartum.

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

7.10 Management of Laboratory Test Results

AST/ALT and HIV testing will be performed at Screening. An additional HIV test will be performed at Enrollment if more than 30 days have passed since the Screening visit. For each study participant, the IoR or designee is responsible for reviewing and monitoring these test results and for ensuring appropriate clinical management of all results. IoR or designee review of laboratory test results should be documented on the lab results report (provided by the lab to the clinic) and/or in chart notes.

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

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

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

7.11 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for product discontinuation (Section 9.3), guidance on clinical management in response to observed AEs (Section 9.4), and management of STI/RTI, genital complaints, and suspected complications of lactation (Section 9.5), HIV infection (Section 9.6), pregnancies (Section 9.7), guidance on participants who reinstate feeding infants (Section 9.8) and early study termination (Section 9.9). Below is a list of conditions that require permanent study product discontinuation:

- Acquisition of HIV infection
- Use of vaginal ring is harmful to participant
- Pregnancy
- Breastfeeding for immediate consumption, banking, or freezing or participant expresses intention to do so
- 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
- Grade 3 AE related to study product use
- Grade 4 AE or higher, regardless of relationship to study product

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