

Section 10. Clinical Considerations

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This section presents information on the clinical procedures performed in MTN-020. The Schedule of Study Visits and Evaluations in Appendix I of the protocol indicates when specific clinical and laboratory assessments are to take place. While the protocol dictates the schedule for data capture, the Investigator of Record or designee should perform the symptom-directed examination at his/her discretion during any visit if s/he determines it to be clinically necessary, particularly if there are any on-going medical or mental health

conditions that require closer follow-up. The participant's research record should include documentation of these procedures. Throughout the SSP, 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.

Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 11. Information on performing laboratory procedures is described in Section 13. Instructions for completing data collection forms associated with clinical procedures are provided in Section 14.

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

10.1.1 Pre-existing Conditions Collection at the Screening Visit

In order to establish each participant's medical status at Enrollment (and also assess medical eligibility), pre-existing conditions will be captured starting at the Screening Visit. The purpose of having pre-existing conditions documented is to ensure that abnormalities that are present at baseline and later observed in follow-up (at the same severity and frequency) are not documented as adverse events (see Section 11 for more information).

Participant-Reported Conditions

In order to obtain a complete, accurate, and relevant participant self-reported medical and menstrual 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. To best do this, it is recommended that sites use the MTN-020 Baseline Medical History Questions sheet (see Appendix 10-1; Word version available on the ASPIRE web page under *Study Implementation Materials*). The Screening Menstrual History CRF also contains probing questions for capturing medically-relevant symptoms and bleeding patterns. Complete an entry on the Pre-existing Conditions CRF for any abnormal bleeding patterns (e.g. amenorrhea, menorrhagia, metrorrhagia) or menstrual symptoms which contribute to a medical condition (e.g. dysmenorrhea, pre-menstrual syndrome).

When collecting medical information from the participant, ask probing questions in order 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.

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.

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

Laboratory Abnormalities and Abnormal Physical and Pelvic Exam Findings

In addition to participant-reported conditions, record all Screening Visit grade 1 and higher lab values on the Pre-existing Conditions CRF (as identified on the Screening Laboratory Results CRF). Also record all medically-relevant physical exam abnormalities (refer to the Screening Visit Physical Exam CRF), pelvic exam abnormal findings (refer to the Pelvic Exam Diagrams and Screening Pelvic Exam CRF) and any identified STIs (per the Screening STI Results CRF).

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

Information documented on the Pre-existing Conditions form 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 determination.

10.1.3 Baseline Medications

The MTN-020 protocol requires documentation of all medications taken by study participants beginning at the Screening Visit and continuing throughout follow-up. Medications include the following:

- Prescription and "over-the counter" medications and preparations
- Medications taken for pre-exposure (PrEP) or post-exposure prevention (PEP) of HIV
- Vaccinations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- Recreational drugs
- Contraceptive medications – see guidance below
 - Record each contraceptive injection as a single entry
 - Record each contraceptive pill pack used as a single entry
 - For implants/IUCDs, record the removal date as the Date Stopped

The Concomitant Medications Log is used to document all concomitant medications in this study. This CRF is first used at the Screening Visit, and entries/pages are added for each participant as needed at the Enrollment Visit throughout follow-up.

Use the information obtained in the medical/menstrual history to probe for additional medications that the participant may have forgotten to report.

It is preferable to record the trade name of a medication on the CRF. If the trade name is not available or not reportable per national guidelines, you may record the generic name of the medication. A combination medication can be recorded as one entry using the generic name. If a combination medication does not have a generic name or the generic name is unknown, each active ingredient must be reported as a separate entry in order to be accurately coded at SCHARP.

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

Medication history information documented on the Concomitant Medications Log at the Screening Visit must be actively reviewed and updated at the Enrollment Visit (prior to randomization). Review the information on this CRF with the participant at the Enrollment Visit and update as applicable.

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

Participant-Reported Follow-up Medical/Menstrual History

An updated participant self-reported medical/menstrual history is required at each scheduled visit during study 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/menstrual history was performed. Documentation that this history was taken is required; this can be done in chart notes 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 either the Adverse Experience Log (AE-1) or the Grade 1 Adverse Experience Log (GAE-1) CRF (see Section 11 for details regarding AE documentation).

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

- was not present at baseline (enrollment);
- is ongoing but has now increased in severity or frequency (includes ongoing baseline conditions or adverse events that increase in severity or frequency during follow-up);
- was ongoing (includes ongoing baseline conditions), 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 (refer to the Pre-existing Conditions Resolution Tracker Sheet, if used) as well as any symptoms listed as “continuing” on an AE-1 or GAE-1 CRF.

If during follow-up a baseline symptom resolves or increases in severity or frequency from baseline, this will need to be documented either in chart notes or using a Pre-existing Conditions Resolution tracker (see Section Appendix 10-2). Such information should not be added to the Pre-existing Conditions CRF, as that form represents a snapshot of the participant's status as of baseline.

Review of Medications History

At each visit in which a medical/menstrual history is performed, review the participant’s Concomitant Medications Log CRF pages and record any new medications the participant reports starting since her last medications assessment. Review all previous entries that are ongoing and ask the participant whether she is still taking the medication (and at the same dose and frequency). It is important to ask whether the participant has taken any new medications, including herbal or traditional therapies, since her last medications assessment. Ensure that concomitant

medications mentioned in previous parts of the visit are rectified with the Concomitant Medications CRF so that records are not discrepant.

10.3 Physical Exams

10.3.1 Considerations at Screening and Enrollment

The goal of the Screening physical exam is to collect detailed information on baseline conditions, as well as to evaluate eligibility. All abnormal signs/symptoms/diagnoses identified during the screening physical exam should be recorded on the Pre-existing Conditions CRF and followed up on at the Enrollment visit (see Section 10.1.3).

A complete physical exam will be conducted at the screening visit and a targeted (abbreviated) physical exam for all subsequent scheduled visits. Per protocol Section 7.8, the following assessments are required at the Screening physical exam (bolded assessments are also conducted in the abbreviated physical exam at enrollment and scheduled follow up visits). The physical exam is documented on the Screening Visit Physical Exam CRF or the Enrollment Abbreviated Physical Exam CRF, as appropriate.

- **General appearance**
- **Weight** (see Section 10.3.3 for further guidance)
- **Vital signs:**
 - **Temperature**
 - **Pulse**
 - **Blood pressure** (See section 10.3.4 for further guidance)
 - **Respiratory rate**
- **Abdomen: palpable spleen, liver**
- Height
- Lymph: palpable cervical, axillary and/or inguinal lymph nodes
- Neck
- Heart: rate, rhythm, murmurs
- Lungs: observation of character of respirations, auscultation
- Extremities
- Skin: rashes, scars, bruising, needle tracks, jaundice
- Neurological
- **Assess any other medical condition that would make participation in the study unsafe or interfere with interpreting the study data or achieving the study objectives.**

10.3.2 Physical Exams Conducted at Follow-up

Physical exams are required Quarterly, Semi-Annually, at the Product Use End (PUEV) visits, and when clinically indicated. All follow-up physical exams should include the bolded assessments outlined in Section 10.3.1 (and protocol Section 7.8). 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.

Physical exams performed during follow-up (including the unscheduled exams that are clinically indicated) are documented using the Abbreviated Physical Exam CRF. Unscheduled physical exams performed to identify new symptoms or findings or to

follow-up on clinical findings during follow up should be documented on the Abbreviated Physical Exam CRF. Abnormal physical exam findings newly-identified during follow-up are recorded and tracked using the Adverse Experience Log (AE-1) CRF or Grade 1 Adverse Experience Log (GAE-1) CRF as applicable. If a particular vital sign (for example, weight, height, blood pressure) is measured during unscheduled time points and further physical evaluation is not performed, these vitals can be noted in the participant's chart notes, as needed, and an Abbreviated Physical Exam CRF is not required. Refer to Section 10.2 for a definition of "newly-reported".

10.3.3 Weight

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

At each site, consistent weighing procedures should be followed for all participants. Each site may choose to consistently weigh participants fully clothed or wearing clinic gowns. Sites with seasonal weather variations should consider using gowns and/or adopting other procedures to ensure that accurate weights are measured throughout the year.

10.3.4 Height

Participant height must be measured as part of the physical exam at the Screening Visit. Height should be measured in centimeters and should be rounded to the nearest whole number. Height measurement devices affixed to weight scales are often inaccurate and are not recommended. For participants with hairstyles that could affect height measurements, a tongue depressor or other device should be held horizontally to the wall chart at the top of the participant's head (not at the top of her hairstyle) to obtain accurate measurements.

10.3.5 Blood Pressure

Blood pressure must be measured as part of each scheduled physical exam and additionally when clinically indicated. Blood pressure devices are expected to be calibrated regularly per manufacturer's directions.

Because MTN-020 is generally expected to enroll young healthy women, hypertension is not expected to be common among study participants. For participants with hypertension, it is recommended that study sites counsel the participant and refer the participant per site SOPs. Antihypertensives, including thiazide diuretics and angiotensin converting enzyme (ACE) inhibitors, are not contraindicated in MTN-020. If treatment is provided at the research clinic, site clinicians should generally follow local standards of care for antihypertensive monitoring and treatment.

10.4 Pelvic Exams

10.4.1 Considerations at Screening

The pelvic exam during the Screening Visit 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 Section 10.4.4. Screening Visit pelvic exams are documented on the non-DataFax Pelvic Exam Diagrams form and the Screening Pelvic Exam CRF.

Any abnormal pelvic exam finding, regardless of grade, should be documented on the Pre-Existing Conditions CRF. Only grade 1 findings may be ongoing at enrollment, otherwise the participant is ineligible.

SPECIAL NOTE:

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

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

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

Note that per LoA#1, a complete pelvic exam is not required at the Enrollment Visit. However, in cases where an exclusionary abnormal exam finding (grade 2 or higher) is identified at the Screening Visit, it will be necessary to re-assess the finding prior to Enrollment to confirm the participant's eligibility. If re-assessment on or prior to Enrollment confirms the exclusionary finding(s) is Grade 1 or below, the participant may be enrolled. Document the re-assessment of abnormal screening pelvic exam findings by completing a new Pelvic Exam Diagrams (non-DataFax form) and updating the severity grade, ongoing status, and other information (as needed) of the abnormal finding's Pre-existing Conditions entry. If the re-assessment is done at the Enrollment Visit, you may also document the abnormal finding's status on the Abbreviated Physical Exam CRF completed for the Enrollment Visit (in addition to the Pelvic Exam Diagrams and PRE entry update).

If a *complete* second pelvic exam (includes external and internal visualization and bimanual exam) is conducted on or prior to Enrollment, complete a new Pelvic Exam Checklist, a new Pelvic Exam Diagrams (non-DataFax) form, and a new Screening Pelvic Exam CRF. The abnormal finding's Pre-existing Conditions entry should be updated as needed (severity grade, ongoing status, other information as needed). If the participant enrolls, fax only the 2nd (closest to Enrollment) Screening Pelvic Exam CRF to SCHARP. No pelvic specimens for storage (gram stain or endocervical swab) should be collected at the second screening pelvic exam if they were collected at the first screening pelvic exam.

Non-exclusionary pelvic exam findings do not require reassessment before enrollment.

10.4.2 Pelvic Exams Conducted at Follow-up

Follow-up pelvic exams are required semiannually, at the PUEV visit, and when clinically indicated. Pelvic exams are considered clinically indicated when new genitourinary complaints are present, i.e., new bleeding, vaginal discharge, pelvic pain. New adverse events for bleeding should prompt a pelvic exam even if the bleeding has subsided by the time of the report. The need for a pelvic exam in

response to new genitourinary complaints (excluding bleeding) that have resolved at the time of the visit is up to clinician discretion. All new symptoms, regardless of resolution date and whether or not a pelvic exam was conducted, should be reported as adverse events per section 11.3 of this manual. Pelvic exams must also be performed before resuming use of VR after product hold due to pregnancy.

Participants may decline to have a study pelvic examination. For pelvic exams scheduled per protocol, if the participant declines, an attempt should be made to conduct the pelvic at the next scheduled visit. If, after the second attempt, the participant still declines, the site may forego asking at that time. For a clinically indicated pelvic exam to evaluate a simple AE that has since resolved (a single bleeding episode deemed to be related to contraception for example), another attempt after an initial decline should be made. If a participant declines the pelvic exam twice, ensure there is a clear clinical note documenting the offer of the exam and the clinical assessment; and that failure to conduct the exam did not pose an apparent safety risk to the participant. For a clinically indicated pelvic exam to evaluate an ongoing AE, particularly if there is a clinical concern about ongoing use of the ring, additional effort should be made to conduct the exam. The site clinician should assess carefully whether to initiate a product hold if a sufficient examination cannot be done. The site should continue to ask at each participant contact/visit to have the procedure conducted until the participant consents.

Ultimately, for any of the above scenarios, the site needs to assess the clinical safety of continued product use on a case-by-case basis. If the site clinician feels that an exam is indicated but cannot conduct the exam, the site should consider whether to continue study product use. A protocol deviation CRF should be completed for each instance in which a participant refuses a required or clinically indicated pelvic exam (as outlined above). Sites should consult the PSRT for guidance on specific situations as needed/required.

Scheduled pelvic exams should be performed according to the guidance provided in the remainder of this section. Exam procedures must be performed in the order shown on the exam checklists provided in Section 7 of this manual. Pelvic exams performed at non-scheduled visits (e.g. interim visits or in response to symptoms) should be targeted to symptoms and staff are not required to complete all components of the complete pelvic exam. Also, pelvic specimens for storage (gram stain and endocervical swab) are not collected for clinically-indicated pelvic exams.

10.4.3 Pelvic Exam Overview

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. For most participants, a Graves speculum is preferred to enable visualization of all anatomic areas and tissues. At Screening, record the type and size of the speculum used on the Pelvic Exam Diagrams form for reference at subsequent exams. Prior to insertion, ensure that the speculum functions properly and has no rough edges.

Exams During Menstruation: Routine pelvic exams, i.e., those required at protocol-specified time points, should be avoided during menses, as the presence of menstrual 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 grade metrorrhagia or spotting, it is reasonable to proceed with a pelvic exam and collection of samples. If she is experiencing greater than mild grade 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.

Exams During Pregnancy: Pelvic exams, including self-administered vaginal swab collections, are considered safe throughout the duration of the pregnancy, and for this protocol, directed exams will continue for pregnant participants up to 24 weeks of gestation. While not required, it is considered safe to continue exams *after* 24 weeks of gestation, and is encouraged by the protocol team. Participants who become pregnant will be managed as described in Section 6.6 of this manual.

Exams for Participants with Hysterectomy: Potential participants who have undergone a hysterectomy are still eligible for enrolment into MTN 020. For women who have had a supracervical hysterectomy, all study procedures will be performed. For women who have had a total hysterectomy and no longer have a cervix, three study procedures will be handled slightly differently: pap smears, endocervical specimen collection, and cervical ectopy assessment. In these instances, clinicians should collect a vaginal pap smear when a pap smear is indicated and note in the comments for the pathologist that the participant is status post hysterectomy. If a vaginal pap smear is collected, this satisfies the requirement for a "pap smear." Endocervical swabs cannot be collected in women who have had their cervix removed. Given that the collection of endocervical swabs is a protocol directed study procedure, a protocol deviation must be completed each and every time this study procedure is missed. Document on the Specimen Storage CRF that the endocervical swab was "not stored" and specify reason as "post-hysterectomy". On the Screening Pelvic Exam and Pelvic Exam CRFs, line through the cervical ectopy field and add a note in the white space "ppt post-hysterectomy", initial and date the note.

10.4.4 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. Ask the participant to remove the VR just prior to the pelvic exam.

Position the Participant: Drape the participant and establish a comfortable examination position that allows for the perineum and vulva to be inspected. Adjust stirrups and back elevation as needed.

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 and vagina.
- Assess for cervical ectopy.

Collect Specimens: Collect specimens in the order listed on the pelvic exam checklist, which is also reflected below. The order of specimen collection is critical to ensure that first specimens collections do not affect subsequent specimens. Collect specimens away from apparent abnormalities and exclude swabbed areas from subsequent examination.

- If required per protocol (at Screening, semi-annually) and/or if clinically indicated, collect a vaginal sample to test for trichomonas with the rapid test kit. Vaginal samples may be collected for this test from the lateral vaginal wall.
- If clinically indicated, collect swab for vaginal saline and/or KOH wet mounts for evaluation of vaginitis (yeast, trichomonas or BV). Sample may be collected for this test from the lateral vaginal wall.
- At Screening, Semi-Annual, and PUEV visits, collect one swab from the lateral vaginal wall for Gram stain evaluation at the MTN Laboratory Center (LC); roll the swab across two labeled slides and air dry.
- At all Screening, Semi-Annual, PUEV visits and if clinically indicated, collect vaginal sample (1 swab) for pH assessment. Swab sample onto pH strip and then determine pH by matching the resulting color of the pH strip to the color scale provided with the strips. The sample must be collected from the lateral vaginal wall for this test. Do not insert the pH strip into the vagina for this test.
- At the Screening, Semi-Annual, and PUEV visits, collect endocervical fluid for biomarker analyses at MTN LC.
- If indicated and per site standard of care, send fluid from a suspicious lesion for additional herpes testing.
- At Screening (if required to confirm eligibility) and PUEV visits, perform Pap Smear. For Pap smear management, see Section 10.5.

Lavage and Removal of Visual Obstruction: After collection of vaginal and endocervical specimens, any obstruction (e.g., mucus, cellular debris) may be removed via lavage with sterile, isotonic, non-bacteriostatic saline if needed. During lavage, avoid contact between the pipette and the epithelium. The lateral fornices

may be lavaged without manipulation by directing the stream into them. Aspirate the fluid with the tip of the pipette against the inner surface of the posterior blade of the speculum. If lavage does not adequately remove the obstruction, or if sites do not have access to a lavage, use a large saline-moistened swab (Scopette) in a gentle dabbing fashion to remove the obstruction. Avoid twisting or rolling the swab over the surface of epithelium. Do not use a dry swab to remove any obstruction at any time, as this may cause trauma to the epithelium. If saline is not available, a swab moistened with water will also suffice.

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

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

10.4.5 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, location, and severity) to ensure appropriate assessment can be provided during the next pelvic exam.

All abnormal findings during screening will be documented on the Screening Pelvic Exam CRF and the Pre-existing Conditions CRF. All abnormal findings identified during follow-up will be documented on the Pelvic Exam CRF. All newly-identified abnormal pelvic exam findings will be documented on an Adverse Experience Log (AE-1) CRF (see Section 10.2 for a definition of “newly-identified”). The results of laboratory test results performed using specimens collected during pelvic exams are recorded on the Screening STI Test Results CRF (or STI Test Results CRF) and the PUEV Laboratory Results CRF (for the PUEV Pap smear assessment).

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 is considered to be neither a normal nor an abnormal finding, but rather, is a required separate assessment. The percentage of cervical ectopy (item 3) on the PE-1 CRF should always be completed when a pelvic exam is conducted. However, the ‘no normal variants or abnormal findings’ box on the pelvic exam diagrams non-DataFax form may be marked if only ectopy is observed. The presence of cervical ectopy is quite common, and should not be factored into the question on the diagrams form.

IUCD strings may be visible upon exam and are also considered a normal finding. If documented, they should be present on the non-DataFax Pelvic Exam Diagrams form. Sites may determine whether they choose to consistently document the presence of IUCD strings (best practice) or not. It is recommended that if a participant has an IUCD but the string not visible upon exam, this be documented and followed up on.

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

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

Figure 10-1 below provides further information to guide and standardize terminology used to describe abnormal pelvic exam findings.

Pelvic exam findings should be documented using terminology corresponding to the FGGT and the study-specific pelvic exam case report forms. 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.

**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. May be sharp or diffuse.
Edema	Intact	Intact	
Petechiae	Intact	Disrupted	≤ 3 mm
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 often but not always deep.

10.5 Pap Smear Results and Management

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

During screening, Pap results are not reported on CRFs but will be used to evaluate eligibility for enrollment. Grade 1 Pap results are not exclusionary, however, if further evaluation is required (i.e. colposcopy and/or biopsy) per site SOPs, enrollment must be delayed until colposcopy and/or biopsy results are available and no treatment is indicated. Biopsies are not considered exclusionary genital/gynecologic procedures in MTN-020 under criterion 7g. However, if more invasive procedures are required (i.e. LEEP), the participant cannot be enrolled for 90 days per criterion 7g.

The required Pap smear at the PUEV is recorded on the PUEV Laboratory Results CRF. Abnormal results obtained at screening should be recorded on the Pre-existing Conditions CRF.

Abnormal Pap smear findings should be initially reported and graded based on the “Pap” row of the FGGT. AGC and AGC-favor neoplastic are not specifically mentioned in the “Pap” row, but should be assigned severity grades 1 and 2, respectively. During follow-up, report and grade abnormal Pap smear adverse events on the AE-1 CRF. If biopsy is performed as part of the evaluation of the abnormal Pap, update the AE-1 CRF to indicate the results of the biopsy (item 1 - AE Diagnosis) and update the severity grade (item 3), as appropriate, per the “Intraepithelial Neoplasia by biopsy” row of the FGGT.

Pap smear results should be managed per local standard of care as specified in site SOPs. If local standards of care require clinical colposcopy and/or biopsy to assess lower grade abnormalities (not requiring hold per protocol), the IoR/designee should advise the participant to remove the vaginal ring on the day of the colposcopy. The removal prevents the ring from interfering with the evaluation, biopsy, or treatment, if needed. The duration of the ring outage will depend on the procedures completed at the time of colposcopy.

- If a biopsy or treatment (excision or cryotherapy) is not undertaken, the participant should be instructed to reinsert the same ring following the colposcopy (as done with IUCD insertion or laparoscopic tubal ligation). A pelvic exam is not required for ring reinsertion, and no Product Hold CRF or pharmacy documentation is required to document the brief removal.
- If a biopsy or treatment is performed, a new clinical product hold should be initiated. Study clinic staff should complete a Product Hold CRF and a vaginal ring request slip marked “hold”. The product hold should continue until a clinically acceptable resolution for the biopsy and/or treatment has occurred according to the judgment of the IoR/designee. Generally, allowing 7 days for healing after biopsy should be sufficient; importantly, adequate healing should be confirmed on pelvic exam before reinstating product use. Assuming no contraindications are identified on pelvic exam, product use will be resumed. If, for some reason, the participant does not want the ring re-inserted (even though the clinician determines it is okay to do so), the additional days off product are not considered part of the product hold. Rather, they count as participant non-adherence, and should be captured as such on the RA-1 CRF completed at the participant’s next visit.

All ring outages, regardless of the reason(s), should be captured on the Ring Adherence CRF completed during the participant’s next scheduled study visit.

10.6 Genital Bleeding Assessment

Genital bleeding other than menstrual bleeding, often referred to as intermenstrual bleeding (IMB) is a common occurrence amongst women of reproductive age, and often is of physiologic or benign etiology. Background rates of IMB in the general population are not known with precision. In a recent survey of HIV-negative and HIV-positive women, 12 percent and 11 percent respectively reported IMB in the last six months. More information on IMB can be found in Section Appendix 10-3.

During follow-up, the following types of genital bleeding are reportable as adverse events on an AE Log CRF:

- each new instance of heavy or prolonged menstrual bleeding or intermittent bleeding (as compared to the participant’s baseline bleeding pattern), regardless as to whether it may be attributed to the initiation of new contraception
- postcoital bleeding (bleeding associated with sexual intercourse) should be reported if not present at baseline

Note that the above conditions are consistent with the parameters set out in the FGGT under the heading ‘abnormal uterine bleeding unrelated to pregnancy’. Heavy, prolonged or intermittent bleeding episodes during follow-up that are consistent with a participant’s baseline bleeding pattern are considered expected and are not reportable as AEs. Note that *shorter* than baseline menses is not included in the FGGT, and should not be considered an adverse event.

10.6.1 Participant Report and Clinician Assessment of Genital Bleeding

As described in Section 10.2, 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.

Study participants will undergo pelvic exams at Screening, Semi-annual visits, and at the PUEV visits as well as to evaluate any participant report of genitourinary complaints (including bleeding) that are different from baseline. The assessment of genital bleeding should begin by determining whether the bleeding (menstrual or non-menstrual) is consistent with baseline bleeding patterns. Refer to the Screening Menstrual History CRF and Pre-existing Conditions CRF (PRE) for information on the participant's bleeding pattern at baseline.

Note that any menorrhagia, metrorrhagia, or menometrorrhagia events ongoing at the time of randomization 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 as AEs.

Any past resolved (not ongoing at the time of randomization) menorrhagia, metrorrhagia, or menometrorrhagia events documented on the PRE CRF should be assigned a grade from 1-4 per the FGGT.

If a newly-identified bleeding episode is determined to be different from a participant's baseline bleeding pattern (i.e., longer, heavier, more frequent), record the episode on an Adverse Experience Log (AE-1) CRF (see Section 10.2 for definition of "newly identified"). One of four terms to describe the bleeding event should be used:

- menorrhagia
- metrorrhagia
- menometrorrhagia
- post coital bleeding

Note that a *shorter* than baseline menses is not considered an AE per the FGGT, though infrequent genital bleeding may be an AE (see section 10.6.2). Grade the episode per the applicable row of the FGGT provided below. If both Menorrhagia and Metrorrhagia are present, a single adverse event should be reported as "Menometrorrhagia" and graded per the Menorrhagia row of the FGGT.

PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
ABNORMAL UTERINE BLEEDING UNRELATED TO PREGNANCY					
Menorrhagia ² (prolonged and/or heavy menstrual bleeding)	Participant report of normal bleeding relative to her baseline	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Metrorrhagia ² (intermenstrual or frequent bleeding)	None or any expected nonmenstrual bleeding	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Postcoital bleeding	None	Occasional (< 25% of coital acts) OR Increase from usual with no or minimal interference with usual social functioning (including sexual functioning)	Frequent (25-75% of coital acts) OR Increase from usual with moderate interference with usual social functioning (including sexual)	Consistent (> 75% of coital acts) OR Incapacitating or severe interference with usual social functioning (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock

Documenting bleeding on the FP-1 CRF: Any menstrual-like bleeding should be documented in items 2, 2a, 2b of the FP-1 CRF. Clinical discretion should be used to determine LMP for the completion of this CRF. Recording LMP should be based on clinical impression and does not need to be consistent with AE reporting terms used to describe the bleeding. That is, bleeding that is captured as an AE can still be considered menstrual-like for the purposes of completing the FP-1 CRF. Note that genital bleeding that is not considered to be menses should *not* be documented on the FP-1 CRF in items 2, 2a, and 2b. Instead, document it in other source documents as applicable (such as the comments section of the FP-1 CRF, a bleeding log, or chart notes), as well as an AE Log CRF, if it meets AE reporting requirements.

Recurrent bleeding AEs in follow-up: Once a bleeding AE has been reported, each subsequent bleeding episode should be assessed to determine whether the episode is consistent with previously reported bleeding AEs, or if it is the first of its kind. Clinician discretion should be used to determine if a new AE needs to be documented or if a previously reported AE is ongoing.

- As needed, update the AE Log CRF to be ‘continuing’. The dates of each irregular bleeding episode do not need to be recorded on the AE Log CRF, but should be captured in source documentation.
- If reviewing files in retrospect, mark for deletion any AE Log CRFs completed for bleeding episodes that can be subsumed under the AE that was initially reported for the event. When/if any AEs are deleted, clearly document the rationale in the relevant source documents.

- If applicable, review the CM-1 CRF “Taken for a reported AE?” and “AE Log page” to ensure that no deleted AEs are reflected on the form.
- Updates to items 5b2 or 6 on the Visit Summary and items 2-2a on the Pelvic Exam CRFs are not needed.
- If a participant has an ongoing (recurrent) bleeding adverse event, a pelvic exam is not required each time the participant reports the same ongoing bleeding, provided that the clinician assesses the bleeding to be consistent with the bleeding captured by the ongoing adverse event. As per SSP Section 11.4, if the AE increases in severity, a new AE Log CRF should be completed to document this change in severity.
- In cases where a previously reported genital bleeding event, such as metrorrhagia, is ongoing and persists at the same severity even after a participant has switched her method of contraception (including switches within the same class or between different classes of medications), the AE should be left open and considered ongoing. If the event is deemed “not related” to study product use, sites can simply state on the item 4 “Record rationale” line, “consistent with contraceptive use”. A new AE Log CRF should not be completed, as the switch in contraceptive use has not caused a new bleeding event at a different severity or frequency to occur. One AE Log CRF suffices to cover the same bleeding event if it persists even with a switch in contraceptive method.

New normal menses pattern established during follow-up: If during follow-up a new recurrent bleeding pattern is considered to be consistent with a normal menstrual cycle, (even if different from the participant’s baseline pattern), any previously reported AEs related to this bleeding should be deleted. Clinical judgment should be used and based on a population definition of normal menses (i.e., regularly timed bleeding approximately 4 weeks apart), regardless of whether it is consistent with the participant’s baseline bleeding pattern.

- It is recommended that the new pattern be established for at least 3 cycles before making this determination.
- When/if any AEs are deleted, ensure the rationale is clearly documented in source documents.
- If an irregular baseline bleeding pattern has resolved, record a resolution date for an irregular bleeding pattern on the Pre-existing Conditions Resolution Tracker.
- As needed, update the FP-1 CRF (items 2, 2a and 2b) from previous visits to document the new normal menstrual pattern as menses.
- If concomitant medications were provided to treat the bleeding episode, update the CM-1 CRF to reflect that these medications were not taken for a reported AE.
- Updates to items 5b2 or 6 on the Visit Summary and items 2-2a on the Pelvic Exam CRFs are not needed.
- If a new normal menses pattern develops for a participant, subsequent bleeding events should be reported as new AEs if, per clinical discretion, the event is generally not consistent with this new pattern.

Tracking bleeding during follow-up: To assist in the recognition of a new menstrual bleeding pattern or changes to bleeding throughout follow-up, it is recommended that sites implement a genital bleeding tracking log so that changes to bleeding patterns can easily be assessed over time. In some cases, a subsequent bleeding event may be the restart of a pre-existing condition that had resolved once a normal

menses pattern emerged in follow-up. If this is the case, the restart of the pre-existing condition should be reported as a new AE.

A Genital Bleeding Decision Tree has been developed to help guide documentation of genital bleeding (see figure on page 10-18). **Above all, clinical discretion should be used to determine if the participant is experiencing normal menstrual bleeding.**

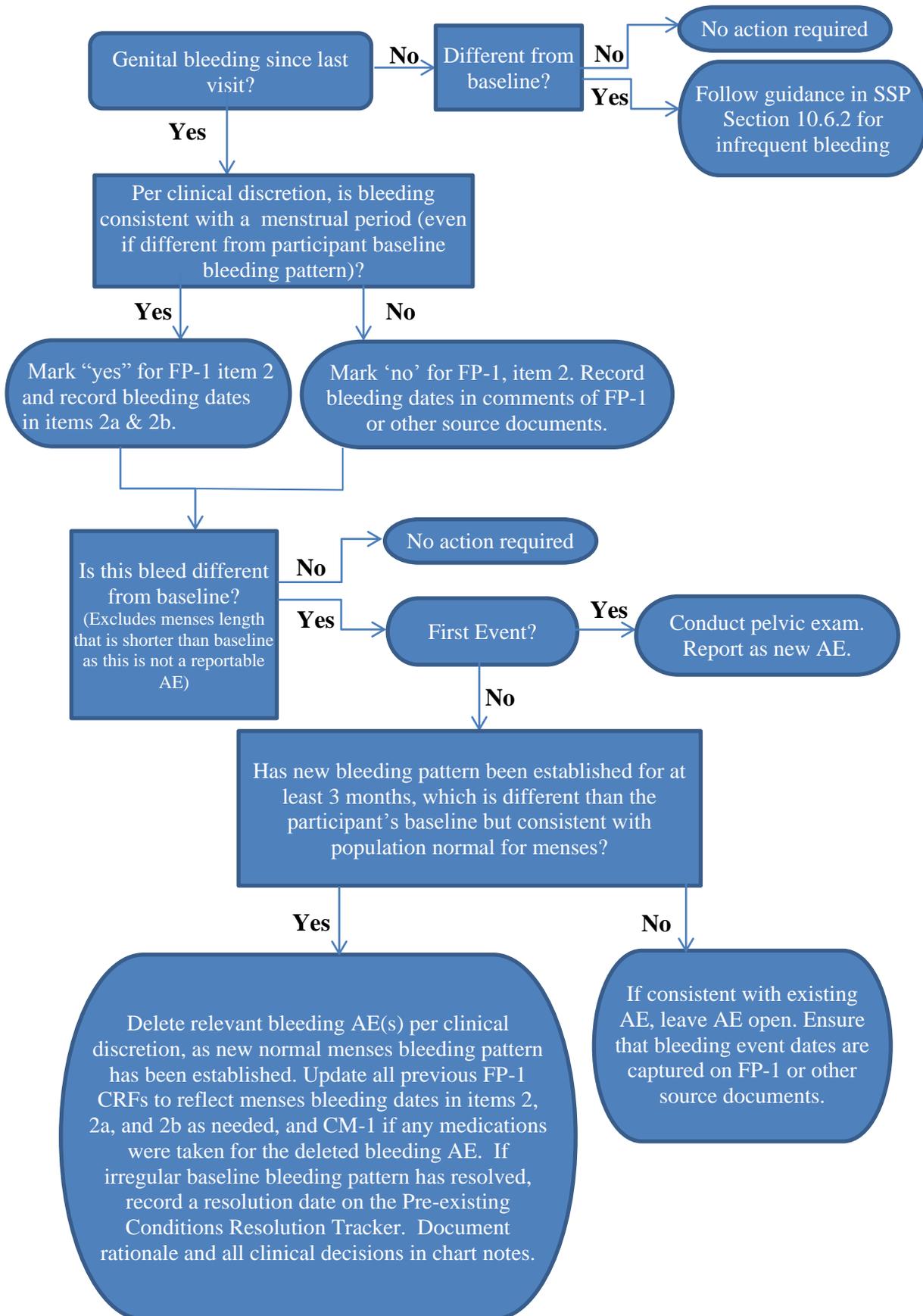
Cervical bleeding associated with study procedures: Cervical bleeding associated with speculum insertion and/or cervical specimen collection judged to be within the range of normal according to the clinical judgment of the IoR or designee is not considered to be an adverse event. If the bleeding exceeds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

GENITOURINARY SIGNS/SYMPTOMS – CERVIX					
Cervical edema and friability	None	Edema without friability	Friable cervix	NA	NA

Bleeding observed during follow-up pelvic exam:

- Bleeding that is associated with an observed abnormal pelvic exam finding should be considered an AE and should be documented and reported, if applicable, using the term associated with the exam finding, with the anatomical location noted. Use the appropriate term as it appears in the FGGT or on the Pelvic Exam CRF, whichever is more specific. For example, if a vaginal laceration is observed on exam, and there is bleeding attributable to the laceration, use the term “vaginal laceration” to document the AE. Document any blood or bleeding associated with the finding on the Pelvic Exam Diagrams form and the Pelvic Exam CRF, and if applicable, in the comments section of the AE Log CRF. Do not use the term “metrorrhagia” to document the AE, since the bleeding is associated with a finding.
- 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 considered an AE and should be documented and reported if applicable using the term “metrorrhagia”. This term refers to bleeding of variable amounts occurring between regular menstrual periods and should be used to report non-menstrual bleeding such as spotting between menses, ovulation bleeding, and breakthrough bleeding. This term should also be used to report blood-tinged discharge and blood observed in the vagina with no identified source.

If there is blood on the self-collected swab, clinical discretion should be used to determine if an unscheduled pelvic exam is necessary (e.g., Is the blood fresh or dried? Is she currently having, or has she recently finished her menses? Does she have a history of metrorrhagia?). Clinical decision-making should be documented in chart notes or other applicable source documents (i.e., document rationale for further investigation of the blood stained swab, or why this was deemed unnecessary).



10.6.2 Infrequent Bleeding

Infrequent genital bleeding (missed menses/oligomenorrhea/amenorrhea) that is present at baseline should be recorded as a pre-existing condition, regardless of cause. Use the following guidelines when documenting infrequent genital bleeding at baseline (pre-randomization) or follow-up (post-randomization):

1. Baseline infrequent bleeding - document on PRE CRF using one of 3 terms specified in Data Communicate #2 (missed menses/oligomenorrhea/amenorrhea). Grade per the “Unexplained infrequent bleeding” row of the FGGT. If the baseline infrequent bleeding is due to contraception, mark as “not gradable”. In the Comments section, record the cause of the infrequent bleeding (for example, “due to DMPA use,” or “for unknown reasons”).
2. Follow-up infrequent bleeding due to known reason – Do not report as an AE any new events of infrequent bleeding during follow-up that are due to contraceptive use, pregnancy, or post-partum status (not reportable per the FGGT). Do document these events in chart notes, and specify a clinical determination which supports not reporting the infrequent bleeding as an AE (e.g., “missed menses due to contraceptive use”).
3. New events of infrequent bleeding during follow-up for unknown reasons or delay of menses for more than one month. Document as an AE on an AE Log CRF using the appropriate term below:
 - For missed menses events of 1-3 months in duration, use the term “missed menses”
 - For missed menses events of 4-5 months in duration, use the term “oligomenorrhea”
 - For missed menses events of 6 months or longer, use “amenorrhea”.

Infrequent bleeding AEs that extend beyond three months or more in duration should be documented by updating the completed AE log CRF for “missed menses” with a new AE term of either “oligomenorrhea” (for missed menses events of 4-5 months in duration) or “amenorrhea” (for missed menses events of 6 months or longer) and with a new severity grade. The updated AE term and severity grade should be assessed per the FGGT row for “unexplained infrequent bleeding”, which excludes cases of missed menses due to hormonal contraception use, pregnancy, or post-partum. A new AE log CRF should not be completed to document an increased duration of the same infrequent bleeding event.

Note that the FGGT should be interpreted as a delay in menses of one month or more from the time when next menses is *expected* (but does not come), and is not one month or more from the time when menses was last experienced. When determining the duration of the infrequent bleeding (i.e., the start date of missed menses/oligomenorrhea/amenorrhea), use the month menses was expected as the start. For example, if a participant’s last menstrual period was in August, 2013 and she had not had her menses by October 2013, she experienced a *delay* in menses for more than one month, so a ‘missed menses’ AE should be reported. The start date for her missed menses is September 2013 (the next time that she typically would have expected menses if it had not been missed). ‘Missed menses’ should not be used for instances when menses was delayed for any amount of time less than one month (i.e. it came 2 weeks late). While this situation may be different from the participant’s baseline pattern, it is not a gradable AE per the FGGT.

Grade the missed menses event per the below “Unexplained infrequent bleeding” row of the FGGT.

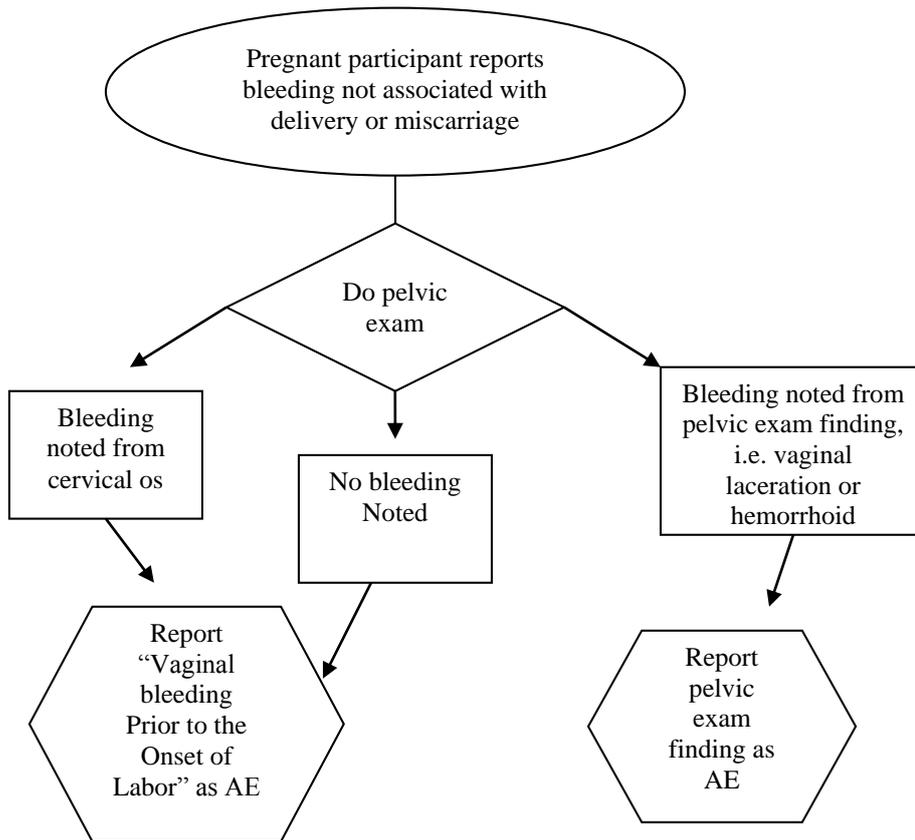
UTERINE BLEEDING AND PREGNANCY COMPLICATIONS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
1 Unexplained infrequent bleeding (excludes expected absence of menses due to hormonal contraception or pregnancy/postpartum)	Participant report of normal or expected bleeding frequency	No menses for 1-3 months (missed menses)	No menses for > 3 months (oligomenorrhea/ amenorrhea)	NA	NA

If a pregnant participant experiences genital bleeding, study staff will clinically manage the participant per local practice standards for pregnancy, making referrals when necessary. Study staff will document the bleeding event and all follow-up actions in the participant’s study records.

As explained in greater detail in Section 11 of this manual, it is not expected that a term such as “metrorrhagia” will be used to document and report genital bleeding during pregnancy. Rather, the term “vaginal bleeding during pregnancy prior to the onset of labor” should be used for bleeding events not associated with labor (for further details on adverse event reporting related to genital bleeding during pregnancy, see Section 11).

If a pregnant participant reports bleeding (not associated with delivery) study staff should investigate the source of the bleeding. If a pelvic exam finding such as a vaginal laceration, a cervical polyp, or hemorrhoids, is identified as the source of the bleeding, the finding should be recorded as the Adverse Event and an explanation provided in the comments section of the Adverse Experience Log (AE-1) CRF that the finding was associated with bleeding. The following algorithm is intended to clarify this point:

Figure 10-2
Overview of Assessment and Reporting Procedures for Genital Bleeding in a Pregnant Participant in MTN-020 — Beginning with Participant Report of Blood/Bleeding



10.7 STI/RTI/UTI

10.7.1 Considerations at Screening/Enrollment

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

Syphilis: If a reactive RPR is identified during screening, a confirmatory test (MHA-TP or TPHA) result must be received, and appropriate clinical management action taken, prior to enrollment in the study. Action required prior to enrollment depends on the current health status of the participant and the availability of medical records documenting her prior infection, as follows:

- If the participant has clinical signs or symptoms of syphilis, she must be treated prior to enrollment. If the participant is otherwise eligible for the study, enrollment may proceed immediately following completion of treatment and resolution of signs and symptoms.

- If the participant has no clinical signs or symptoms of syphilis, but credible medical records are not available to document adequate treatment of a prior syphilis infection (per WHO guidelines), the participant must be treated prior to enrollment. If the participant is otherwise eligible for the study, enrollment may proceed immediately following completion of treatment. Should the IoR or designee judge for any reason that treatment is not required, approval to enroll the participant without providing treatment must be obtained from the PSRT prior to enrollment.
- If the participant has no clinical signs or symptoms of syphilis, and credible medical records are available to document adequate treatment of a prior syphilis infection (per WHO guidelines), and the participant's current RPR titer is 1:4 or lower, the participant may be enrolled in the study without providing treatment at the discretion of the IoR or designee, without consulting the PSRT.

If syphilis is diagnosed during screening, 'syphilis seropositivity' should be recorded on the Pre-Existing Conditions CRF, and the screening RPR titer included ("RPR titer: 1 to X"). A pre-existing condition of syphilis seropositivity should be marked 'ongoing' at baseline. A test or cure (i.e., four-fold decrease in titer) is not required prior to enrollment; however, repeat serology is expected 6 months after treatment for clinical management purposes.

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

Vaginal candidiasis: Chronic (recurrent) vaginal candidiasis is exclusionary for enrollment (see Section Appendix 4-2), and is defined by the participant reporting receipt of treatment 4 times or more in the past year. Participants diagnosed with symptomatic vaginal candidiasis during screening are eligible once they have completed treatment and symptoms have resolved.

10.7.2 STI/RTI/UTI Diagnosis

Clinical and laboratory evaluations are performed throughout the course of MTN-020 to diagnose the following STIs and RTIs:

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

Signs and symptoms commonly associated with the above-listed infections are presented in Figure 10-3 below. 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.

Figure 10-3
Signs and Symptoms Commonly Associated with STIs/RTIs

STI/RTI	Common Signs and Symptoms
Bacterial vaginosis	Excessive or malodorous discharge is a common finding. Other signs or symptoms include erythema, edema, and pruritis of the external genitalia.
Candidiasis	Clinical presentation includes whitish vaginal discharge and erythema, edema, and pruritis of the external genitalia.
Chlamydia infection	Most infections are asymptomatic, but infection may be accompanied by cervicitis (defined as the presence of endocervical mucopurulent discharge, easily induced cervical bleeding, and/or edematous ectopy).
Genital herpes	Single or multiple vesicles which can appear anywhere on the genitalia. Vesicles spontaneously rupture to form shallow ulcers that may be painful. Lesions spontaneously resolve with minimal scarring.
Gonorrhea infection	Commonly asymptomatic but women may have abnormal vaginal discharge, or dysuria.
Syphilis infection — primary	The classical chancre is a painless indurated ulcer, located at the site of exposure.
Syphilis infection — secondary	Patients may have a highly variable skin rash, mucous patches, condylomata lata (fleshy, moist tissue growths), lymphadenopathy, alopecia, or other signs.
Syphilis infection — latent	Patients are without clinical signs of infection.
Trichomoniasis	Excessive, frothy, diffuse, yellow-green discharge is common, although clinical presentation varies from no signs or symptoms to erythema, edema, and pruritis of the external genitalia. Dysuria and dyspareunia are also frequent. The type of symptoms or signs alone does not distinguish the microbial etiology.

Adapted from: *Contraceptive Technology* (20th Revised Edition, 2011); Chapter 21: Reproductive Tract Infections; Alphabetic Catalog of Reproductive Tract Infections; pages 571-620.

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; 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-020 based solely on the presence of symptoms indicative of a possible UTI and graded per the infection row of the DAIDS Toxicity Table. The following symptoms are considered indicative of a possible UTI:

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

Other methods of diagnosis (ie urine culture or dipstick) may be performed per site standard of care per site SOP. Results must be documented in chart notes and/or on

other site-specific source documents. If culture or urinalysis are used, UTI should be graded per the UTI row of the FGGT if criteria are fulfilled.

Incidental findings of STI/RTI on Pap: At some study sites, Pap smear results may include notations of findings associated with certain STIs (e.g., trichomoniasis). Because Pap smear methods are neither adequately sensitive nor 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.
- If protocol-specified STI testing was performed on other specimens (i.e., blood, urine, vaginal samples) collected on the same day as specimen collection for Pap smear, the results of the protocol-specified testing overrule STI-related findings noted on the Pap smear result report. Provide treatment as needed based on the results of the protocol-specified tests.
- If protocol-specified testing was not performed on other specimens (i.e., blood, urine, vaginal samples) collected on the same day as specimen collection for the Pap smear, collect specimens for indicated protocol-specified STI testing at the participant's next study visit after receipt of the Pap test result report. Provide treatment as needed based on the results of the protocol-specified tests.

10.7.3 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 treated per site standard of care and applicable site standard operating procedures (SOPs). Asymptomatic BV does not require treatment per current WHO guidelines. Per the MTN-020 protocol, 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.

Current WHO guidelines can be accessed at:

<http://www.who.int/reproductivehealth/topics/rtis/evidence/en/index.html>

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-020, but may be recommended for pregnant participants per local guidelines. However, clinical management of syphilis infections should include repeat serology (RPR) at semi-annual intervals following diagnosis and treatment to confirm treatment effectiveness. For enrolled participants who are treated for syphilis during the screening period, a four-fold decrease in titer (for example, a drop from 1:32 to 1:8) is expected at the 6-month follow-up check after completion of treatment. If the RPR titer does not decrease four-fold or revert to seronegative within six months, the PSRT should be consulted for further management and to determine if an

Adverse Event has occurred. Of note, the syphilis row of the FGGT should be used to grade syphilis adverse events.

10.8 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 cervicitis, yeast, trichomoniasis, and/or bacterial vaginosis, among other conditions. Site clinicians are encouraged to thoroughly evaluate complaints and/or findings of abnormal vaginal discharge as per their discretion. Per protocol, whether to treat the underlying cause of the abnormal vaginal discharge will depend on 1. what the underlying diagnosis is and 2. whether the participant is symptomatic. If the evaluation reveals an underlying sexually transmitted infection such as trichomoniasis, the participant and her partner(s) should be offered treatment regardless of symptoms. If the evaluation reveals bacterial vaginosis or yeast, the participant should be offered treatment only if she is symptomatic.

Section 11.2.1 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 filed 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.

10.9 Self-collection of Vaginal Fluid

At the Enrollment, Monthly, Quarterly, Semi-Annual, and PUEV visits exam and Study Exit visits participants will collect vaginal fluid (1 Dacron swab) from the posterior fornix for biomarker analyses at MTN LC. This should be collected prior to the participant removing the vaginal ring from her previous visit. If she comes to the clinic without a ring in, the swab should be collected prior to insertion of a new ring. It is recommended that the participant collect the specimen before or after urine collection (order does not matter), but the clinician may also collect this swab if a pelvic exam is being conducted (or as needed), as long as the previous ring is still in place when this is done. Sites should have a holder available to keep the tube upright while the participant is collecting the sample. This procedure can still be conducted if the participant is on menses or if genital blood is present; if there is extremely heavy menses, contact the clinical staff for guidance.

Instruct participants on the following series of steps for conducting self-collection of vaginal fluid:

1. Wash and dry your hands and undress from the waist down
2. Carefully unwrap the kit package and remove threaded cap from vial and set aside.
3. Partially peel open the swab envelope, exposing the stick end of the swab

4. Being careful not to lay it down on any surface, remove the swab from the package
5. While separating the labia with one hand, use the other hand to hold the plastic swab shaft between your thumb and forefinger and insert the soft tip of the swab into your vagina approximately 4-5 cm (about the length of your little finger). Move the swab for 10-20 seconds, attempting to touch all walls of the vagina
6. Carefully withdraw the swab and insert the swab into the vial
7. Break off the swab shaft, leaving the soft end of the swab and throw the top portion away
8. Put the cap back on the vial, wash hands again, and give vial to the clinical staff

NOTE: if the swab is dropped in this process, please ask for a new test kit and repeat the entire process above. If there is blood on the swab, reference section 10.6.1.

A visual poster outlining these steps can be found on the ASPIRE website under *Study Implementation Materials*. Sites should modify the instructions above as well as the supplemental materials as needed per their site-specific process.

10.10 Pregnancy and Breastfeeding Considerations

Despite the MTN-020 eligibility criteria related to pregnancy intentions and use of contraception, as well as provision of contraception and contraception counseling throughout the study, it is expected that some study participants will become pregnant. All such participants should be managed as described in Section 6.6 of this manual. Adverse events that may be associated with pregnancy (for example, nausea), should still be graded per the DAIDS Toxicity Table and reported as an adverse event as needed. Refer to SSP Section 11.3.3 Reporting Considerations for Pregnant Participants and Figure 11-1 Adverse Event Reporting During Pregnancy by Gestational Age for reporting AEs for pregnant participants.

After a pregnancy hold, VR use should not be resumed earlier than 2 weeks after a 1st trimester loss, or earlier than 4 weeks after 2nd trimester (or later) pregnancy loss or delivery (note that breastfeeding must also be completed by the time of product restart). Product restart timelines should begin when the pregnancy is lost (i.e., bleeding, elective termination, etc). This restart timeline should only be based off a negative pregnancy test if the date of pregnancy loss is completely unknown. Per protocol, a negative pregnancy test and a pelvic exam are required before resumption of product use.

The MTN-020 eligibility criteria exclude women who are breastfeeding from the study; any amount of breastfeeding or suckling is exclusionary. For women who may become pregnant and give birth during follow-up, use of study product will be held until after complete cessation of breastfeeding.

During screening and during follow-up, all women should be counseled and encouraged to breastfeed in accordance with WHO guidelines and local and/or national guidelines applicable at the study site. Further background information for study staff that is intended to guide counseling of participants related to breastfeeding is provided in Section Appendix 10-4.

10.11 Care and Support for Seroconverters

During follow-up, HIV testing will be performed as described in Section 13.7.2 of this manual and participants who become infected with HIV will have modified study procedures as described in Section 6.5 of this manual. These participants are encouraged to continue follow-up visits per their original study schedule until their originally scheduled study exit date and are offered co-enrollment in MTN-015.

All participants with confirmed HIV infection will be counseled and actively referred to available sources of medical and psychosocial care and support, per site SOPs (see also Section 12.1). Site staff must actively follow-up on all referrals at each subsequent follow-up visit to determine if the participant actually sought the care to which she was referred, the outcome of the referral, and whether additional referrals are needed. All referrals, outcomes, and follow-up plans and actions must be fully documented in participant study records.

While neither MTN-020 nor MTN-015 can provide clinical care and treatment for HIV infection, protocol-specified examinations and laboratory tests will provide information upon which appropriate clinical care decisions can be made. In particular, the studies will provide information on participants' stage of HIV disease, HIV RNA PCR, and CD4+ T cell count; information on HIV drug resistance will also be available when clinically indicated.

Given the above, study staff must be well positioned to refer participants to non-study HIV care providers when they meet criteria for initiation of antiretroviral therapy (ART), may be experiencing a drug-related toxicity, or may need to consider changing ART regimens due to resistance. Study staff will provide and explain all study examination findings and test results to participants. They also will provide copies of laboratory test result reports to participants and their non-study providers. Study investigators will be available to consult with non-study providers on optimal clinical care and treatment decisions for participants.

Routine resistance testing will be completed for every participant who has a confirmed positive HIV test after enrollment. The Stanford Drug Resistance Database HIVdb Program (<http://sierra2.stanford.edu/sierra/servlet/JSierra>) will be used to generate resistance interpretations.

The database categories resistance as follows:

Resistance Category	Definition
Susceptible	No evidence of reduced susceptibility compared with wildtype
Potential low-level resistance	The virus is likely to be fully susceptible yet it contains mutations that may be indicative of previous exposure to the ARV class of the drug
Low-level resistance	Virus isolates of this type have reduced in-vitro drug-susceptibility and/or patients with viruses of this genotype may have a suboptimal virologic response to treatment compared with the treatment of a wildtype virus
Intermediate resistance	The genotype suggests a degree of drug resistance greater than low-level resistance but lower than high-level resistance
High-level resistance	The genotype is similar to that of isolates with the highest levels of in vitro drug resistance and/or patients infected with isolates

	having similar genotypes generally have little or no virologic response to treatment with the drug
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Plasma specimens designated by SCHARP will be sent to the LC during routine monthly shipments. Resistance testing will take place at the Virology Core (VC) lab (Pittsburgh) and results and necessary counseling messages will be provided from the VC to site IoRs as they are available. This information should be filed in the participant binder and shared with the participant and her HIV care provider. The participant should be counseled accordingly, based on guidance provided by the VC. Members of the LC and VC will be available to site leadership to talk through all resistance results. If there are any questions related to clinical next steps, the IoR should contact the PSRT for further guidance.

As these results are provided while the study is ongoing, care will be taken to maintain blinding. Results that show resistance will not determine whether the resistance was transmitted or developed due to taking an active study product. Counseling messages will take this important consideration into account.

10.12 Management of Laboratory Test Results

Hematology, liver function (AST/ALT), and creatinine testing will be performed at quarterly visits throughout the course of MTN-020. For each study participant, the IoR or designee is responsible for monitoring these test results over time and for ensuring appropriate clinical management of all results. All reviews of laboratory test results should be documented on the lab results printout (provided by the lab to the clinic) and/or in chart notes.

All sites must establish SOPs for reporting and managing critical laboratory values in MTN-020. At a minimum, all test results of severity grade 3 and higher, and all results requiring product hold, should be considered critical and urgently reported to a study clinician; lower grade results also may be considered critical at the discretion of the IoR.

The IoR or designee should routinely review MTN-020 participant study records to ensure proper monitoring and clinical management of laboratory test results, and documentation thereof. All reviews performed by the IoR or designee should be documented in participant study records.

10.13 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for product hold and discontinuation (Section 9.3), guidance on product hold and discontinuation in response to observed AEs (Section 9.4), and management of STI/RTI (Sections 9.5), HIV infection (Sections 9.6), pregnancies (Section 9.7), and early study termination (Section 9.8).

All specifications of protocol Sections 6 and 9 must be followed; IoRs are encouraged to consult the PSRT with any questions related to proper interpretation of the protocol and proper management of study product use in particular. Conditions requiring product hold or permanent discontinuation are summarized in Figure 10-4 below. The flow charts provided in Section Appendix 10-5 are intended to further guide study staff in following the specifications of protocol Section 9.

Participants should be advised to remove the vaginal ring prior to a laparoscopic tubal ligation or IUCD insertion procedure. The participant may reinsert the same vaginal ring after completion of the procedure unless, as a result of the procedure, the participant experiences any complications that would prompt a product hold per protocol section 9. All ring outages should be captured on the Ring Adherence CRF completed during the participant's next scheduled study visit. No product hold CRF or pharmacy documentation is required to document these brief removals for the procedure. However, if a new clinical hold is initiated following the procedure due to complications/AEs, the participant's ring should be returned to the study clinic and study staff should complete a Product Hold CRF, a new AE Log form, and a vaginal ring request slip marked "hold" should be sent to the pharmacy. The IoR/designee should follow relevant guidance in protocol section 9 regarding resumption of product use. If, for some reason, the participant does not want the ring re-inserted (even though the clinician determines it is okay to do so), the additional days off product are not considered part of the product hold. Rather, they count as participant non-adherence, and should be captured as such on the RA-1 CRF completed at the participant's next visit.

All clinical and product use management must be fully documented in participant study records. When the PSRT is consulted in relation to clinical and product use management, completed PSRT query forms (including a response from the PSRT) must be printed and filed in participant study records. Product holds and discontinuations must be communicated to site pharmacy staff using the Vaginal Ring Request Slip, as described in Section 9.6 of this manual. Product holds and discontinuations also must be documented on Product Hold/Discontinuation Log case report forms.

**Figure 10-4
Conditions Requiring Product Hold or Permanent Discontinuation**

Condition	Temporary Hold	Permanent Discontinuation
Positive HIV Rapid	X	
Confirmed HIV infection		X
Allergic Reaction to the Vaginal Ring		X
Pregnancy	X	
Breastfeeding	X	
Use of PEP for HIV Exposure	X	
Grade 3 AE Related to Study Product Use not in Section 9	X	
Grade 4 AE not in Section 9	X	
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.	X	
Superficial epithelial disruption (abrasion/peeling) which has worsened after re-evaluation in 3-5 days	X	
Deep epithelial disruption (ulceration)	X	
Symptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) which has worsened after re-evaluation in 3-5 days	X	
Asymptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) which has worsened after re-evaluation at the next scheduled visit	X	
Generalized erythema or severe edema (area >50% of vulvar surface or combined vaginal and cervical surface)	X	

Unexpected genital bleeding due to deep epithelial disruption	X	
Cervicitis (inflammation and/or friability)	X	
Coenrollment	X	

**See Protocol Section 9 for complete guidelines on clinical management and study product holds. Note that when the protocol specifies to 'remove study VR' this is equivalent to a temporary product hold, and a Product Hold/Discontinuation CRF should be completed.*

Section Appendix 10-1
MTN-020 Baseline Medical History Questions sheet

PTID: _____

Staff Initials/Date: _____

MTN-020 Baseline Medical History Questions Sheet

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Complete at the Screening Visit. Record relevant baseline conditions on the Pre-existing Conditions CRF. Relevant conditions include (but is not limited to): hospitalizations; surgeries; allergies; conditions requiring prescription or chronic medication (lasting for more than 2 weeks); and any conditions currently experienced by the participant.

Have you ever experienced any significant medical problems involving the following organ system/disease?		Yes	No
1	Head, eyes, ears, nose, or throat	<input type="checkbox"/>	<input type="checkbox"/>
2	Gynecologic	<input type="checkbox"/>	<input type="checkbox"/>
3	Lymphatic	<input type="checkbox"/>	<input type="checkbox"/>
4	Cardiovascular	<input type="checkbox"/>	<input type="checkbox"/>
5	Respiratory	<input type="checkbox"/>	<input type="checkbox"/>
6	Liver	<input type="checkbox"/>	<input type="checkbox"/>
7	Renal (including urinary symptoms)	<input type="checkbox"/>	<input type="checkbox"/>
8	Gastrointestinal	<input type="checkbox"/>	<input type="checkbox"/>
9	Musculoskeletal (including bone fractures)	<input type="checkbox"/>	<input type="checkbox"/>
10	Neurologic	<input type="checkbox"/>	<input type="checkbox"/>
11	Skin	<input type="checkbox"/>	<input type="checkbox"/>
12	Endocrine/Metabolic	<input type="checkbox"/>	<input type="checkbox"/>
13	Hematologic	<input type="checkbox"/>	<input type="checkbox"/>
14	Cancer	<input type="checkbox"/>	<input type="checkbox"/>
15	Drug Allergy	<input type="checkbox"/>	<input type="checkbox"/>
16	Other Allergy	<input type="checkbox"/>	<input type="checkbox"/>
17	Mental Illness	<input type="checkbox"/>	<input type="checkbox"/>
18	Have you ever experienced any of the following genital symptoms?	Yes	No
18a	genital sores	<input type="checkbox"/>	<input type="checkbox"/>
18b	genital/vaginal bleeding or blood-tinged discharge not related to your period/menses	<input type="checkbox"/>	<input type="checkbox"/>
18c	genital/vaginal burning	<input type="checkbox"/>	<input type="checkbox"/>
18d	genital/vaginal itching	<input type="checkbox"/>	<input type="checkbox"/>
18e	genital/vaginal pain during sex	<input type="checkbox"/>	<input type="checkbox"/>
18f	Genital/vaginal pain not during sex	<input type="checkbox"/>	<input type="checkbox"/>
18g	abnormal genital/vaginal discharge	<input type="checkbox"/>	<input type="checkbox"/>
18h	unusual genital/vaginal odor	<input type="checkbox"/>	<input type="checkbox"/>
18i	Genital warts	<input type="checkbox"/>	<input type="checkbox"/>
18j	Pelvic inflammatory disease	<input type="checkbox"/>	<input type="checkbox"/>
18k	Abnormal pap smear	<input type="checkbox"/>	<input type="checkbox"/>
18j	Urinary tract infection	<input type="checkbox"/>	<input type="checkbox"/>

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Section Appendix 10-3 Information on Intermenstrual Bleeding for Study Staff

Genital bleeding other than menstrual bleeding, often referred to as intermenstrual bleeding (IMB), is a common occurrence amongst women of reproductive age, 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. While combination oral contraceptive pills contain both progesterone and estrogen derivatives, the predominant effect is one of progestin. Depo-provera and Lunelle, common progesterone only methods, also exert a progestin effect. Progesterone is known to thin the endometrial lining which can expose underlying vessels and lead to IMB. It is important to note that IMB attributable to contraceptive use is not dangerous and does not impact the effectiveness of the method assuming the woman has been using the method as instructed. Use of intrauterine contraceptive devices (IUCDs), smoking, and chlamydia infection have also been identified as risk factors for IMB. Though very unusual in a young healthy woman, 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 applicator insertion, sexual activity).

Background rates of IMB in the general population are not known with precision. In a recent survey of HIV-negative and HIV-positive women, 12 percent and 11 percent respectively reported IMB in the last six months. In clinical trials of oral contraceptives, IMB rates have ranged from five percent to over 50 percent. The high variability in IMB rates seen in these studies is likely due to different methods of data collection and reporting as well as cultural factors. Regardless, since oral contraceptive trials generally are not placebo controlled, it is difficult to assess how rates reported in those trials compare to background rates in the general population.

Similar to observations in contraceptive trials, variable rates of IMB have been observed in Phase I microbicide trials, many of which have not included a control group. While IMB has been reported in microbicide trials, IMB has not been associated with anemia or hemodynamic instability in those trials. Increased rates of IMB also might affect a study product's acceptability.

Section Appendix 10-4 Information on Breastfeeding for Study Staff

Women who are breastfeeding are not permitted to enroll in MTN-020, and women who enroll in MTN-020 are not permitted to use study rings while breastfeeding. Key counseling messages for participants related to this are as follows:

- The medicine in the rings being tested in MTN-020 may pass into breast milk.
- The effects of having this medicine in breast milk are not well known. It is possible that having this medicine in breast milk could cause bad effects for babies who drink the breast milk.
- To avoid any possible bad effects:
 - It is very important that these women breastfeed their babies for as long as recommended by their doctors, so their babies can be as healthy as possible.
 - Women who are currently breastfeeding and who wish to join the study may be able to join later, when they are no longer breastfeeding.
 - To protect the health of their babies, women are asked to honestly inform the study staff of whether they are breastfeeding or not. Study staff will then give information to help women understand how best to protect their health and the health of their babies.
- Until more studies have been done to determine the safety of use of dapivirine vaginal rings among breastfeeding women and their infants, MTN-020 is making every effort to avoid infant exposure to dapivirine.

**Section Appendix 10-5
Clinical and Product Use Management Flow Charts**