Section 10. Clinical Considerations

This section presents information on the clinical procedures performed in MTN 004. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 11. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 12. Instructions for completing data collection forms associated with clinical procedures are provided in Section 14.

10.1 Baseline Medical/Menstrual/Genitourinary History and Ascertainment of Concomitant Medications

A focused baseline medical/menstrual/genitourinary history is obtained from potential study participants at the Screening 1, Screening 2, and Enrollment Visits. Medications used by the participant also are ascertained and documented at this time. The purpose for obtaining this information during screening is to:

- Assess and document participant eligibility for the study at the Screening and Enrollment visits
- Assess and document the participants' baseline medical conditions and symptoms and symptoms, for comparison with signs, symptoms, and conditions that may be identified or reported during follow-up
- Monitor any potential AEs associated with the use of the gel during the course of the study

10.1.1 Focused Baseline Medical/Menstrual/Genitourinary/Genitourinary History

The non-DataFax Baseline Medical History form is a recommended source document for collecting pertinent baseline medical/menstrual history data. Alternative site-specific history forms also may be used. For enrolled participants, all baseline conditions identified as ongoing at the time of the Enrollment Visit are documented on the (DataFax) Pre-existing Conditions form. Recurring and/or chronic conditions are considered ongoing whether or not they are present/active at baseline.

The non-DataFax History of Genital Symptoms form is the recommended source document for collecting data on genitourinary symptoms, including intermenstrual bleeding/spotting, that the participant has experienced from the time she became sexually active through her last Screening Visit. The Baseline Genital Symptoms form is the source document for collecting data on genitourinary symptoms that the participant experienced from the time of her last Screening Visit through Enrollment.

When obtaining a focused baseline medical/menstrual history and completing the History of Genital Symptoms form for MTN 004, it is not necessary to document the participant's lifetime medical history and/or history of genitourinary symptoms. Rather, focus on conditions that have occurred and symptoms that were experienced since the participant became sexually active, and probe for the most accurate information available on the participant's current health and reproductive status vis-à-vis the reported history. Several additional guidelines are presented below:

- Use the listing of body systems on the Baseline Medical History form to probe for history related to each system.

- Record symptoms, illnesses, allergies, and surgeries.

- Record both chronic and acute conditions, as well as both ongoing and resolved conditions.

- For menstrual history, document the details of the participant's usual menstrual cycle and flow. Also enter the first and last day of the participant's last menstrual period, and the average number of bleeding days (e.g., 3-5 days) she experiences during her regular menses. Note the participant's age of menarche and any menstrual problems she may have, such as irregular menses, amenorrhea, menorrhagia, etc. Document the type and severity of any usual menstrual symptoms.

- Document any usual or typical non-menstrual genital bleeding patterns experienced by the participant. This includes any breakthrough genital bleeding/spotting associated with the participant's contraceptive use. Include the frequency of bleeding, the average duration, type of flow (e.g. light, moderate, heavy) and any associated symptoms.

- For all genitourinary subcategories listed on the History of Genital Symptoms and Baseline Genital Symptoms form, probe for and record as much detail as possible. Detailed baseline information in these categories is critical, since changes from baseline will be considered adverse events (AEs; see Section 11). As part of the "other" genitourinary subcategory, explore whether the participant experiences bleeding during or after vaginal intercourse and whether she has experienced (or continues to experience) any type of sexual trauma.

- For reproductive history, record the number, date, and outcome of each of the participant's pregnancies, as well as any gynecologic and obstetrical procedures/surgeries.

- Record the participant's history of contraceptive use. If applicable, enter details of the participant's current contraceptive method on the Concomitant Medications Log form. Per Section 5 of the study protocol, spermicides, diaphragms, and contraceptive vaginal rings should not be used during participation in MTN 004. Participants who report current use of these contraceptive products and devices during screening must be counseled regarding the use of alternative methods and should be referred to family planning services if needed for provision of alternative methods prior to enrollment in the study.

- Document medications currently taken for all ongoing conditions, including usual menstrual symptoms, on the Concomitant Medications Log form, as described in Section 10.1.2.

Site clinicians are encouraged to use their clinical experience and judgment — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in English (and Spanish for the San Juan, PR site) to elicit complete and accurate history information from study participants.

10.1.2 Initial Ascertainment of Concomitant Medications

The MTN 004 protocol requires documentation of all medications taken by study participants beginning at the Screening 1 Visit and continuing throughout follow-up. For purposes of this study, medications include all of the following, regardless of route of administration:

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

Other routes of administration, including intravaginal and rectal medications/preparations and topical medications/preparations applied to the external genitalia are of particular interest for this study, as are douches and vaginal cleansers. Be sure to record all such medications/preparations.

The Concomitant Medications Log form is the recommended source document for collecting information on participants' use of medications. When recording the route of medications/preparations that are applied intravaginally, mark the box labeled "VAG". When recording the route of medications/preparations that are applied rectally, mark the box "REC."

It is recommended that study clinicians ascertain participants' baseline medication information in the context of conducting the baseline medical/menstrual history. In addition to asking open-ended questions to elicit participant report of current medications, use the information obtained in the medical/menstrual history to probe for additional medications that the participant may forget to report. For example, if the participant reports recurrent headaches as part of her medical history, but does not spontaneously list any medications taken for headaches, ask her if she takes any medications for the headaches. Similarly, if a participant reports taking a medication for a condition that she inadvertently did not report when providing medical history information, add the condition to the Baseline Medical History form and Pre-existing Conditions form as appropriate.

10.1.3 Pre-existing Conditions

As noted above, a key purpose of conducting the baseline medical/menstrual history — as well as the abdominal exam and Screening 1 pelvic exam described below — is to document participants' baseline medical conditions, for comparison with signs, symptoms, and conditions that may be identified or reported at subsequent scheduled or interval study visits. For MTN 004, all ongoing medical conditions, problems, signs, symptoms, and (abnormal) findings that are observed and/or reported *at enrollment* are considered pre-existing conditions. Such conditions should be documented per the screening and enrollment visit guidance provided in Sections 4 and 7 of this manual, as well as in the remainder of this section.

For participants who enroll in the study, all conditions observed and/or reported at the Enrollment Visit should be reported on the Pre-existing Conditions form. This case report form is completed at the Enrollment Visit, based on all other screening and enrollment source documents, including the Baseline Medical History form, Physical Exam form, Screening 1 Pelvic Exam form, all screening laboratory results, chart notes, and any other site-specific source documents.

As is described in greater detail in Section 11, the Pre-existing Conditions form serves as the "starting point" from which study clinicians must determine whether medical conditions, problems, signs, symptoms, and other abnormal findings identified or reported during follow-up are adverse events (AEs). By definition, pre-existing conditions are present at the time of randomization/enrollment in the study and are therefore are not considered AEs. However, new conditions identified during follow-up that were not present at the time of enrollment/randomization, and any pre-existing conditions that increase in severity or frequency during follow-up, are considered AEs. With this in mind, when completing the source documents listed above, as well as the Pre-existing Conditions form, study clinicians should document as much detail as possible about the severity and frequency of each pre-existing condition. When completing the Pre-existing Conditions case report form, it is recommended that this information be recorded in the "Comments" section for each condition.

10.2 Interval Medical/Menstrual/Genitourinary History and Updating of Concomitant Medications

For enrolled participants, an interval medical/menstrual/genitourinary history and update of concomitant medications is obtained at each scheduled follow-up visit. This procedure also is performed at interim visits when clinically indicated. An interval medical/menstrual/genitourinary history is considered clinically indicated at interim visits if the participant presents for the interim visit complaining of any symptoms since the last visit. The purpose of these procedures is to determine whether participants have experienced any new illnesses, symptoms, etc., since the last study visit. An interval medical/menstrual/genitourinary history also should be performed at interim visits to obtain updated information on previously reported adverse events when applicable.

10.2.1 Interval Medical/Menstrual/Genitourinary History

The non-DataFax Follow-up Medical History Form is a recommended source document for collecting interval medical/menstrual history data.

At the first One-Week Clinic Visit (day 6-8), retrieve the participant's non-DataFax Baseline Medical History and Pre-existing Conditions forms for reference. At the Two- and Three-Week Clinic Visits, retrieve the participant's Follow-up Medical History (non-DataFax) form from the prior visit for reference. When completing each interval history, it is not necessary to actively review/inquire about every body system listed on the Follow-up Medical History Form. Rather, for all systems except genitourinary, it is acceptable to actively inquire about the current status of conditions recorded as ongoing at the time of the prior visit, and then to ask the participant an open-ended question such as "Have you had any other symptoms or health problems since your last visit?" to complete the history. The Follow-up Genital Symptoms form is a source document used to document genitourinary symptoms experienced during follow-up. Unlike the Follow-up Medical History form, DO NOT refer to any previously completed genital symptoms forms (i.e., History of Genital Symptoms, Baseline Genital Symptoms, Follow-up Genital Symptoms) when completing the Follow-up Genital Symptoms form for the current visit. Rather, for each genital symptom listed on the form, actively inquire as to whether the participant experienced the symptom since her last study visit.

See Section 10.6 below for more information on assessing participant reports of genital bleeding.

Site clinicians are encouraged to use their clinical experience and judgment — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in English (or Spanish for the San Juan, PR site) to elicit complete and accurate follow-up information from study participants.

10.2.2 Updating of Concomitant Medications Information

At each visit in which an interval medical/menstrual history is obtained, retrieve the participant's Concomitant Medications Log, record any new medications taken by the participant, and actively inquire as to whether the participant is still taking medications listed previously, at the same dose and frequency. Also actively inquire as to whether the participant has begun taking any new medications since her last visit, including medications obtained outside the study (not provided by the study staff). To further probe for updates, if the participant reports any intercurrent illnesses, symptoms, etc., since her last visit, inquire as to whether she took any medications for these. Add all new information to the form in log fashion, using additional form pages as needed. Similarly, if a participant reports taking a new medication for a condition that she inadvertently did not report when providing interval medical/menstrual history information, add the condition to the Follow-up Medical History form, and Pre-existing Conditions form (if present at enrollment).

10.3 Behavioral Measures

Each study site will have a computer terminal connected to the Web that the participants will use three times during the study to respond to Behavioral Measures. This computer terminal will be placed in such way to assure the confidentiality of the participants' responses (i.e. the screen will be out of site of staff members or other participants while answers are being entered). Behavioral Measures are:

- Baseline Behavioral Questionnaire, taken at the Enrollment Visit,
- Acceptability and Adherence Questionnaire, taken at the Two-Week Clinic visit,
- Study Burden Questionnaire taken at the Three-Week Clinic Visit

Note: *It is recognized that study clinicians will be unable to review participants' responses to the behavioral measures (BM) prior to conducting interval medical/menstrual histories. It also is acknowledged that detailed clinical probing of responses may identify discrepancies between the BM data and the history information recorded by the clinician. In the event that discrepancies occur, information recorded by the clinician will be considered primary for purposes of monitoring participants' clinical condition and documenting clinical study endpoints. To preserve the standardization of behavioral data collection, however, BM responses will not be amended to correspond with the information recorded by the clinician.*

10.4 Physical Exams

An assessment of vital signs and an abdominal exam are required at the Screening 1, Enrollment, One-Week, Two-Week, and Three-Week Clinic Visits. Site clinicians may use their discretion to determine whether or not to conduct a more complete physical exam, in response to reported symptoms or illnesses present at the time of the exam. Following is a list of the required vital sign assessments, as well as a list of clinical assessments.

Vital signs:
- Weight
- Height
- Oral temperature
- Blood pressure
- Pulse
- Respirations

Clinical assessments of:
- Head and eyes (HE)
- Ears, nose, and throat (ENT)
- Neck
- Lymph nodes
- Heart
- Lungs
- Abdomen
- Extremities
- Neurological
- Skin
- Breasts

The non-DataFax Physical Exam form is a recommended source document for recording physical exam findings. For participants who enroll in the study, abnormal physical exam findings identified at the Enrollment Visit also are recorded on the Pre-existing Conditions form.

Physical exams may identify additional baseline medical history information that participants inadvertently do not report in their baseline medical/menstrual history. For example, the clinician may identify a skin condition during the physical exam and upon further inquiry learn that the participant has had the condition since age 15. In such situations, the clinician should add the newly identified information to the non-DataFax Baseline Medical History form, and the Pre-existing Conditions form as well, sine the condition was present at the time of enrollment.

10.5 Pelvic/Colposcopic Exams

Pelvic exams are performed in MTN 004 for purposes of determining eligibility and identifying primary study safety outcomes. As such, they are critical to meeting the study objectives and ensuring the ongoing safety of study participants. Pelvic exams are performed at Screening 1 Visit and all study visits thereafter per the schedule in protocol Section 7. Exams also are performed when clinically indicated to evaluate genital symptoms.

Colposcopy is required at the Enrollment and Two-Week Clinic Visits. If clinically indicated, colposcopies may be performed at the One-Week and Three-Week Clinic Visits as well.

Pelvic/colposcopic exams are performed, and findings classified, according to the CONRAD/World Health Organization (WHO) Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004 (available at www.conrad.org), and the remainder of this section. Exam procedures must be performed in the order shown on the exam checklists in Section 7 of this manual. All procedures listed on the exam checklists should be performed during routinely scheduled exams. When additional exams are performed to assess genital symptoms, only clinically indicated procedures should be performed. As indicated in greater detail below, exam findings are reported on the following forms provided by the MTN SDMC:

- Screening 1 and Enrollment Pelvic Exam (SPE-1-2)
- Screening 2 Pelvic Exam (RSP-1)
- Follow-up Pelvic Exam (FPE-1-3)
- Pelvic Exam Diagrams (non Datafax form)
- Pelvic Laboratory Results (PLR-1)

For participants who enroll in the study, abnormal exam findings identified at the Enrollment Visit (that are not exclusionary per the study eligibility criteria) also are recorded on the Pre-existing Conditions form.

10.5.1 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 assure 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 to adjust equipment.

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. Prior to insertion, ensure that the speculum functions properly and has no rough edges. The speculum may be lubricated with warm water if needed. No other lubricant may be used.

Record the length and axis of the vagina, position of the cervix, and type and size of speculum after each participant's first examination (e.g., on the exam checklist or Pelvic Exam Diagrams form). This information can then be reviewed prior to subsequent exams to reduce the risk of iatrogenic injury.

Lavage and Removal of Visual Obstruction: During the exam, after assessment of vaginal pH and collection of vaginal swabs, if necessary remove any obstruction (e.g., mucus, cellular debris) by lavage with sterile, isotonic, non-bacteriostatic saline. 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. Do not lavage prior to assessing pH and collecting swabs for wet prep, Gram Stain, cytokines and innate factors testing, quantitative vaginal culture, and GUD testing, per study visit requirements.

If lavage does not adequately remove the obstruction, use a large saline-moistened swab (scopette) in a gentle dabbing fashion to remove the obstruction. Avoid twisting or rolling the swab over the surface of epithelium. Do not use a dry swab to remove any obstruction at any time, as this may cause trauma to the epithelium.

Specimen Collection: Perform specimen collection during each exam in the sequence specified on the pelvic exam checklists (see Section 7 of this manual).

Use of Magnification: For each area examined, i.e., the external genitalia, cervix, and vagina, first perform naked eye exam. Then proceed to colposcopic exam using low power (x4-10 magnification) and no filter to more closely examine the tissues. Colposcopic examination of the external genitalia must precede insertion of the speculum.

Documentation of Findings: Document all exam findings — both normal and abnormal — on the Pelvic Exam Diagrams form. Document abnormal findings only on the appropriate pelvic exam form case report form. Both the Screening Pelvic Exam form and the Follow-up Pelvic Exam forms are recommended source documents for recording relevant descriptors and details of abnormal findings. However, supplemental information may be recorded on the Pelvic Exam Diagrams form, in chart notes, and/or on other source documents. For participants who enroll in the study, abnormal exam findings identified at the Screening 1 Visit (that are not exclusionary per the study eligibility criteria) also are recorded on the Pre-existing Conditions form. See Section 10.5.3 for detailed instructions on classifying and documenting exam findings.

Imaging: Records of digital colposcopic images are required for enrollment and for any findings at follow up visit examinations. The colposcopist will document findings in the participant's chart notes and on the study case report forms. When there are findings on the follow up visits, the clinician should retain digital video images in order to complement documentation of baseline findings, abnormal findings or injury. Save images before probing or swabbing any findings. The informed consent document will include consent to obtain these digital images.

Organizing Colposcopy Images: A large number of colposcopic images will be obtained at each study site. The following naming and filing procedures will ensure consistent organization across sites and facilitate review of images.

Folders for each Subject:

Each subject will have her own dedicated file in which all that participant's saved colposcopic images will be stored. The following format should be used to name the subject's main study folder: Site_PTID

Example: Tampa_300123456

Folders for each Visit:

Within each subject's main study folder there will be subfolders for different visits. The following format should be used to name the subject's subfolder:

Site_PTID_datecollected_colposcopist's initials

Example: PR_301123456_29Oct08_MC

Library for each Visit, if needed for image capture software:

The Library should be named using the following format:

Site_PTID_datecollected_ colposcopist's initials

Example: Pitt_302123456_29Oct08 _MC

Videos of images:
Videos and images will be saved using the following format:

Site_PTID_datecollected_anatomiclocation_#

Examples: PR_301123456_29Oct08_cervix_1

Uploading Colposcopy Images:

Each study site is asked to upload all colposcopy images and videos collected for the first five participants enrolled under protocol version 3.0. Sites should upload all images and videos collected for each participant, starting with images/videos from the Enrollment Visit.

Sites should be certain to collect and upload at least one image each from the following anatomical locations: vulva, cervix, fornix-right, fornix-left, fornix-anterior, and fornix-posterior. All videos/images should be uploaded within 2 business days of the visit.

When you are ready to upload an image or video files:

1. To upload colposcopy image/video files, you will need:
   a) The image and video files available on the computer to access the Atlas web portal
   b) You will need to know the PTID, Visit Code, and Date of Procedure (Exam Date) for each set of participant files you wish to upload.
   c) You will need to have already renamed each image and video file you plan to upload, and will need to know the location of the files on the computer, using the following convention:

      Site_PTID_datecollected_anatomiclocation_#

      For example, an image file from the Tampa site collected for PTID 300-12345-6 on 29-Oct-2008 would be named “Tampa_300123456_29Oct08_cervix_1”. If a second image was taken on this same day for the same PTID and location, it would be named “Tampa_300123456_29Oct08_cervix_2”. For the San Juan, Puerto Rico site, use “PR” for the site in the filename (ex. PR_301123456_29Oct08_cervix_1). For the Pittsburgh site, use “Pitt” for the site in the filename (ex. Pitt_302123456_29Oct08_cervix_1)

      Note: Files for upload must not exceed 250 MB and ALL files must be named uniquely.

2. Go to the MTN 004 Atlas web page by accessing this link: **https://atlas.scharp.org/cpas/project/MTN/004/begin.view**, or, in your web browser, type in "atlas.scharp.org", click on the "MTN" button, and then click on "MTN 004."
3. Make sure you are signed in to Atlas – in the upper right-hand corner of the screen, click on "Sign in". Enter your full email address along with your Atlas password. If you have any problems signing in, email **atlas@scharp.org**.
4. On the MTN 004 Atlas web page, in the paragraph under the "004 Colposcopy Images and Videos" heading, click on the "Colposcopy Image and Video Upload Screen" text
5. You should now be on the page titled "Colposcopy Image and Video Upload Screen". Complete the "Participant Information" fields - Participant ID (PTID), Visit Code, and Date of Procedure. If you are unsure about how to complete these items, see the examples listed and/or place your mouse over the "?" present to the immediate left of each data field for additional information
6. Upload up to two video files and up to 10 photo files using the "Browse" buttons to search for files on your computer or network.
7. Once you have browsed and selected all of the image and video files you wish to upload for the participant, enter any relevant comments in the text box provided. Once you are ready to have the files upload, click the "Submit" button at the bottom of the page. Remember that files will not be uploaded until you have submitted the form by clicking the "Submit" button.
8. Once the "Submit" button has been clicked, a confirmation page will appear, indicating that all fields have been correctly completed on the upload screen. If you have any questions or problems uploading files, please email atlas.scharp.org

10.5.2 Detailed Procedural Instructions

Study-specific pelvic exams should not be performed during menses, since the presence of menstrual blood will likely interfere with visualization of the vagina and cervix, elevate the vaginal pH, and complicate interpretation of wet prep findings. If a participant is menstruating when she presents for a visit in which a pelvic/colposcopy exam is required, perform other protocol-specified procedures at the visit and schedule the participant to return for the pelvic exam and associated specimen collections as soon as possible after menses, within the allowable visit window. If a participant is menstruating when she presents for an interim visit complaining of genital symptoms, every effort should be made to perform a pelvic exam to evaluate her symptoms at that time. However, if this is not possible the participant should be instructed to return for a pelvic exam as soon as possible after menses.

See Section 6 of this manual for procedural modifications to be followed with pregnant participants.

Prior to the Exam: Prepare all required equipment, supplies, and paperwork. Verify that all equipment is in good working order and that the colposcope, computer, software, and printer are warmed up and ready for use (for exams involving colposcopy). Review documentation of prior exams (if any) and other relevant documentation from the current visit and prior visits. While the participant is clothed, explain the procedure and equipment to her and answer any questions she may have.

Position the Participant: Establish a comfortable examination position for the participant that allows for the perineum and vulva to be inspected. Adjust stirrups and back elevation as needed. Provide socks if the room is cold; provide a fan for the participant's face if the room is warm. Drape the participant and point out distractions such as photos on the ceiling or music if available.

Examine the External Genitalia:

- Do not insert the speculum prior to examining the external genitalia.
- Spread the participant's knees as far apart as is comfortable for her.
- Palpate the inguinal lymph nodes to assess for enlargement and/or tenderness.
- Perform naked eye examination of the external genitalia including the perineum, perianal area, and the epithelial lining of the introitus.
- For exams involving colposcopy, proceed to colposcopic examination of the same areas, using appropriate magnification.
- Note all findings on the Pelvic Exam Diagrams form. Further document abnormal findings on the appropriate pelvic exam case report form.

Examine the Cervix:

- The speculum may be lubricated with warm water if needed. No other lubricant may be used. Gently insert the speculum and open it once past the pelvic floor muscles, using gentle downward pressure, so as to avoid trauma while enabling visualization of the cervical face and upper vagina.
- If the cervix is poorly visualized, to avoid iatrogenic injury, remove the speculum and use a gloved finger (lubricated with warm water if needed) to establish the position of the cervix. Then re-insert the speculum.
- Perform naked eye exam without manipulation, observing the general state of the cervix, the size and shape of the cervical os, and any other findings.
- During exams not involving colposcopy, assess cervical ectopy at this time. During exams involving colposcopy, assess cervical ectopy during the colposcopic exam.
- Assess for homogeneous discharge. Record outcome on the Pelvic Laboratory Results form. If any abnormal vaginal or cervical discharge and/or blood-tinged discharge are also present, document the discharge on the Pelvic Exam Diagrams and on the appropriate pelvic exam form (Screening 1 and Enrollment Pelvic Exam form, Screening 2 Pelvic Exam form, or the Follow-up Pelvic Exam form).
- Place pH indicator strip against lateral vaginal wall, just until the paper is moistened. Avoid contact with cervical mucus, which has a high pH. Alternatively, vaginal fluids may be collected via swab and then swabbed onto the pH strip (instead of inserting the pH strip into the vagina). Match the resulting color of the pH strip to the color scale provided with the strips to determine the pH value. Record the pH on the Pelvic Laboratory Results form.

- Collect vaginal fluids via (dry) swab for wet prep, Gram Stain, and quantitative culture, as required by the visit. Collect fluids from the lateral vaginal wall, away from any apparent abnormalities. Collect cervical fluids (dry) swab for cytokines and innate factors testing. Collect fluids from the cervical canal, away from any apparent abnormalities. Exclude swabbed areas from subsequent examination. Document specimen collection for Gram Stain on the Screening Pelvic Exam form or the Follow-up Pelvic Exam form. See Section 12 of this manual for detailed wet prep and Gram Stain slide preparation and assessment procedures.

  Wet prep slides are to be read by local laboratory or site research staff, and results should be recorded on the Pelvic Laboratory Results form. Gram stains are to be read at the MTN Network Laboratory (NL), so results will be forwarded directly to SCHARP by the NL.

- If needed, lavage the cervix and vagina as described in Section 10.5.1 and complete naked eye exam.

- For exams involving colposcopy, proceed with colposcopic examination of the cervix, fornices (anterior, right lateral, left lateral, and posterior), and adjacent cervical trunk using appropriate magnification (usually 4-10X). If excessive glare occurs, reposition to alter the illumination angle. If necessary, manipulate the speculum slightly so the fornices may be adequately visualized. The lateral fornices are best exposed by placing a saline-moistened large swab (scopette) into the contralateral fornix and pressing toward the participant's head and laterally. For example, to view the right lateral fornix, place the moistened swab into the left lateral fornix and press gently toward the participant's head and left side. Do not use dry swabs for this purpose.

- Note all findings (variants of normal and abnormal) on the non-DataFax Pelvic Exam Diagrams form. See the variants of normal in section 10.5.3 below. Further document abnormal findings on the appropriate pelvic exam case report form. Save images of abnormal colposcopic findings per Section 10.4.1.

Examine the Vagina: To examine the rest of the vagina, slowly withdraw the speculum with the blades moderately open, re-focusing as needed. Alternatively, the speculum may be rotated ninety degrees to allow visualization of the anterior and posterior vaginal walls; retract the speculum away from the cervix and close the blades to rotate. Note all findings on the Pelvic Exam Diagrams form. Further document abnormal findings on the appropriate pelvic exam case report form.

Collect Genital Ulcer Swabs: If any genital ulcers are observed during follow-up, swab the base of the ulcer using a dry plastic shaft Dacron swab. Use a different swab for each ulcer. If a cluster of ulcers is observed, sample each ulcer in the cluster with the same swab. Otherwise use a different swab for each ulcer. Document specimen collection on the Follow-up Pelvic Exam form. See Section 12 of this manual for further instructions for proper swab handling and storage prior to testing at the MTN Network Laboratory.

Collect Pap Smear: A Pap smear is required at the Screening 1 Visit if there is no documentation of a normal result in the form of a written report within the 12 calendar months prior to screening. If no such documentation exists, collect ecto- and endocervical cytobrush specimens after completing all naked eye and colposcopic tissue examinations. Document specimen collection on the Pelvic Laboratory Results form and transcribe results, once they become available, to that same form. Participants with abnormal results will not be eligible for the study. Pap smears will be reported as per the 2001 Bethesda System and will be presumed normal in the absence of intra-epithelial lesion or malignancy.

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

10.5.3 Documentation of Findings

Document all exam findings, both variants of normal and abnormal, on the Pelvic Exam Diagrams form.

The following findings are considered normal:

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

Per the CONRAD/WHO Manual, 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 considered deep)

Color:

- Normal
- Slightly red
- Red
- White
- Other (includes "pale")

Blood Vessels

Integrity:

- Intact
- Disrupted

Figure 10-1 provides information to guide and standardize terminology used to describe abnormal pelvic exam findings. Examining clinicians also are encouraged to consult the Photo Atlas for Microbicide Evaluation developed by Bollen, Kilmarx, and Wiwatwongwana (MOPH-US CDC Collaboration, 2002) for further examples of terminology applied to pelvic exam findings in microbicide studies.

The Screening 1 and Enrollment Pelvic Exam form, the Screening 2 Pelvic Exam form (if applicable, and the Follow-up Pelvic Exam form are recommended source documents for recording relevant descriptors and details of abnormal findings; however supplemental information may be recorded on the Pelvic Exam Diagrams form, in chart notes, and/or on other source documents. Iatrogenic findings such as those caused by speculum trauma should be included among the "abnormal" findings documented for the exam, with notations added to source documents and case report forms to specify the cause of the finding.

10.5.4 Quality Control

A quality control measure will be implemented to ensure that sites are recording colposcopic findings consistently. All digital images obtained from the first five participants enrolled at each site after study resumption will be sent to the University of Pittsburgh colposcopy consultants for review. Should there be discrepancies in reporting between sites and/or participants, additional colposcopic training can be arranged.

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

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

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

10.6 Genital Bleeding Assessment

Genital bleeding other than menstrual bleeding, often referred to as "intermenstrual bleeding" or "IMB" is a common occurrence among reproductive age women, and often is of physiologic or benign etiology. Some women normally experience mid-cycle bleeding or pre-menstrual bleeding. IMB is common in oral contraceptive users, particularly new and/or inconsistent users. Use of intrauterine contraceptive devices, smoking, and chlamydia infection have been identified as risk factors for IMB, and IMB may be associated with genital tract pathology such as cancer or polyps. IMB also may be associated with traumatic injury to the cervicovaginal epithelium (e.g., due to speculum insertion, product 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. The main concern raised by observation of IMB in microbicide trials is that candidate microbicides that are associated with increased rates of IMB may increase, rather than decrease, the user's risk of HIV infection, presumably by disrupting the cervicovaginal epithelium and blood vessels. Increased rates of IMB also might affect the microbicide's acceptability.

The MTN 004 Protocol Team has carefully considered the potential risks that may be associated with IMB and has developed procedures to evaluate, monitor, and report on genital bleeding throughout the course of the study. These procedures are described below and several possible genital bleeding assessment scenarios are presented in Appendix 10-1.

10.6.1 Genital Bleeding Assessment for Pregnant Participants

The remainder of this section provides procedural instructions and guidance for assessment of genital bleeding among non-pregnant participants. If a pregnant participant reports genital bleeding, study staff will clinically manage the participant per local practice standards for pregnancy. In particular, study staff will refer the participant to a qualified clinician for further evaluation, care, and treatment; pelvic exams may be performed by qualified clinicians unless contraindicated. Study staff will document the bleeding event and all follow-up actions in the participant's study records. When reporting the event as an AE, it is not expected that a term such as "intermenstrual bleeding" or "metrorrhagia" will be used to describe the AE. Rather clinically appropriate terminology reflecting the cause or source of the bleeding (e.g., "threatened abortion") should be used, if possible, and the bleeding itself should be graded according to the "First trimester bleeding", "Second/third trimester bleeding", or "Postpartum hemorrhage" row of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 December 2004, Addendum 1 (The Female Genital Grading Table for Use in Microbicide Studies) as appropriate. Any questions related to genital bleeding assessment or AE reporting for pregnant participants should be submitted to the MTN 004 PSRT as described in Section 11.

10.6.2 Participant Reports of Genital Bleeding

As part of the MTN 004 informed consent and enrollment process, study participants will be counseled to report all occurrences of genital bleeding — other than usual menstrual bleeding — to the study site as soon as possible after identification of the bleeding. Study staff will provide site contact information to each participant upon enrollment. Thereafter, at each study follow-up visit, contact information will be reiterated and active reporting of genital symptoms including unexpected menstrual bleeding and unexpected non-menstrual genital bleeding will be emphasized.

As described in Section 10.2, at each study visit, clinicians will obtain interval medical/menstrual history information from participants, including active ascertainment of whether any genitourinary symptoms including genital bleeding were experienced since the last study visit. Any changes in participants' use of concomitant medications, including contraceptives and topical and intravaginal medications/preparations, also will be actively ascertained. Reports of genital bleeding should be recorded on the Baseline Genital Symptoms form (at enrollment) or on the Follow-up Genital Symptoms form (for follow-up visits).

10.6.3 Clinician Assessment of Genital Bleeding

Study participants will undergo pelvic exams at the Screening 1 Visit, Enrollment and at every weekly visit thereafter. Pelvic exams also will be performed to evaluate any participant report of unexpected menstrual bleeding and/or unexpected non-menstrual genital bleeding. Pelvic examinations will be performed and documented as described in Section 10.5.

Figures 10-2a and 10-2b outline the genital bleeding assessment and reporting procedures that will be followed at all sites. As shown in the figures, the sequence of procedures will differ depending on whether genital bleeding is first reported by the participant or first observed on pelvic exam. The Genital Bleeding Assessment form (see Section 14) will be used at all sites to guide and document clinicians' assessment of both participant-reported genital bleeding and clinician-observed genital bleeding when applicable (see more below). The Genital Bleeding Assessment form guides clinicians to collect and consider information on the many factors that may contribute to the observation of genital bleeding, to help determine whether the bleeding may be related to product use, or whether it may be more likely attributable to another cause. These factors include:

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

Assessment of genital bleeding should begin by determining whether the bleeding is *expected* or *unexpected*, and then proceed to determining whether the bleeding is *menstrual* or *non-menstrual*. Expectedness will be determined based on the participant's baseline medical/menstrual history (e.g., whether she reports genital bleeding as a pre-existing condition) as well as any other relevant factors such as hormonal contraceptive use. If a participant reports bleeding consistent in amount and duration with her baseline menstrual history, or that is consistent with use of her hormonal contraceptive method, the bleeding will be considered *expected.* In particular, intermenstrual genital bleeding occurring within the first three months of initiating a hormonal contraceptive method will be considered expected, unless the study clinician determines that the bleeding is inconsistent with bleeding patterns usually associated with that method. Lochia also will be considered expected.

A pelvic exam must be performed to evaluate all episodes of unexpected genital bleeding. Pelvic exams are not required to evaluate expected bleeding events; however, such exams may be performed at the discretion of the IoR or designee.

The Genital Bleeding Assessment form must be completed for participants who:

- Self-report genital bleeding other than their normal menses, unless the bleeding is determined to be expected before completing the form

- Do not self-report genital bleeding, but have genital blood/bleeding observed on pelvic exam that is not associated with an abnormal exam finding (e.g., laceration).

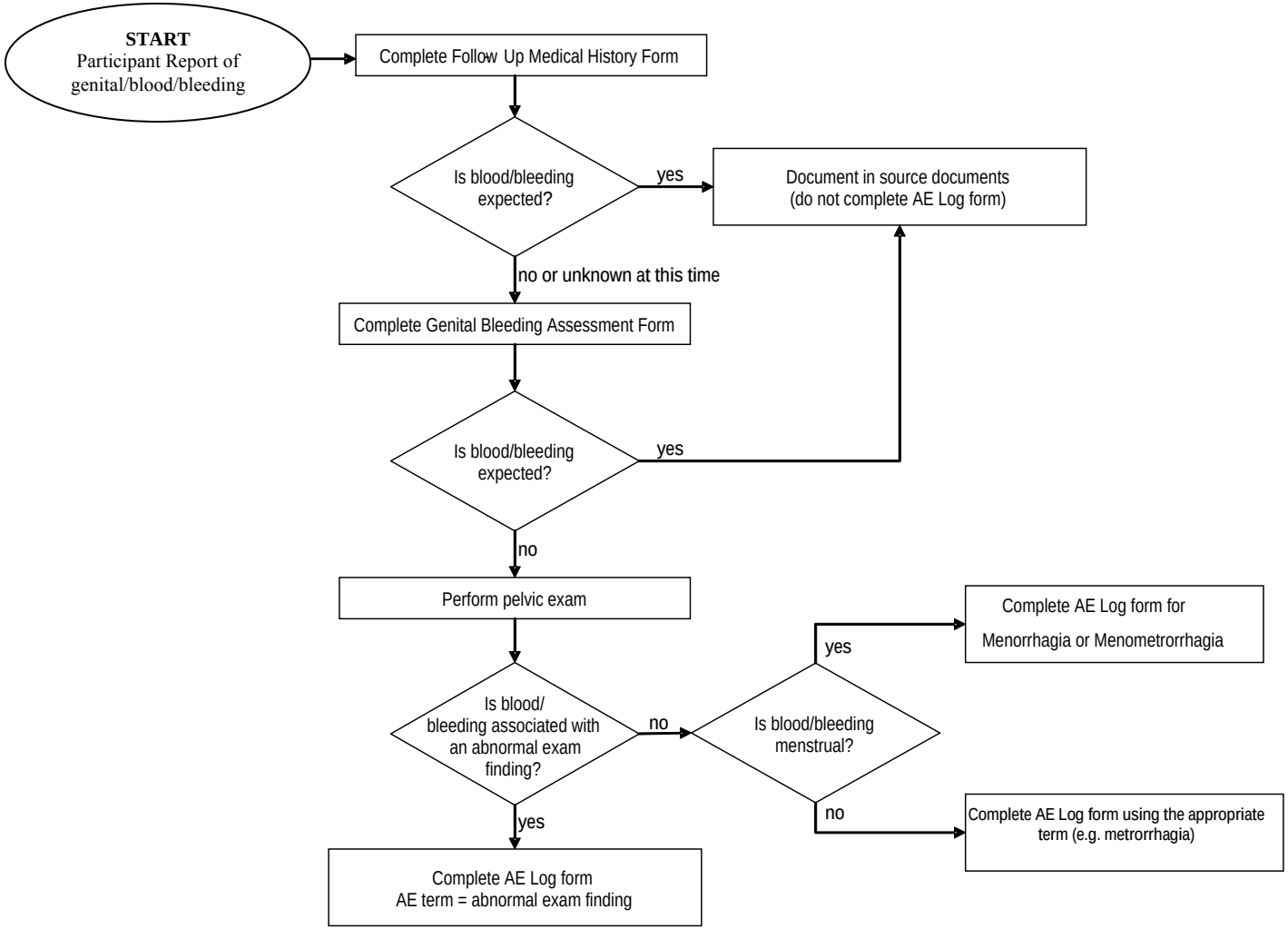
The Genital Bleeding Assessment form is not required to be completed for participants who:

- Self-report genital bleeding that is determined to be expected prior to completion of the form

- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is associated with an abnormal exam finding.

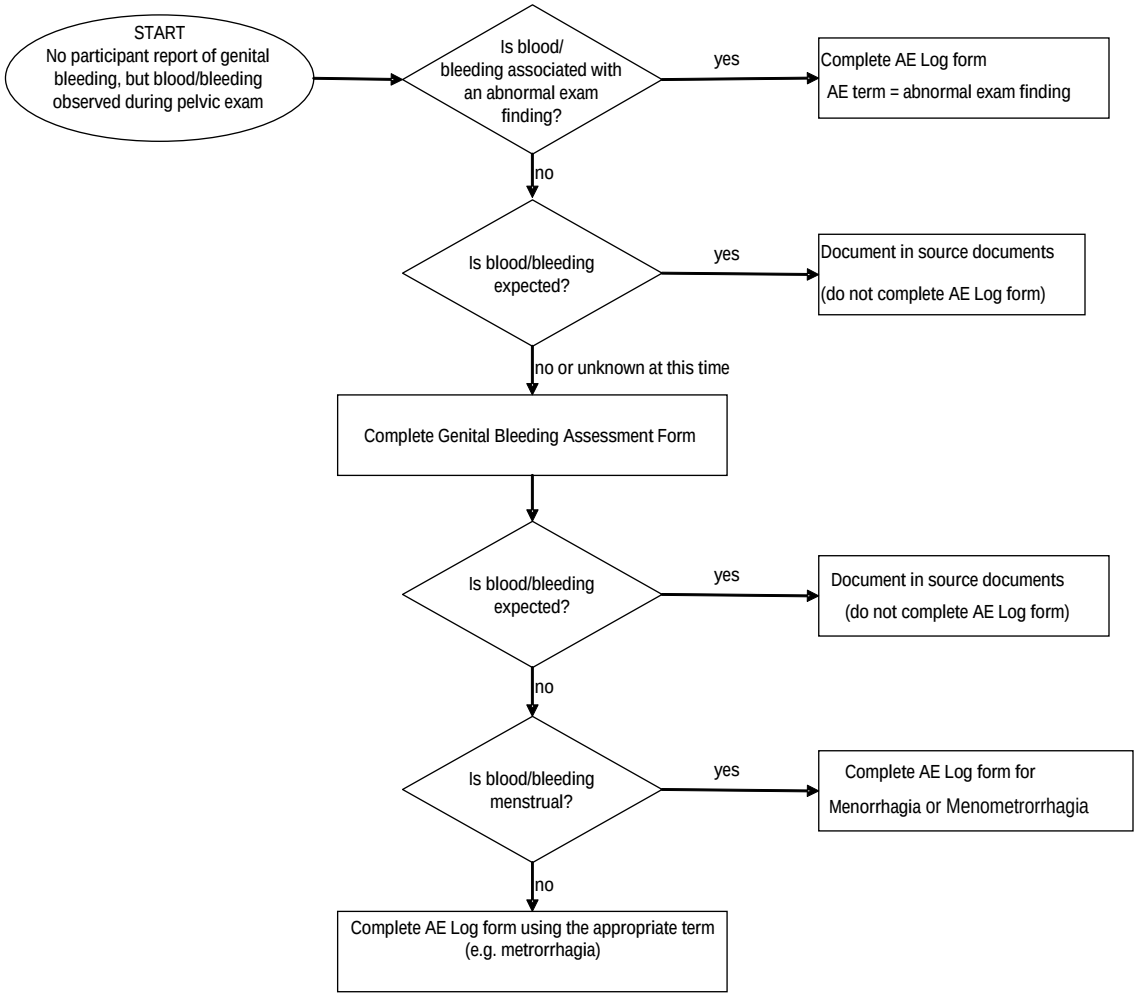
- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is determined to be menstrual bleeding before completing the form.

Figure 10-2a
Overview of Assessment and Reporting Procedures for Genital Bleeding in MTN 004 — Beginning with Participant Report of Bleeding



Note: This algorithm is followed for non-pregnant participants only (see Section 10.6) and does not apply to genital hemorrhage. See Section 10.6.4 for more information on terminology and severity grading for adverse events (AEs) involving genital bleeding.

Figure 10-2b
Overview of Assessment and Reporting Procedures for Genital Bleeding in MTN 004 — Beginning with Clinical Observation of Blood/Bleeding



Note: This algorithm is followed for non-pregnant participants only (see Section 10.6) and does not apply to genital hemorrhage. See Section 10.6.4 for more information on terminology and severity grading for adverse events (AEs) involving genital bleeding.

10.6.4 Documentation of Genital Bleeding

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

All cases of participant-reported genital bleeding occurring between usual menstrual periods will be documented on the Follow-up Genital Symptoms form. All clinically observed genital blood/bleeding will be documented on the Pelvic Exam Diagrams form and the Follow-up Pelvic Exam form. In addition, certain episodes of genital bleeding will be documented on the Genital Bleeding Assessment form, as specified in Section 10.6.3 above.

All episodes of unexpected menstrual bleeding and unexpected non-menstrual genital bleeding — whether participant-reported or clinician-observed or both — will be considered adverse events (AEs) that must be documented on Adverse Experience Log case report forms. Detailed information on AE reporting is provided in Section 11, however when reporting genital bleeding events, reference also should be made to the points below, which standardize the terminology that should be used at all sites when reporting AEs involving genital bleeding.

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

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

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

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

- Expected non-menstrual bleeding should not be reported as an AE.

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

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

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

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

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

10.7 STI/RTI Management

Clinical and laboratory evaluations are performed throughout the course of MTN 004 to diagnose the following sexually transmitted diseases and other reproductive tract infections (STIs/RTIs):

- Bacterial vaginosis (BV)
- Candidiasis (any species)
- Chlamydia infection
- Genital ulcer disease

- Gonorrhea infection
- Syphilis infection
- Trichomoniasis

Signs and symptoms commonly associated with the above-listed infections are presented in Figure 10-3. 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 evaluations 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 and symptoms include erythema, edema, and pruritis of the external genitalia.
Candidiasis	Clinical presentation varies from no signs or symptoms to erythema, edema, and pruritis of the external genitalia. Symptoms and signs alone do not distinguish the microbial etiology.
Chandroid	The combination of painful ulcer and tender inguinal adenopathy, symptoms occurring in one third patients, suggests a diagnosis of chancoid; when accompanied by suppurative inguinal adenopathy, these signs are almost pathognomonic.
Chlamydia infection	Many infections are asymptomatic and probably chronic. Mucopurulent discharge may not be recognized by the patient or may not be perceived as abnormal.
Genital herpes	Single or multiple vesicles, which usually are pruritic can appear anywhere on the genitalia. Vesicles spontaneously rupture to form shallow ulcers that may be very painful. Lesions spontaneously resolve with minimal scarring.
Gonorrhea infection	Women may have abnormal vaginal discharge, abnormal menses, or dysuria, or most commonly are asymptomatic. Pharyngeal gonorrhea can produce symptoms of pharyngitis.
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 do not distinguish the microbial etiology.
Pelvic Inflammatory Disease (PID)	Patients must meet three criteria for PID: symptoms and exam findings of lower abdominal pain and tenderness, cervical motion tenderness, and adnexal tenderness. Additionally patients may present with fever, abnormal cervical or vaginal discharge, and cervicitis.
Cervical or Vaginal Warts	Patients usually present with a painless cauliflower lesion(s), sessile or on a stalk. Patients usually present with a painless cauliflower lesion(s), sessile or on a stalk.

Adapted from: *Contraceptive Technology* (18th Revised Edition, 2004); Chapter 8: Reproductive Tract Infections; Alphabetic Catalog of Reproductive Tract Infections; pages 201-218.

10.7.1 STI/RTI Treatment

STIs/RTIs will be treated in accordance with current (2006) CDC Sexually Transmitted Diseases Treatment Guidelines.

Should updated guidelines be issued by the CDC during the study, the updated guidelines will then be followed.

Note: *Neither asymptomatic bacterial vaginosis nor asymptomatic vaginal candidiasis require treatment per CDC guidelines.*

Figure 10-5 summarizes the 2006 CDC treatment guidelines for each of the conditions listed above. In day-to-day practice, the CDC guidelines — or local site treatment guidelines based on the CDC guidelines — should be referenced to obtain complete information on treatment regimens, contraindications, etc. To optimize cure rates, and thereby optimize the validity of study endpoint data, directly observed single dose treatment regimens should be provided whenever possible.

Figure 10-4
(2006) CDC Sexually Transmitted Diseases Treatment Guidelines
for STI/RTI Diagnosed in MTN 004

STI/RTI	CDC Sexually Transmitted Diseases Treatment Guidelines
Bacterial vaginosis	For symptomatic patients only. Recommended: • Metronidazole, 500 mg orally twice daily for 7 days Alternative: • Clindamycin vaginal cream 2%, 5 g intravaginally, at bedtime for 7 days • Metronidazole gel 0.75%, 5 g intravaginally, twice daily for 5 days • Clindamycin, 300 mg orally, twice daily for 7 days • Clindamycin, ovules 100 mg intravaginally once at bedtime for 3 days

Figure 10-4
(2006) CDC Sexually Transmitted Diseases Treatment Guidelines
for STI/RTI Diagnosed in MTN 004

STI/RTI	CDC Sexually Transmitted Diseases Treatment Guidelines
Candidiasis	For symptomatic patients only. Recommended: • Butoconazole 2% cream 5g intravaginally once daily for 3 days Alternative: • Butoconazole 2% cream 5g (Butoconazole 1-sustained release), single intravaginal application • Clotrimazole, 1% cream 5g intravaginally, once daily for 7-14 days • Clotrimazole, 100 mg vaginal tablet, once daily for 7 days • Clotrimazole, 100 mg vaginal tablet, two tablets daily for 3 days • Miconazole 2% cream 5g intravaginally, once daily for 7 days • Miconazole 100 mg vaginal suppository, once daily for 7 days • Miconazole 200 mg vaginal suppository, once daily for 3 days • Miconazole 1,200 mg vaginal suppository, once daily for 1 day • Nystatin, 100 000 IU intravaginally, once daily for 14 days • Ticonazole 6.5% ointment 5g intravaginally in a single application • Terconazole 0.4% cream 5g intravaginally, once daily for 7 days • Terconazole 0.8% cream 5g intravaginally, once daily for 3 days • Terconazole 80 mg vaginal suppository, once daily for 3 days • Fluconazole 150 mg orally, one tablet in a single dose
Chlamydia infection (uncomplicated anogenital infection)	Recommended: • Azithromycin, 1 g orally, as a single dose • Doxycycline, 100 mg orally, twice daily for 7 days (contraindicated in pregnancy and lactation) Alternative: • Erythromycin base, 500 mg orally, four times daily for 7 days • Erythromycin ethylsuccinate, 800 mg orally, four times daily for 7 days • Ofloxacin, 300 mg orally, twice daily for 7 days • Levofloxacin, 500 mg orally, once daily for 7 days
Genital herpes (first clinical episode)	Recommended: • Acyclovir, 400 mg orally, three times daily for 7-10 days • Acyclovir, 200 mg orally, five times daily for 7-10 days • Famciclovir, 250 mg orally, three times daily for 7-10 days • Valacyclovir, 1000 mg orally, twice daily for 7-10 days
Genital herpes (recurrent episodes of genital lesions)	Recommended: • Acyclovir, 400 mg orally, three times daily for 5 days • Acyclovir, 800 mg orally, twice daily for 5 days • Acyclovir, 800 mg orally, three times daily for 2 days • Famciclovir, 125 mg orally, twice daily for 5 days • Famciclovir, 1,000 mg orally, twice daily for 1 day • Valacyclovir, 500 mg orally, twice daily for 3 days • Valacyclovir, 1000 mg orally, once daily for 5 days

Figure 10-4
(2006) CDC Sexually Transmitted Diseases Treatment Guidelines
for STI/RTI Diagnosed in MTN 004

STI/RTI	CDC Sexually Transmitted Diseases Treatment Guidelines
Gonorrhea infection (uncomplicated anogenital infection)	Recommended: • Ceftriaxone, 125 mg IM injection, as a single dose • Cefixime, 400 mg orally, as a single dose • Ciprofloxacin, 500 mg orally, as a single dose (contraindicated in pregnancy, not recommended for children or adolescents) • Ofloxacin 400 mg orally, as a single dose • Levofloxacin, 250 mg orally, as a single dose
Syphilis infection (early infection)	Recommended: • Benzathine benzylpenicillin, 2.4 million IU, IM injection, at a single session (usually two injections at separate sites) Alternative: • Procaine benzylpenicillin, 1.2 million IU, IM injection, daily for 10 consecutive days Alternative for penicillin-allergic non-pregnant patients: • Doxycycline, 100 mg orally, twice daily for 14 days • Tetracycline, 500 mg orally, four times daily for 14 days
Trichomoniasis	Recommended: • Metronidazole, 2 g orally, as a single dose • Tinidazole, 2 g orally, as a single dose Alternative: • Metronidazole, 500 mg orally, twice daily for 7 days

STI/RTI tests of cure are not required in MTN 004; however clinical management of syphilis infections should include repeat serology (RPR) following diagnosis of a new infection to confirm treatment effectiveness. If syphilis is diagnosed during screening, the participant is not eligible for inclusion but should be followed as clinically indicated. Please contact the MTN NL with any questions related to quarterly testing to confirm treatment effectiveness and/or interpretation of unusual syphilis test results.

10.7.2 Screening and Enrollment Considerations

Potential study participants diagnosed during screening with an STI/RTI per 2006 CDC guidelines via laboratory tests will be excluded from enrollment. The only exception to this are women with clinical evidence or laboratory evidence of BV or vulvovaginal candidiasis but who are asymptomatic.

At some study sites, Pap smear results may include notations of findings associated with certain STIs (e.g., trichomoniasis). Because Pap smear methods are not adequately sensitive and specific for STIs, Pap smear findings associated with STIs should not be considered diagnostic of any infections. Rather, such findings should be handled as follows:

- Do not consider STI-related notations on Pap smear result reports when assessing participant eligibility for the study. Use only the results of protocol-specified STI tests for purposes of eligibility determination.

- If protocol-specified STI testing was performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for Pap smear, the results of the protocol-specified testing overrule STI-related findings noted on the Pap smear result report. Provide treatment as needed based on the results of the protocol-specified tests.

- If protocol-specified testing was not performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for the Pap smear, collect specimens for indicated protocol-specified STI testing at the participant's next study visit after receipt of the Pap test result report. Provide treatment as needed based on the results of the protocol-specified tests.

10.7.3 Adverse Event Reporting Considerations

Per the MTN 004 eligibility criteria, no participant may enter the study with an active STI/RTI diagnosed per 2006 CDC guidelines via laboratory tests. Also, no participant may enter the study with a history of STI diagnosis and/or treatment (except HSV recurrence) in the 6 months prior to enrollment. Since no treatable STI or RTI should be recorded as a pre-existing condition for an enrolled participant, any curable STI/RTI identified during follow-up in MTN 004 is considered an AE that must be documented on an Adverse Experience Log case report form. Detailed information on AE reporting is provided in Section 11. When reporting STI/RTI AEs, the severity of the event should be graded according to the "Genitourinary Infections" section of the Female Genital Grading Table (with the exception of asymptomatic bacterial vaginosis).

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

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

- For HPV, genital warts present before randomization are considered a pre-existing condition: report on the Pre-existing Conditions form.

- Any outbreaks that occur after randomization are considered AEs, regardless of whether the viral infection was pre-existing before randomization: report on an Adverse Experience Log form.

10.8 Urinary Tract Infections

Dipstick urinalyses will be performed at Screening 1, and when clinically indicated during follow up, to diagnose urinary tract infections (UTI). See Section 12 or details on the required laboratory procedures. Record results on applicable testing log sheets and then transcribe results onto the STI Laboratory Results form.

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

When clinically indicated, a urine culture and sensitivity should be performed, and the culture should be documented on the STI Laboratory Results form. The sensitivity test results should be documented in the participant's chart notes only. Once a diagnosis has been made, treatment will be provided per site standards of care and applicable site standard operating procedures (SOPs).

10.9 Product Use Management

For this study, product use management may involve temporarily holding or permanently discontinuing gel use for individual study participants, to protect their safety and well-being while in the study. Product use management in this study will not involve modification of the dose (one applicatorful) or route (intravaginal) of product administration by any participant. It is the responsibility and obligation of the IoR/PI and other authorized study clinicians to assess participants' eligibility for continued product use throughout their participation in the study.

Certain product use management decisions and actions must be undertaken, per protocol, under the direction of the study site IoR/PI. Other product use management decisions and actions are undertaken, under the direction of the IoR/PI, in consultation with the MTN 004 PSRT as described in Section 11.

10.9.1 Circumstances In Which Product Use Must Be Either Temporarily Held or Permanently Discontinued

Product use must be temporarily held in the following circumstances (Refer to Protocol Appendix II):

- Have a pelvic exam finding involving deep epithelial disruption (ulceration) excluding findings observed by colposcopy only

- Have a pelvic exam finding of generalized erythema or severe edema involving an area of more than 50% of the vulvar surface or combined vaginal and cervical surface affected by erythema excluding findings by colposcopy only

- Have abnormal vaginal discharge noted on pelvic exam

- Have presumed cervicitis (findings on exam such as mucopurulent cervical discharge)

- Experience an AE that meets the criteria for expedited reporting to DAIDS (see Section 11 of this manual) that is judged by the IoR or designee to be probably not, possibly, probably, or definitely related to product use. With written approval from the PSRT, participants who experience such an AE may resume product use after the AE resolves (returns to baseline) or stabilizes at a non-reportable severity grade. To obtain approval for resumption of product use from the PSRT, the IoR or designee should submit a query to the PSRT, via the MTN 004 Protocol Safety Physicians, using the MTN 004 PSRT query form as described in Section Appendix 11-3. The PSRT will consider the query and provide a written response (or request more information) via email within three business days.

Product use must be permanently discontinued in the following circumstances:

- Have signs or symptoms of STI(s)/RTI(s) requiring treatment according to the judgment of the investigator

- Experience study product-related toxicity

- Become pregnant or are breastfeeding

- Complete the study regimen as defined in the protocol

- Refuse further study gel use

- Present with any other clinical reason to discontinue study product use, as determined by the IoR/PI.

- Experience a Grade 4 EAE that is judged by the site investigator or designee to be definitely, probably, possible, or probably not related to the study gel or applicator

- Because a herpetic outbreak is a self-limited condition in an immunocompetent host, a participant who experiences a herpes outbreak does not necessarily require treatment. In such cases, a treatment decision will be made based on the clinician's and participant's assessments. If treatment is provided, participants will be permanently discontinued from study product. If treatment is not warranted, participants may continue study product.

  Per protocol, participants at all study sites will continue to be followed as a study participant regardless if they have had study gel temporarily held or permanently discontinued.

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

Product use may be either temporarily held or permanently discontinued, at the discretion of the IoR, under the following circumstances, in consultation with the PSRT:

- The participant is unable or unwilling to comply with required study procedures

- The participant might otherwise be put at undue risk to her safety and well-being by continuing product use

10.9.3 Documentation of Product Use Management

All product use management decisions must be thoroughly documented in participant's study charts. It is expected that signed and dated chart notes, together with correspondence to and from the PSRT, when applicable, will serve as the primary source documentation for these decisions; however other site-specific source documents also may be used. In addition to this documentation, product holds should be communicated to study pharmacy staff using the MTN 004 Study Gel Request Slip, as described in Section 6 and a Product Hold/Discontinuation case report form should be completed and faxed to the MTN SDMC, as described in Section 14.

10.9.4 Participant Follow-Up During Periods of Product Use Discontinuation

Participants who either temporarily or permanently discontinue product use will not routinely be withdrawn from the study. Rather, every effort will be made to complete all protocol-specified follow-up visits and procedures with these participants (with the exception of product-related procedures that are not applicable during the period of product use discontinuation).

10.9.5 Collection of Product Supplies During Periods of Product Use Discontinuation

If a participant becomes pregnant or experiences an adverse event that requires permanent discontinuation of product use, any unused applicators remaining in her possession should be collected from her as soon as possible and returned to the pharmacy on the day of collection.

It is not necessary to collect remaining unused (unopened) applicators from participants for whom gel use is temporarily held for an expected short period of time. However, applicators may be collected from such participants, to protect their safety, if it is suspected that the participant may not comply with clinic staff instructions to refrain from gel use for the duration of the temporary hold.

For all product holds requiring collection of unused applicators, if the applicators are not collected within five working days of initiating the product hold, the MTN 004 PSRT must be informed, using the PSRT Query Form as described in Section Appendix 11-3. When informing the PSRT, please describe the reason for the product hold, actions taken to try to collect the unused applicators, and plans and timelines for further action to collect the applicators.

10.10 Pregnancy Management

Please refer to the Section 6 of this manual for procedural instructions for management of participant pregnancies that may occur during follow-up.

Section Appendix 10-1

Scenarios for AE Grading using Female Genital Grading Table for Use in Microbicide Studies

10-1.1 During the Screening/Enrollment Visit, Ms. X reports that her menses usually occur every four weeks and last for five to seven days. She gives no previous history of intermenstrual or prolonged/heavy bleeding. When she returns for her final Three-Week Clinic Visit, she reports that her menses started that day, approximately one week earlier than expected. What procedures should be followed?

- Depends on the clinician's judgment. If the clinician considers this event to be early onset menses of menses, this event should not be reported as an AE. However, if the clinician considers this event to be unexpected bleeding, then report this genital bleeding as an AE using the term metrorrhagia and grade according to the Female Genital Grading Table under "Abnormal Uterine Bleeding Unrelated to Pregnancy". The Clinician should perform a pelvic exam for further evaluation.

Why? This event is considered metrorrhagia if it is unexpected (i.e. her baseline history does not have any previous history of intermenstrual bleeding).

10-1.2 Continuing from the scenario above, suppose the clinician judged the genital bleeding to be unexpected and decided to conduct a safety visit post termination to follow up on the AE of metrorrhagia. At the follow up Safety Visit, nine days later the participant is still bleeding. What would you do?

- Update the AE log to change the previous report of metrorrhagia to an AE of menometrorrhagia, and grade according to menorrhagia row in the Female Genital Grading Table under "Abnormal Uterine Bleeding Unrelated to Pregnancy". The clinician should perform a pelvic exam for further evaluation. The clinician should attempt to follow this AE until resolution (post termination).

Why? The prolonged menses is part of the same bleeding event reported on the previous visit; therefore the term used to described this event needs to be updated to reflect the participant's current bleeding symptoms. Grade this event per the Female Genital Grading table.

10-1.3 Ms. Y reports at her Two-Week Clinic Visit that she had menstrual cramps during her last period that were so painful that she stayed home from work, in bed, for two days. Generally this participant has very mild menstrual symptoms, if any. What would you do?

- Report this event as an AE using the term dysmenorrhea and grade according to the "Dysmenorrhea" row of the Female Genital Grading Table. The Clinician should perform a pelvic exam for further evaluation.

Why? The reported menstrual cramps are a change from this participant's baseline menstrual symptoms. It is important that the clinician evaluates if there is an anatomical reason why the participant is having pain.

Section Appendix 10-1

Scenarios for AE Grading using Female Genital Grading Table for Use in Microbicide Studies

10-1.4 Suppose instead, Ms. Y reports to the Clinic at her Two-Week Clinic Visit and reports that two days ago, she experienced some vaginal spotting after having sex with her partner. What would you do?

- Report this event as an AE of Postcoital Bleeding, and grade according to the "Postcoital Bleeding" row in the Female Genital Grading Table. Clinician should perform a pelvic exam for further evaluation (e.g. anatomical location of bleed).
- If the clinician identifies the anatomical source of bleeding, the adverse event should be reported using the anatomical site (e.g., cervical friability)

Why? Postcoital bleeding is considered unexpected non-menstrual bleeding, and should be considered an AE. The term "metrorrhagia" (intermenstrual bleeding) *should not* be used to describe this AE.

10-1.5 Ms. Z reported at baseline that her usual menstrual cycle is about 29 days and that she usually has 8 menstrual bleeding days per cycle. At her last weekly visit, Ms. X reported that her last menses lasted 9 days. Should this be reported as an AE?

- If the reported length of bleeding is greater than baseline, you must grade according to the "Menorragia" row under "Abnormal Uterine Bleeding Unrelated to Pregnancy" in the Female Genital Grading Table and determine whether an increase in severity has occurred. If there is an increase in severity you would need to report the occurrence of menorrhagia at the higher severity grade as an AE.

Why? Ms. Z should be considered to have menorrhagia as a pre-existing condition (menses lasting longer than 7 days). At baseline you will need to grade the pre-existing menorrhagia based on the guidance provided in the Female Genital Grading Table under "Abnormal Uterine Bleeding Unrelated to Pregnancy" and record the grade on the Baseline Medical History form and Pre-Existing Conditions form. By having this information recorded on the Baseline Medical History form and Pre-Existing Conditions form, you will be able to assess whether or not an AE has occurred and the grade of the AE.

Section Appendix 10-1

Scenarios for AE Grading using Female Genital Grading Table for Use in Microbicide Studies

10-1.6 At her Two-Week Clinic Visit, Ms. P has a positive pregnancy test. She discontinues study gel use per protocol, but she agrees to stay in the study for follow up. At her Three-Week Clinic Visit, she reports genital bleeding. What should you do?

- Take a detailed history and determine whether the bleeding, and possible abortion, was induced or spontaneous.
- Report this AE using clinically appropriate terminology reflecting the cause or source of the bleeding. If this is a spontaneous abortion, use the correct terminology including the term spontaneous. Grade this AE according to the "Complications of Pregnancy" section of the Female Genital Grading Table. The participant should be referred to a qualified clinician for further evaluation, care and treatment.
- If this is an elective abortion (e.g. the patient took an herbal inducement) this would not be an adverse event and should only be reported if the bleeding is unexpected.

Why? The term "metrorrhagia" (intermenstrual bleeding) should not be used in this case because the participant is pregnant, and the bleeding may be associated with complication in pregnancy.

10-1.7 Suppose Ms. W reports at her One-Week Clinic Visit she had a vaginal itching, rash, and vaginal discharge two days before the clinic visit. On the day of the visit, the clinician performs a pelvic exam and notices an area with erythema and another area with edema. What do you do?

- Determine if all these sings and symptoms could be group together as a condition. Since all these symptoms/signs are related, report this event as an AE and grade according to the Female Genital Grading Table under "Composite Signs/Symptom."

Why? Whenever possible and particularly if two or more signs/symptoms are present, you will use a diagnosis for reporting instead of individual categories.

10-1.8 At her Two-Week Clinic visit, Ms. T reports vaginal discharge. During the pelvic exam, a wet prep is collected for Wet Mount testing. When the wet prep slide is read, yeast is observed. What do you do?

- Complete an AE log for Candida or Yeast Vaginitis and grade according to the Genitourinary Infection section of the Female Genital Grading Table. Treat this participant in accordance with current (2006) CDC Sexually Transmitted Diseases Treatment Guidelines, and discontinue this participant from study gel use.

Why? Product is permanently held for this participant because per the MTN 004 protocol, Section 9.4.1, product must be permanently discontinued if the participant has signs or symptoms of STI(s)/RTI(s) requiring treatment according to the judgment of the investigator.