Section 7. Clinical Considerations

This section presents information on the clinical procedures performed in MTN-030/IPM 041. 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, and documented on the Baseline Medical History Log CRF. Ongoing medical conditions, problems, signs, symptoms, and findings identified prior to enrollment are considered pre-existing conditions. Pre-existing conditions must be graded and are assigned severity grades in the same way that severity is assessed for AEs. If a pre-existing condition worsens (increases in severity or frequency) after enrollment, the worsened condition is considered an AE and is reportable on the AE Log CRF. If a pre-existing condition resolves after enrollment, but then recurs at a later date, the recurrence is considered an AE. The purpose of having pre-existing conditions documented is to ensure that abnormalities present at baseline and later observed during follow-up, at the same severity and frequency, are not documented as adverse events (see Section 8 for more information).

7.1.2 Participant-Reported Conditions

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

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

To obtain a complete, accurate, and relevant participant self-reported medical history, it will be necessary to ask the participant about her past medical conditions and surgeries, as well as any conditions she is currently experiencing at the time of the Screening and Enrollment visits. It is recommended that sites use the MTN-030/IPM 041 Baseline Medical History Questions sheet (as a source document) in conjunction with the Baseline Medical History Log CRF and/or chart notes to guide and document medical history taking. Sites may also use a site-specific form per standard site procedure. Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit complete and accurate information from the participant. This is especially important with regard to details about severity and frequency of baseline medical history conditions.

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

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

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

Clinicians should also assess if the participant meets the exclusion criterion of having any contraindications to a progestin-only contraceptive method, as defined by a category 3 or 4 CDC US Medical Eligibility Criteria for Contraceptive Use (2016) condition (see appendix 7-1). Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit complete and accurate information from the participant.

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

Sites should complete an entry on the Baseline Medical History Log CRF for any abnormal genital bleeding patterns (per the DAIDS Female Genital Grading Table for Use in Microbicide Studies) reported by the participant. Site staff should carefully consider any abnormal bleeding patterns since participants must have regular menstrual cycles of approximately 21-35 days' duration to be eligible for study participation, and ideally, menses must not coincide with the 14 days of product use. Although changes in genital bleeding will not be considered an AE during follow-up (unless also deemed to be an SAE), such changes will be assessed (via SMS and the Vaginal Bleeding Assessment CRF), so it is important to document a participant's baseline abnormal genital bleeding patterns to the extent possible.

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 only once before in her lifetime, it is still important for the site clinician to document these events as a pre-existing condition on the Baseline Medical History Log CRF. In this example, record the condition/event as "allergic reaction to peanuts" and note types of symptoms (e.g., "throat swelling" or "shortness of breath") in the "Description of medical condition/event" field including severity grade. Assign the severity grade per the "acute allergic reaction" row of the DAIDS Toxicity Table when this event occurred. At the Enrollment Visit, check "yes" to the question, "Is the condition ongoing?" and check "no" for the question "Is condition/event gradable?", as the participant was not experiencing an anaphylaxis event at the time of enrollment/randomization. An AE submission for an anaphylactic reaction is required if this same event occurs after enrollment or during study follow-up.

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

Information documented on the Baseline Medical History Log CRF at the Screening Visit must be actively reviewed and updated at the Enrollment Visit, especially for those conditions that were ongoing at the Screening Visit. This includes a review and update of the condition's description and severity grade. Make sure the "Is the condition ongoing?" field is completed/updated for each entry prior to final eligibility confirmation.

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

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

7.1.4 Baseline Medications

The MTN-030/IPM 041 protocol requires documentation of all medications taken by a study participant, beginning at her Screening Visit and continuing throughout her study follow-up period. The Concomitant Medications Log CRF is used to document all concomitant medications used by a given participant during her study participation. Medications include the following:

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

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

Participants must not be using or plan to use antibiotics, corticosteroids, CYP3A inhibitors or inducers during the time of their planned study participation. Common examples of prohibited medications are provided in SSP Section 6, appendices 6-3, 6-4 and 6-5. Of note, single dose oral fluconazole for the treatment of vaginal fungal infections is permitted. If site staff have questions about a specific medication and whether or not it is prohibited, they should contact the PSRT for guidance.

In addition, per protocol section 5.2, participants must be using an effective form of non-hormonal contraception at the time of enrollment. To be eligible, participants must also state a willingness to refrain from the use of any non-study vaginal products (e.g., tampons, spermicides, female condoms, diaphragms, contraceptive VRs, vaginal medications, menstrual cups, cervical caps (or any other vaginally applied barrier method), vaginal douches, lubricants and moisturizers, sex toys etc.) 24 hours prior to enrollment and for the duration of study participation.

7.2 Clinical Instructions for Checking Ring Placement

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

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

After correct placement is confirmed, the clinician should ask the participant to feel the position of her ring. This will help ensure that she understands what correct placement feels like, should she need to check this between study visits. This instruction may be repeated at any visit, as needed.

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

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

7.3.1 Participant-reported Follow-up Medical and Menstrual History

An updated participant self-reported medical and menstrual history is required at each scheduled visit during follow-up. A history should also be performed at interim visits when a participant presents complaining of symptoms or when the purpose of the visit is to re-assess previously-identified adverse events (AEs). One purpose of the participant-reported follow-up history is to determine whether previously-documented conditions have changed with regard to severity or frequency. Any changes are recorded on the Baseline Medical History Log CRF (for updates to pre-existing conditions) or the AE Log CRF (for updates to AEs), as appropriate. A second purpose is to determine whether new symptoms, illnesses, conditions, etc., have occurred since the last medical history was performed. The form itself, chart notes, or a site-specific tool, if desired, may serve as the source document. All newly-identified participant-reported symptoms and conditions will be documented on the AE Log CRF (see Section 8 for details regarding AE documentation).

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

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

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

If, during follow-up, a pre-existing condition resolves or increases in severity or frequency from baseline, this must be documented on the Baseline Medical History Log CRF. Resolution of a pre-existing condition is documented by changing the response to "no" for the question, "Is the condition ongoing?", and entering the date the condition resolved in the field "Date medical condition/event ended/resolved". If the condition increases in severity or frequency from baseline, enter the date the severity/frequency increased in "Date medical condition/event ended/resolved", and complete an AE Log CRF to document the new AE (i.e., the baseline condition at an increased severity and/or frequency). The Onset Date of the AE should be the same as the "Date medical condition/event ended/resolved" on the Baseline Medical History Log CRF, and the AE Log CRF should have the "yes" box marked for the question, "Was this AE a worsening of a baseline medical condition?".

7.3.2 Review of Medications History

At each follow up visit, review the participant's concomitant medications history and document this review by completing the Concomitant Medications Summary and Concomitant Medications Log CRFs. Ask the participant if she has started taking any new medications, and record on the Concomitant Medications Log CRF any new medications she reports having started since her last medications assessment. In addition, review all previous entries that do not have a "Date Stopped" entered and ask the participant whether she is still

taking the medication (and at the same dose and frequency). If the participant has stopped taking a medication, enter the last date the participant used the medication in the "Date Stopped" field. If the participant is taking the same medication but at a different dose or frequency, enter in the "Date Stopped" field the date the participant last used the medication at the original dose or frequency, and complete a new Concomitant Medications Log form/entry for the new dose or frequency. Ensure that concomitant medications mentioned in previous parts of the visit are documented correctly and consistently on the Concomitant Medications Log CRF, so that study records are not discrepant.

7.4 Physical Exams

The goal of the physical exam during the Screening and Enrollment Visits is to collect detailed information on baseline conditions, as well as to evaluate eligibility. A complete physical exam will be conducted at the Screening and Enrollment visits. Per protocol Section 7.9, the following assessments are required at the Screening and Enrollment Visit physical exams:

- 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)*
- Waist measurement (see Section 7.4.3 for further guidance)*
- Abdomen
- Lymph nodes
- Neck
- Heart
- Lungs
- Extremities
- Skin
- Neurological

** Note: Height and waist measurement is only required at the Screening Visit*

A modified physical exam is required at the Day 14 visit and if indicated at all other times. The following assessments are required at the Day 14/PUEV/Early Termination Visit 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 and Vital Signs CRFs.

7.4.1 Weight

Participant weight must be measured as part of each scheduled physical exam and additionally when clinically indicated. Weight should be measured in kilograms and should

be rounded to the nearest whole number. Scales should be calibrated at least twice per year, and more frequently if required per local practice standards.

7.4.2 Waist measurement

Waist measurement is only required at the Screening Visit and will be measured in centimeters. This measurement may be taken without clothing (directly over the skin) or taken over light clothing. Measurement should be taken with the participant's arms crossed over her chest. Locate the upper hip bone and the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is made at the end of a normal expiration.

7.4.3 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.

7.4.4 Body Mass Index (BMI)

Height and weight measurements must be used to calculate BMI at the Screening Visit. If the participant's BMI is greater than 35 kg/m^2, she is ineligible for enrollment. Sites are encouraged to use the BMI calculator, available on the MTN-030 Study Implementation webpage to calculate BMI. If a site uses this calculator, once the data are entered, site staff should print out a copy for the participant chart.

7.4.5 Blood Pressure

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

7.5 Pelvic Exam Overview

The pelvic exam during the Screening and Enrollment visits is necessary to evaluate protocol exclusion criteria and to collect detailed information on baseline genital/genitourinary conditions. Guidance on the conduct of pelvic exams can be found in the remainder of this section. Pelvic exams are documented on the Pelvic Exam CRF, which may be source documented on the Pelvic Exam Diagrams (non-Medidata form) or another site-specific source document, as specified in the site's Source Documentation SOP.

Note that cervical bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the 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, and complicate interpretation of vaginal assays. If a participant is experiencing mild spotting, it is reasonable to proceed with a pelvic exam and collection of samples. If she is experiencing greater than mild bleeding when she

presents for a visit in which a routine pelvic exam is required, perform other protocol-specified procedures at the visit and schedule the participant to return for the pelvic exam as soon as possible after menses, within the visit window (as part of a split visit, if allowable; refer to Section 11 of this manual). If this is not possible conduct the pelvic exam, collect all required pelvic specimens (including PK), and note the bleeding in her chart and on applicable CRFs (i.e., Pelvic Exam CRF, Vaginal Bleeding Assessment CRF). If a participant is experiencing genital bleeding when she presents for an interim visit complaining of genital symptoms, every effort should be made to perform a pelvic exam to evaluate her symptoms at that time.

7.5.2 Detailed Procedural Instructions

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

The study clinician should remove the VR just prior to speculum insertion at the Day 14 visit; however, on Days 3 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.
- Note: participant must have intact uterus and at least one ovary to be eligible for study

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

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

Complete Examination of the Cervix and Vagina: To complete the naked eye examination of the vagina, slowly withdraw the speculum with the blades moderately open, re-focusing as needed. Alternatively, the speculum may be rotated ninety degrees to allow visualization of

the anterior and posterior vaginal walls; retract the speculum away from the cervix and close the blades to rotate.

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

7.5.3 PK Cervicovaginal Fluid (CVF) Collection

At Enrollment, Days 1, 2, 3, 7, 14, 15 and 16 visits, cervicovaginal fluid (CVF) for PK will be collected from all participants. Two (2) pre-weighed dacron swabs will be inserted into the upper vagina (approximately 5cm/2 inches) and held for a slow count to 10 seconds (one swab each for DPV and LNG levels). Collection of CVF swabs should occur prior to the collection of all other vaginal/cervical specimens, and prior to the insertion of the speculum.

Collection timepoints are included in the table below. Note: For single PK collection timepoints (Days 1-7, 15 and 16) as well as multiple PK collection time-points (Enrollment and Day 14; post ring insertion and/or removal collection only), CVF should ideally be collected within 15 minutes of PK blood collection.

Study Visit	Timing of CVF Collection
Enrollment	Pre-ring insertion; hours 1, 2, 4 and 6 post ring insertion; as close as possible to collection of other PK samples
Days 1, 2, 3 and 7	As close as possible to collection of other PK samples
Day 14	Prior to ring removal; hour 6 post ring removal; as close as possible to collection of other PK samples
Day 15 and 16	As close as possible to collection of other PK samples

Refer to section 9.7.6 of this manual for instructions on weighing, processing and storage of the swab for PK.

7.5.4 Documentation of Findings

All exam findings (normal and abnormal) should be documented on the site-designated source document, as specified in the site's Source Documentation SOP. All abnormal findings must be thoroughly documented (e.g., to include type, size, anatomical location, and severity grade) on the Pelvic Exam CRF, and any other relevant source documents as desired, to ensure appropriate assessment can be provided during the next pelvic exam.

All abnormal findings observed during the Screening and Enrollment Visits will be documented on the Pelvic Exam CRF and the Baseline Medical History Log CRF. All abnormal findings identified during follow-up will be documented on the Pelvic Exam CRF. All newly-identified abnormal pelvic exam findings will be documented on an AE Log CRF. The results of site local laboratory test results performed using specimens collected during pelvic exams are recorded on the STI Tests CRF.

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

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

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

Epithelium

Integrity:

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

Color:

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

Blood Vessels

Integrity:

- Intact
- Disrupted

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

7.6 STI/RTI/UTI

7.6.1 Considerations at Screening/Enrollment

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

7.6.2 STI/RTI/UTI Diagnosis

Clinical and laboratory evaluations for gonorrhea, chlamydia, syphilis, and trichomonas are required at screening, and only conducted if indicated at all other visits. If an STI, RTI, or UTI is identified during follow-up, it should be documented as an AE. Infections should be considered “symptomatic” when a participant self-reports or complains of symptoms associated with the infection. Symptoms should not be confused with “signs” of infection that may be observed during clinical examinations performed by study staff.

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

Urinary tract infections (UTIs): UTIs may be diagnosed in MTN-030/IPM 041 based solely on the presence of symptoms indicative of a possible UTI, or other method of diagnosis (i.e.,

urine culture or dipstick) as per site standard of care. See SSP Section 8 for guidance on documenting UTI AEs based on symptoms or culture.

The following symptoms are considered indicative of a possible UTI:

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

7.6.3 STI/RTI/UTI Management

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

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

Asymptomatic BV does not require treatment per current CDC guidelines. Asymptomatic vaginal candidiasis also should not be treated. During screening, these asymptomatic infections are not exclusionary and during follow-up these asymptomatic infections are not considered AEs; however, they will be captured on the STI CRF.

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-030/IPM 041, but may be recommended per local guidelines.

7.7 Vaginal Discharge

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

7.8 Genital Bleeding Assessment

At each scheduled follow-up visit, study staff will actively ascertain if there are any updates to the participant's menstrual history and whether any genital bleeding was experienced since her last visit. This information is documented on the Vaginal Bleeding Assessment CRF, which is required to be completed at all protocol-specified follow-up visits. In addition, participants will be counseled to report all occurrences of unusual genital bleeding to study staff as soon as possible after identification of the bleeding. Per protocol section 8.3.1, changes in genital bleeding will not be reported as an AE, unless deemed to be a Serious Adverse Event. Incidences of abnormal bleeding, regardless of whether AE/SAE criteria are met, should be documented on the Vaginal Bleeding Assessment CRF.

7.9 Management of Laboratory Test Results

Serum creatinine, CBC with platelets and differential, AST/ALT, and HIV testing will be performed at Screening, Enrollment, and Day 14. Sex hormone-binding globulin (SHBG), albumin, serum progesterone, and estradiol will be tested at enrollment; and SHBG and albumin will also be tested at the Day 14/PUEV/Early Termination Visit. The SHBG/albumin and progesterone/estradiol tests are for research purposes only, and clinical management of results is not required. 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 (i.e., severity Grade 1 and higher), regardless of grade, on the Baseline Medical History Log CRF. Abnormal laboratory test results from the Enrollment Visit will not be considered exclusionary, but will be documented as pre-existing conditions. These abnormal findings will be graded and may result in product discontinuation as per Protocol Section 9.

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

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

7.10 Clinical and Product Use Management

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

- Acquisition of HIV infection
- Allergic reaction to the vaginal ring
- Pregnancy
- Breastfeeding
- Reported use of PEP for HIV exposure
- Reported use of PrEP for HIV prevention
- Non-therapeutic injection drug use
- Study ring had been out of the vagina for more than 3 consecutive days

- Participant reports use of prohibited medications, as listed in Section 7.1.4 and further described in the appendices of Section 6
- 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

All specifications in 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.

Flow sheets outlining product management procedures can be found on the MTN-030/IPM 041 Study Implementation Materials webpage. 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.

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