Section 10. Clinical Considerations

This section presents information on the clinical procedures performed in HPTN 059. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 11. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 12. Instructions for completing data collection forms associated with clinical procedures are provided in Section 13.

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

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

- To assess and document participant eligibility for the study at the Screening and Enrollment visits
- To assess and document the participants' baseline medical conditions and symptoms, for comparison with signs, symptoms, and conditions that may be reported during follow-up
- To 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 History

The non-DataFax Baseline Medical History form is a recommended source document for collecting pertinent baseline medical/menstrual history data. For enrolled participants, all baseline conditions identified as ongoing at the Enrollment Visit, prior to randomization also 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 HPTN 059, 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, menorhagia, etc. Document the type and severity of any typical 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 forms, 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.
- 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 judgement — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in local languages to elicit complete and accurate history information from study participants.

10.1.2 Initial Ascertainment of Concomitant Medications

The HPTN 059 protocol requires documentation of all medications taken by study participants beginning at Screening and Enrollment 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 vaginal and rectal

Intravaginal 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, check the box labeled "VAG" on the form.

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 reporting 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.

10.2 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 through study exit (Week 24 Visit/Early Termination for non-CHBV participants and Week 36 Visit/Early Termination for CHBV participants). These procedures also are performed at interim visits when clinically indicated. An interval medical/menstrual history is considered clinically indicated at interim visits if the participant presents for the interim visit complaining of any symptoms since the last visit. An interval history of genital symptoms (via completion of the Follow-up Genital Symptoms form) is clinically indicated if the participant presents for the interim visit complaining of genitourinary 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 the recommended source document for collecting interval medical/menstrual history data.

At the first follow-up visit, retrieve the participant's non-DataFax Baseline Medical History and Pre-Existing Conditions forms for reference. At each subsequent visit, retrieve the participant's Follow-up Medical History 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 it is acceptable to actively inquire about the current status of conditions recorded as ongoing at the prior visit, and then to ask a 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, actively inquire as to whether the participant experienced each of the genitourinary symptoms listed on the form since her last visit.

If a participant reports any genital bleeding event that is outside of her usual bleeding pattern (more frequent, heavier flow), and/or a site clinician observes unexpected genital bleeding without an identifiable source, a Genital Bleeding Assessment form should be completed to determine whether or not the bleeding should be reported as an AE. See Section 10.6.1 of this SSP Manual 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 local languages to elicit complete and accurate follow-up information from study participants.

At the Enrollment, Week 4, 12 and 24 Visits, participants will complete Behavioral and Adherence Assessments prior to the pre-test counseling and clinical portion of the visit (but after the urine pregnancy test). The Behavioral Assessment collects standardized participant reports of various contraceptive methods and vaginal products used.

At the Week 4, 12 and 24 visits, participants will also complete the Acceptability Assessment prior to the clinical portion of the visit (but after the urine pregnancy test). The Acceptability Assessment collects data about the participant's experience with the gel, and their thoughts and opinions about the gel. Clinicians are advised to use the Assessment responses as a basis for probing for updates to record in applicable sections of the Follow-Up Medical History form.

It is acknowledged that detailed clinical probing of the assessment responses may identify discrepancies between the assessment data and the history information recorded by the clinician. For example, a participant might report insertion of an intrauterine device (in error) in her Behavioral Assessment, but then identify that no such procedure took place after more in-depth discussion with the study clinician. In the event that such discrepancies occur, information recorded by the clinician will be considered primary for purposes of monitoring participants' clinical condition and documenting clinical study endpoints. In order to preserve the standardization of behavioral, acceptability and adherence data collection, however, assessment responses should <u>not</u> be amended to correspond with the information recorded by the clinician. Clinicians will explain such discrepancies in notes entered in participant study records whenever possible.

For the Behavioral Assessments, different forms will be used for the coitally dependent and daily use cohorts.

At the Week 24 Visit for non-CHBV participants, and the Week 36 Visit for CHBV Participants, a Study Burden Assessment will be completed. The purpose of this assessment is to find out the participant's thoughts and feelings about her participation in the study, and to elicit any difficulties she experienced as a result of her study participation.

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 provided to the participant by study staff, 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, ask what, if any, medications were also taken. 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 Condition form (as appropriate).

10.3 Physical Exams

A targeted physical exam is required at Screening. This exam should include the assessments listed below

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

Additional assessments may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam.

The non-DataFax Physical Exam form is the recommended source document for recording physical exam findings. For participants who enroll in the study, abnormal physical exam findings identified at Screening also are recorded on the (DataFax) 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 Baseline Medical History form.

10.4 Pelvic/Colposcopic Exams

Pelvic exams are performed in HPTN 059 for purposes of determining eligibility and identifying primary study safety outcomes. As such, they are critical to meeting the study objectives and to ensuring the ongoing safety of study participants. Pelvic exams are performed at Screening, Enrollment, and Week 4, 12 and 24 Visits, per the schedule in protocol Section 5 and Appendix I. Exams also are performed when clinically indicated to evaluate genital symptoms.

At Enrollment and Week 4, 12 and 24 Visits, colposcopy is included as a required component of pelvic exams.

Pelvic/colposcopic exams will be 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 Appendix F of the SSP Manual), 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 HPTN SDMC:

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

10.4.1 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. The size of the speculum will be recorded on the site specific visit checklists, and this will be used to determine the approximate length of participants' vaginas, and the type of speculum that should be used. 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 and cervical 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 smear (vaginal and cervical), cytokine and chemokine testing, quantitative vaginal culture (US only) and GUD testing.

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 Pelvic Exam form. It is recommended that the Pelvic Exam form be used as a source document 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. See Section 10.4.3 for detailed instructions on classifying and documenting exam findings.

Imaging: Digital imaging may be used to document abnormal colposcopic exam findings when clinically appropriate. After obtaining IRB/EC approval of the protocol and associated informed consent forms, study sites may choose to use digital imaging to also document normal findings/conditions at baseline (i.e., at Final Screening/Enrollment).

- Save at least one image of each abnormal finding. Save images before probing or swabbing any findings, and take as many images as needed to capture all abnormal findings. Use appropriate magnification to ensure that all margins are captured in the image.
- Adjust the light intensity to produce the best image possible.
- Instruct the participant to hold her breath during imaging.
- Save all images electronically; back up all media routinely. Label and store printed images in participant study charts. The PTID; the date of the image and the anatomical location of the finding should be recorded either on a label or on the back of the image. *Note the magnification used.*

10.4.2 Detailed Procedural Instructions

Note: *Routine pelvic exams, i.e., those required at protocol-specified timepoints, 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*

routine pelvic exam is required, perform other protocol-specified procedures at the visit and schedule the participant to return for the required 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.

Note: As stated in SSP Section 10.6.2, pelvic exams will be performed to evaluate any participant report of unexpected genital bleeding.

Note: *See Section 6.8 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. 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.
- 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 Pelvic Exam form. Save digital images of abnormal colposcopic findings per Section 10.4.1.

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.

- Assess cervical ectopy during the colposcopic exam.

- Assess for homogenous discharge. Record outcome on the Pelvic Laboratory Results form. Additionally report abnormal vaginal or cervical discharge and/or blood-tinged discharge in item 1 on the Pelvic Exam form.

- Place pH indicator strip (See Section 12.8.1 on pH indicator strip to be used) 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, vaginal Gram smear, and quantitative culture (US only). Collect fluids from the lateral vaginal wall, away from any apparent abnormalities. Collect cervical fluids via (dry) swab for cervical Gram smear, cytokine and chemokine testing. Collect fluids from the cervical canal, away from any apparent abnormalities. Exclude swabbed areas from subsequent examination. Document specimen collection for on the Pelvic Exam form. See Section 12.6 of this manual for detailed wet prep and Gram smear slide preparation and assessment procedures. If wet prep slides are read in-clinic by clinical staff, record results directly onto the Screening Laboratory Results form (at screening), the Enrollment Laboratory Results form (at Enrollment) or the Pelvic Laboratory Results form (at follow-up). If slides are read by lab staff (either in the local laboratory or in a designated in-clinic lab area), record results onto laboratory log sheets or other laboratory source documents and then transcribe the results onto the appropriate case report form.

- If needed, lavage the cervix and vagina as described in Section 10.4.1 and complete naked eye exam.

- 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 – See list of variants of normal in Section 10.4.3 below) on the Pelvic Exam Diagrams form (non DataFax). Further document abnormal findings on the Pelvic Exam 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. Pelvic Exam form. Save images of abnormal colposcopic findings per Section 10.4.1.

Collect Genital Ulcer Swabs: If any genital ulcers are observed at Screening, Enrollment or 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, ulcers in the same cluster may be swabbed with a single swab. Otherwise use a different swab for each ulcer. Document specimen collection on the Pelvic Exam form. See Section 12.6.4 of this manual for further instructions for proper swab handling and storage prior to testing at the HPTN Central Laboratory.

Collect Pap Smear: At the Screening visit a Pap smear is required (per protocol Section 5), unless the participant can provide documentation of a normal result from a Pap test conducted in the 90 days prior to Screening. Collect ecto- and endocervical cytobrush specimens after completing all naked eye and colposcopic tissue examinations. Document specimen collection on the Pelvic Exam 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. Sites must follow site specific SOPs for management of abnormal Pap results.

In the event that Screening specimens collected for Pap smear are not evaluable, the participant should be scheduled for an additional visit (within 56-day Screening window) to retest. A normal Pap smear result is an eligibility criterion for study entry, and thus required by all participants who enroll in the study.

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.

10.4.3 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

Table 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. Requests for free copies of the CD-ROM or booklets of the Photo Atlas can be sent to:

The Thailand MOPH – U.S. CDC Collaboration, DMS 6 Building, 2nd floor, Ministry of Public Health, Tivanon Road, Nonthabur 11000, Thialand
Tel. (66-2) 591-8358
Fax. (66-2) 591-5443

Email. Lbollen@tuc.or.th
Email. pbk@cdc.gov

The Pelvic Exam form is the recommended source document 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.

10.4.4 Definitions

Vaginitis

Vaginitis would specifically include a diagnosis of bacterial vaginosis, candida vaginitis, or trichomoniasis based upon the clinical, as well as symptoms of pruritis for women with yeast.

Cervicitis

Cervicitis will be defined as the presence of either GC or CT by lab testing and/or presence of mucopurulent discharge, or any other signs such as sheets of white blood cells in wet mount or cervical tenderness.

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

Term	Status of Epithelium	Status of Epithelium	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.	

Table 10-1 continued
CONRAD/WHO Terminology for Pelvic Exam Findings

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.

10.5 Amenorrhea Reporting

Amenorrhea is defined by the absence of menstruation, whether primary (a woman who has never menstruated) or secondary (the absence of menses for the equivalent time of the last 3 cycle intervals or 6 months, whichever is shorter). The list of potential causes of amenorrhea is long, ranging from anatomic problems with outflow obstruction to environmental causes of exogenous medication, stress, or malnutrition. It is unlikely that the products used in this Phase II study will, through local or systemic effects, cause amenorrhea. In addition, amenorrhea, as a symptom, is not harmful in itself nor is it thought to increase the transmission of HIV or other pathogens, but amenorrhea and other abnormal menstrual patterns should be evaluated in this trial for acceptability reasons.

The following are clinical scenarios where amenorrhea may occur as a new symptom (i.e. not present at baseline) without the symptom itself needing further reporting as an Adverse Event (AE). It should be noted, that for the purpose of this trial, a positive pregnancy test or use of concomitant medications should be reported as per the protocol. Situations where the symptom amenorrhea is expected and therefore should not need to be reported as an AE are:

- Pregnancy
- Lactation
- Absence of uterus (congenital or surgical)
- Menopause
- Depot Medroxyporgesterone Acetate use
- Hormonal Contraceptive Implant use
- Hormonal Intrauterine Contraceptive use
- Continuous use of combine hormonal contraceptives (oral contraceptives, patches, contraceptive vaginal rings)

The protocol already includes routine pregnancy testing that will identify pregnancy at regularly scheduled and interim study visits. Questions posed during the medical history review would help to identify other potential causes of amenorrhea in the above list. In addition to questions regarding the date of the last menstrual period and the length of the participant's usual menstrual cycle questions on the non-DataFax Baseline and Follow-up Medical History forms regarding gynecologic and contraceptive history could elicit the presence of the remaining potential causes of amenorrhea in the above list (i.e., hysterectomy, menopause, hormonal contraceptive use and dates (of last injection, Implant or IUD

insertion). As with the case of genital bleeding (see the following section 10.5), amenorrhea, which is expected due to one of the above causes, should be noted in source documents.

It is recommended that amenorrhea only be reported as an AE when it is unexpected (i.e. not due to any of the above) or is due to an unknown cause. This would include amenorrhea due to an etiology identified for which a clinical work-up has been completed whether or not it is related to the study product.

10.6 Genital Bleeding Assessment

Genital bleeding other than menstrual bleeding, often referred to as "intermenstrual bleeding" or "IMB" is not an uncommon 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 acceptability.

The HPTN 059 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.

10.6.1 Genital Bleeding Assessment for Pregnant Participants

The remainder of this section 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 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" 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. Any questions related to genital bleeding assessment or AE reporting for pregnant participants should be submitted to the HPTN 059 PSRT.

10.6.2 Participant Reports of Genital Bleeding

As part of the HPTN 059 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 and/or unexpected non-menstrual genital bleeding will be emphasized.

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

10.6.3 Clinician Assessment of Genital Bleeding

Study participants will undergo pelvic exams at Enrollment, Week 4, 12, and 24 Visit, and as clinically indicated. **Pelvic exams also will be performed to evaluate any participant report of unexpected menstrual and/or unexpected non-menstrual genital bleeding**. Pelvic examinations will be performed and documented as described in Section 10.4.

Figures 10-1a and 10-1b outlines 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 13.6) 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 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
- STI or reproductive tract infection (RTI)/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 will also 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. Expected genital bleeding episodes are not required to be assessed using the Genital Bleeding Assessment Form.

For additional information on unexpected Intermenstrual Bleeding, refer to Protocol Appendix II , "Outcomes, Diagnostics, and Follow Up Evaluations".

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 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, all episodes of unexpected genital bleeding which are self-reported by the participant and/or clinically observed with no identifiable source will be documented on the Genital Bleeding Assessment form, as specified in Section 10.6.3 above.

As noted above, a pelvic exam will be performed to evaluate all episodes of participant-reported genital bleeding (and routinely per protocol regardless of participant report). All exam findings will be recorded on the Pelvic Exam Diagrams form (non-DataFax) and all abnormal findings will be recorded on the Follow-up Pelvic Exam form. The Follow-up Pelvic Exam form includes items to specifically document whether blood and/or active bleeding were observed upon exam, regardless of whether genital bleeding was reported by

the participant.

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 five points below, which standardize the terminology that should be used at all sites when reporting AEs involving genital bleeding.

i. **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."

ii. **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 using one of the following AE terms:

- Menorrhagia: prolonged (more than 7 days) or excessive (>80mL) uterine bleeding
- Menometrorrhagia: prolonged uterine bleeding occurring at irregular intervals

Severity grading: AEs reported using the above terms should be graded according to the guide for estimating severity grade on page 3 of the DAIDS Toxicity Table.

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

iv. **Unexpected non-menstrual bleeding** that is associated with an observed abnormal pelvic exam finding should be reported using the term associated with the exam finding. 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 "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 using the following AE term:

- Intermenstrual bleeding (IMB): bleeding of variable amounts occurring between regular menstrual periods

Note: This term will be used to report all types of unexpected non-menstrual bleeding such as metrorrhagia, spotting between menses, ovulation bleeding, vaginal spotting, and breakthrough bleeding. This term also will be used to report blood-tinged discharge and blood observed in the vagina with no identified source.

Severity Grading: AEs reported using the above term should be graded according to the listing for IMB on page 13 of the DAIDS Toxicity Table.

v. **Genital hemorrhage** should be reported using the AE term "hemorrhage" together with terminology indicating the anatomical location of the hemorrhage (i.e., vaginal, cervical, or uterine,). Alternatively, if the location is not known, the term "genital hemorrhage" should be used.

Severity Grading: AEs reported using the above term should be graded according to the listing for hemorrhage on page 6 of the DAIDS Toxicity Table.

Figure 10-1a
Overview of Assessment and Reporting Procedures for Genital Bleeding in HPTN 059 — Beginning with Participant Report of Bleeding

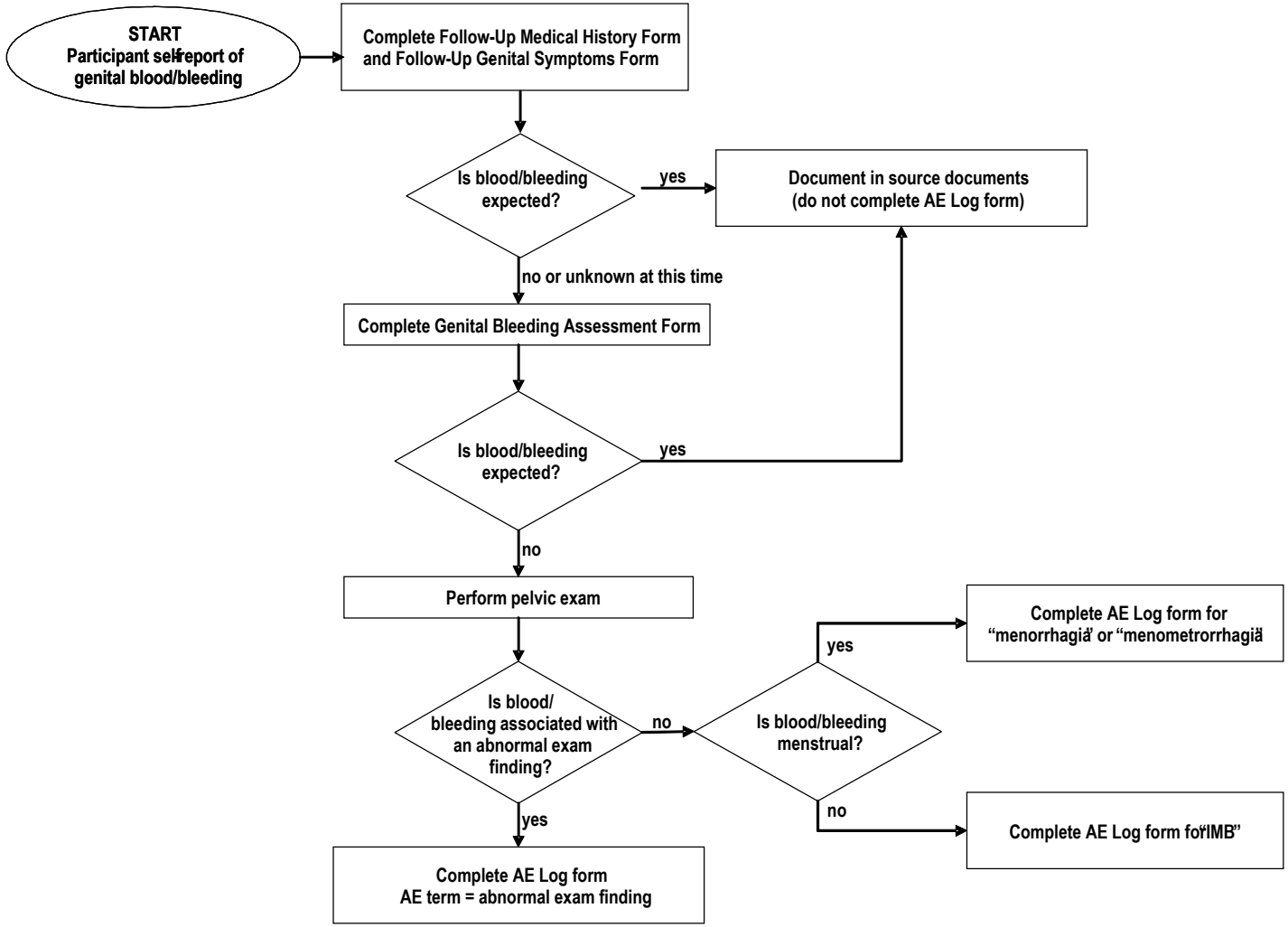
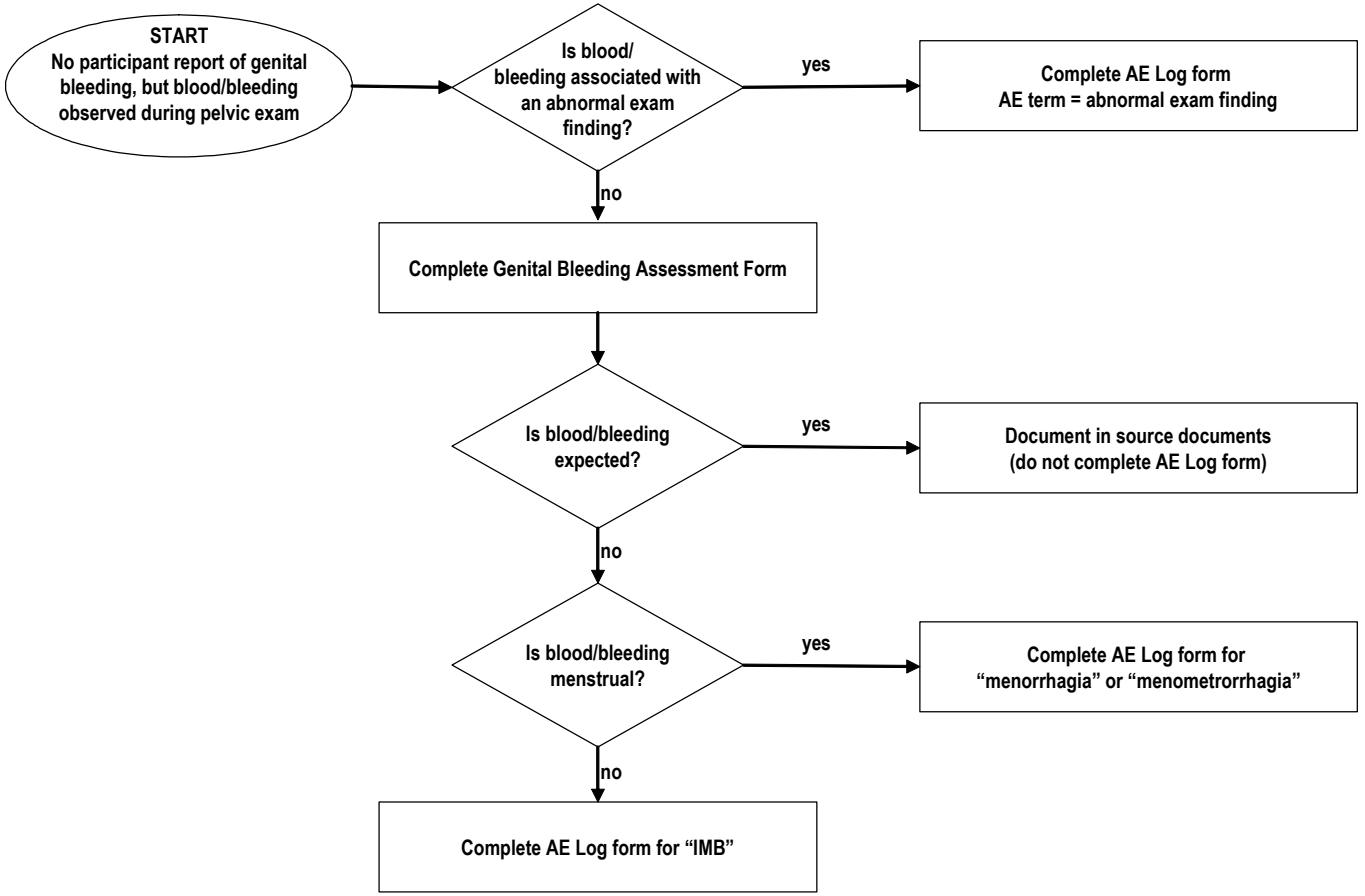


Figure 10-1b
Overview of Assessment and Reporting Procedures for Genital Bleeding in HPTN 059— Beginning with Clinical Observation of Blood/Bleeding



10.7 STI/ RTI Management

Clinical and laboratory evaluations are performed throughout the course of HPTN 059 to diagnose the following STIs/RTIs:

- Bacterial vaginosis
- Candidiasis
- Chlamydia infection
- Genital ulcer disease
- Gonorrhea infection
- HSV-2
- Syphilis infection
- Trichomoniasis

Signs and symptoms commonly associated with the above-listed infections are presented in Figure 10-4. 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.

Table 10-2
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.

Table 10-2
Signs and Symptoms Commonly Associated with STIs/RTIs

STI/RTI	Common Signs and Symptoms
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.

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 the CDC Sexually Transmitted Diseases Treatment Guidelines 2002

Should updated guidelines be issued by 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.*

See the 2002 CDC treatment guidelines in Appendix E 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.

STI/RTI tests of cure are not required in HPTN 059; 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, a four-fold decrease in titre is not required prior to enrollment. Assuming the participant is otherwise eligible for the study, enrollment may proceed following treatment and resolution of any symptoms, (see also Section 10.6.2 and Section Appendix 4-1). For enrolled participants, if syphilis is diagnosed during follow-up, and the RPR titre does not decrease four-fold within three months of treatment, treatment should be repeated.

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.

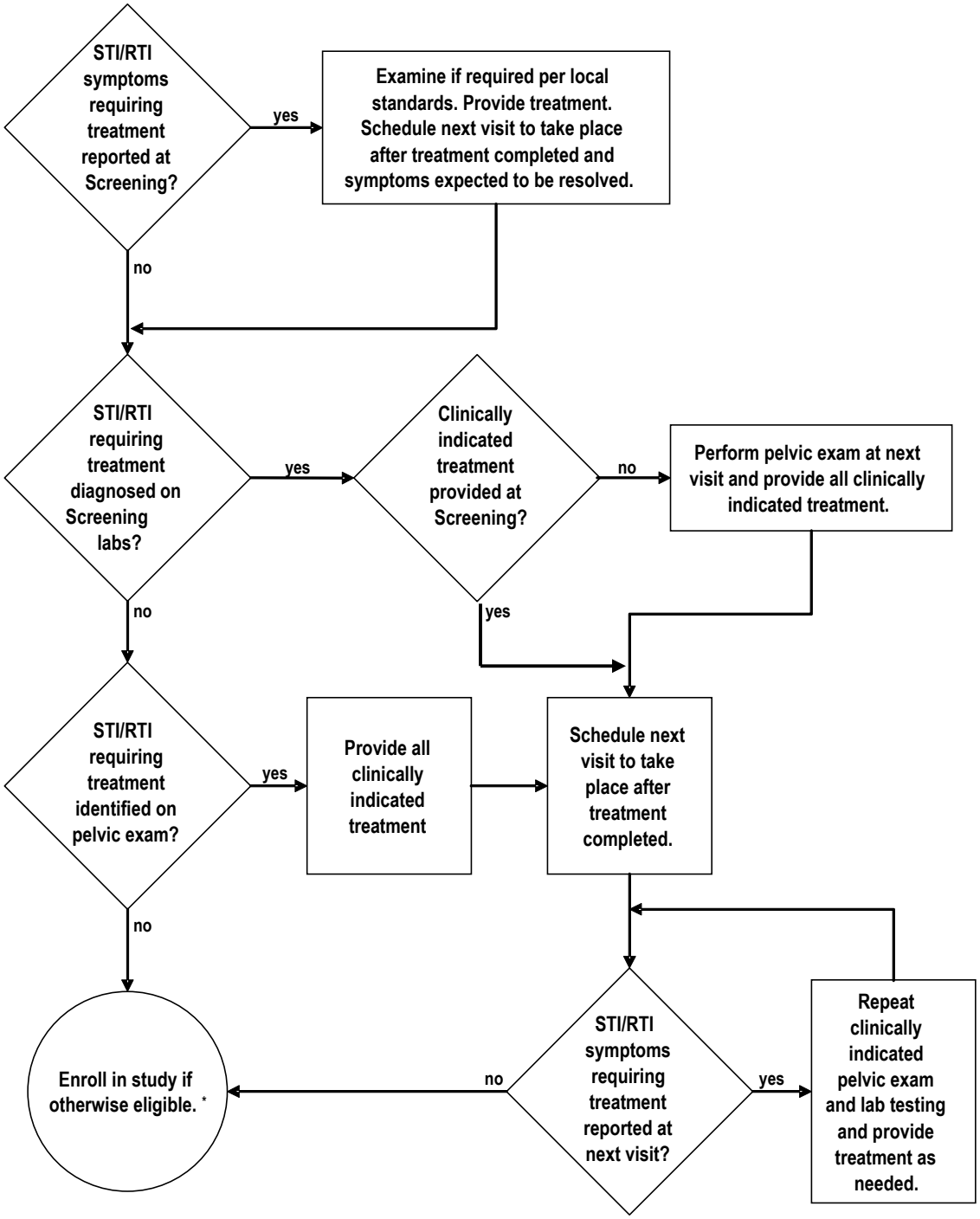
- If protocol-specified STI testing was performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for Pap smear, the results of the protocol-specified testing overrule STI-related findings noted on the Pap smear result report. Provide treatment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

10.7.2 Screening and Enrollment Considerations

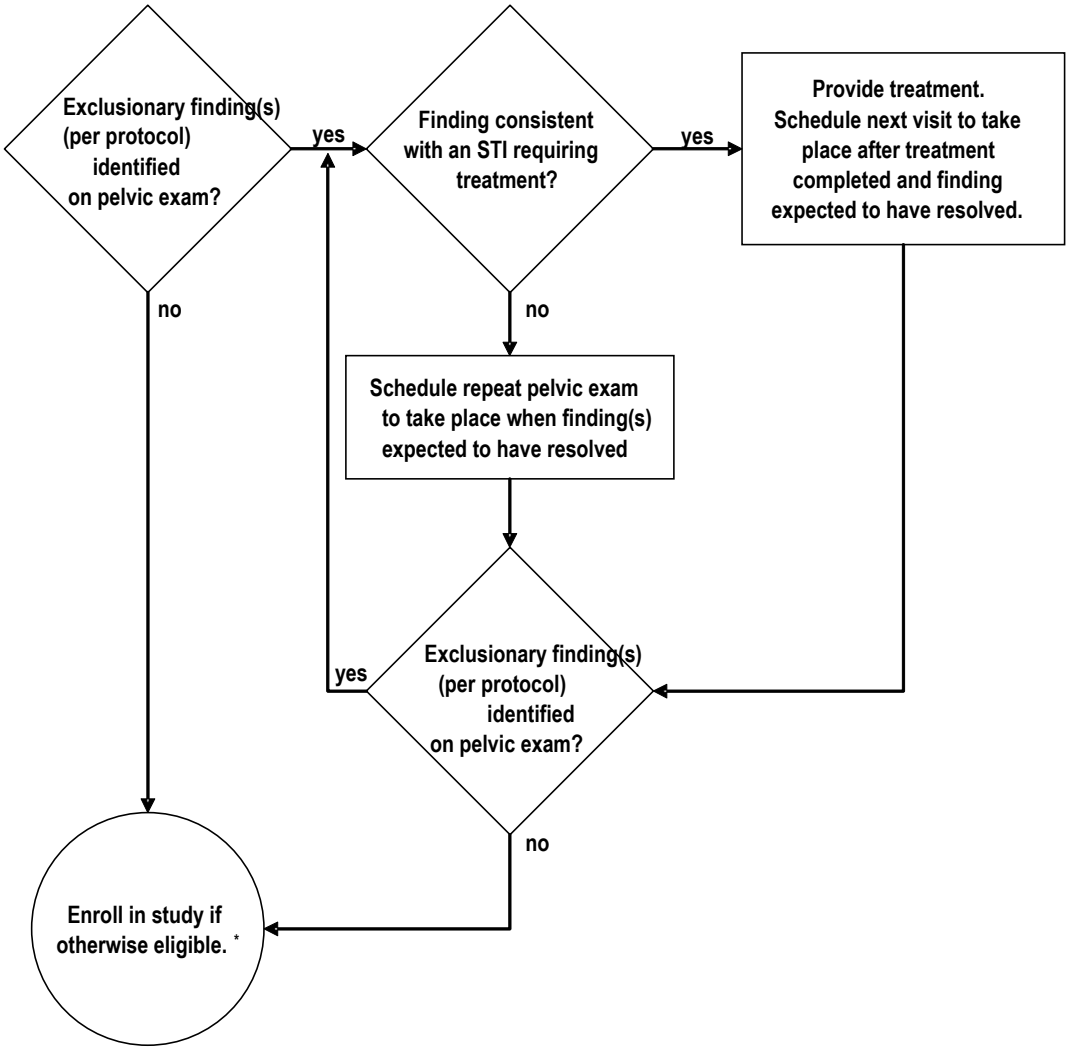
Potential study participants diagnosed at Screening and/or Enrollment with an STI/RTI requiring treatment per CDC guidelines — other than asymptomatic bacterial vaginosis and asymptomatic candidiasis — and/or who have a Screening or Enrollment pelvic exam finding involving deep epithelial disruption, severe erythema, and/or severe edema (as defined in protocol Appendix II) may be enrolled in the study after completing treatment (if applicable) and all symptoms have resolved. All required treatment must be completed and all exclusionary conditions resolved within 56 days of beginning the screening process (see also Section 4 of this manual) before study enrollment. Flow charts depicting the sequence of events required prior to enrollment are presented in Figures 10-2 and 10-3. Summary information also is provided in Table 10-4. Further detailed guidance is provided on the visit checklists provided in Section 7 of this manual. The screening and enrollment scenarios in Appendix 4-1 also provide examples of STI/RTI treatment and management vis-à-vis enrollment in the study.

Figure 10-2
STI/RTI Diagnosis and Treatment Algorithm for Screening and Enrollment in HPTN 059



*Enrollment must take place within 56 days of providing informed consent for screening. Otherwise all screening procedures must be repeated.

Figure 10-3
Pelvic Exam finding Management Algorithm for Screening and Enrollment in HPTN 059



*Enrollment must take place within 56 days of providing informed consent for screening. Otherwise all screening procedures must be repeated

Table 10-3
STI/RTI Management Summary for Screening and Enrollment in HPTN 059

STI/RTI symptoms reported at Screening	Evaluate clinically if required per local standard of care. Treat per CDC guidelines if applicable (single dose therapy is always preferred if available as standard therapy). Schedule next visit (Final Screening/Enrollment) to occur after treatment is expected to be completed, symptoms are expected to be resolved, and Screening lab test results are expected to be available.
STI/RTI symptoms reported at Final Screening	Evaluate clinically during protocol-specified pelvic exam, taking into account Screening STI test results and Screening and Final Screening/Enrollment wet prep results. Treat per CDC guidelines (single dose therapy is always preferred if available as standard therapy) based on all available test results and exam findings. This visit will be considered part of Screening procedures Schedule next visit (Enrollment) to occur after treatment is expected to be completed, symptoms are expected to be resolved, lab test results (if any) from current visit are expected to be available. All enrollment procedures should be conducted at this next visit, if participant is otherwise eligible.
Lab-based STI/RTI diagnosis at Screening or Final Screening, no symptoms reported (excluding asymptomatic BV and candidiasis)	Treat per CDC guidelines (single dose therapy is always preferred if available as standard therapy). If single dose treatment is provided at Final Screening, and participant is otherwise eligible for the study, proceed with enrollment. If single dose treatment is not provided, schedule next visit (Enrollment) to occur after treatment is expected to be completed. All enrollment procedures should be conducted at this next visit, if participant is otherwise eligible.

10.8 Urinary Tract Infections

Dipstick urinalyses for leukocytes and nitrites will be performed when clinically indicated to screen for urinary tract infection (UTI), both during the screening visit and during follow-up. See Section 12.4.3 for details on the required laboratory procedures. Record results on applicable testing log sheets and then transcribe results onto the (Data Fax) STI Laboratory results case report 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

For participants who test positive for either leukocytes or nitrites, a urine microscopy and culture are required. Lab results should be transcribed onto the STI Laboratory Results form, and then filed in the participant chart. 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

See also protocol Section 4.6. 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 Investigator of Record (IoR) 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. Other product use management decisions and actions are undertaken, under the direction of the IoR, in consultation with the HPTN 059 Protocol Safety Review Team (PSRT). Further specification of these two types of decisions and actions is provided below.

10.9.1 Circumstances When Product Use Must Be Discontinued

Per protocol, participants at all study sites must be discontinued from product use if they:

- Have a pelvic exam finding involving deep epithelial disruption (ulceration). Product use must be discontinued until evaluated
- 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. Product use must be discontinued until further evaluated
- Have vaginitis noted on pelvic exam. With the exception of asymptomatic candida vaginitis and asymptomatic bacterial vaginosis, product use must be discontinued until further evaluated
- Have Intermenstrual bleeding/spotting (excludes endometrial bleeding with no other source). Product use must be discontinued until clinical evaluation
- Become pregnant
- Experience an adverse event (AE) that meets criteria for expedited reporting to DAIDS (see Section 11 of this manual) that is judged by the IoR or designee to be probably or definitely related to product use (study gel and/or applicator). Product use must be discontinued until further evaluated
- Become infected with HIV

Participants who become pregnant during the study will discontinue gel use while they are pregnant; however they will continue with their follow up visits. Participants who become pregnant during the course of the study will discontinue study gel use while they are pregnant, but will not routinely be withdrawn from the study. Rather, if the participant does not withdraw her consent, every effort will be made to complete the safety evaluations according to Appendix I, and/or as specified in Appendix II, and will follow the modified

study procedures described in Section 5.9.2, until their study exit date or their pregnancy outcome is ascertained, whichever is longer.

Participants who become pregnant may resume product use after giving birth or pregnancy termination, as evidenced by a negative pregnancy test and normal pelvic exam performed by study staff. A normal post partum or post-termination pelvic exam should include healing of any delivery or procedure related trauma (e.g. lacerations) and cessation of post-partum bleeding.

Participants who discontinue product use due to a probably or definitely related AE that meets criteria for expedited reporting (EAE) may resume product use after the AE resolves (returns to baseline) or stabilizes at a non-reportable severity grade, at the discretion of the clinician as per the protocol, and in consultation with the PSRT.

Participants who become infected with HIV will discontinue gel use, but will be asked to continue study follow-up visits.

Participants found to have a high-grade squamous intraepithelial lesion (H-SIL) or more severe abnormality when the Pap smear is performed at screening may be enrolled in the study at the clinician's discretion after treatment and resolution of the abnormality. For participants at sites where local standards of care require clinical colposcopy and biopsy to assess lower grade abnormalities, the participant will be enrolled after the three-week period beginning one week before the required procedure and ending two weeks after the required procedure (assuming no further intervention or treatment is needed).

10.9.2 Circumstances When Product Use May Be Discontinued

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

- A participant has a pelvic exam finding of petechial hemorrhage, ecchymosis, superficial epithelial disruption (abrasion/peeling) and/or suspected cervicitis that has significantly worsened after reevaluation (as observed on exam 48-72 hours after finding first identified). Product use may be continued at clinician's discretion

- A participant has experienced localized erythema or edema (area of less than 50% of vulvar surface or combined vaginal and cervical surface that has significantly worsened after reevaluation (as observed on exam 5-7 days after finding first identified). Product use may be continued at clinician's discretion

- The participant is unable or unwilling to comply with required study procedures *(Note: participant will be asked to continue to follow-up in the study)*

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

Participants who discontinue product use due to a possibly or probably not related EAE, a pelvic exam finding (i.e., deep epithelial disruption, petechial hemorrhage), erythema or edema, vaginitis, cervicitis and/or intermenstrual bleeding/spotting may resume product use after evaluation by the site investigator or designee per protocol Appendix II. For decisions regarding permanent discontinuation of study gel, the IoR or designee should submit a query to the HPTN 059 Safety Physicians using the HPTN 059 PSRT query form (see Section Appendix 10-1). The PSRT will consider the query and provide a written response via email within three business days.

While waiting for a response from the PSRT, the IoR may instruct the participant to discontinue product use, or not, based on his/her clinical judgement and prioritizing the safety and well-being of the participant. When the IoR chooses to discontinue product use while waiting for the PSRT response, arrangements should be made to re-contact the participant as soon as possible after the PSRT response is received, if necessary, to communicate any modified product use instructions received from the PSRT.

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 HPTN 059 Study Product Request Slip, as described in Section 6.6.2, and a Product Hold/Discontinuation case report form should be completed and faxed to the HPTN SDMC, as described in Section 13.6.

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 tubes of gel remaining in her possession should be collected from her as soon as possible and returned to the pharmacy on the day of collection. Similarly, for HIV-infected participants, any unused tubes of gel remaining in the participant's possession should be collected as soon as possible after infection is confirmed per the algorithm in protocol Appendix III and returned to the pharmacy on the day of collection.

It is not necessary to collect remaining tubes of gel from participants for whom gel use is temporarily held for less than two weeks. However, gel 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.

10.10 Pregnancy Management

Please refer to the Section 6.8 of this manual for procedural instructions for management of participant positive pregnancy tests that may occur during follow-up.

Section Appendix 10-1
HPTN 059 Protocol Safety Review Team Query Form, Page 1 of 2

Instructions: Email completed form to brynah@uic.edu **and** nconnolly@mail.magee.edu . IMPORTANT: Complete all required fields so the PSRT has all information needed to respond to your query.

Site: **Query Date (dd-MMM-yy):**
Completed by: **Email address:**

PTID: **Participant Age** (in years):
Enrollment Date (dd-MMM-yy):

Reason for query:
- ☐ Product use consultation:
  - ☐ Should use of study gel be temporarily discontinued?
  - ☐ Should use of study gel be permanently discontinued?
  - ☐ Should use of study gel be resumed?
- ☐ Request for consultation on AE management
- ☐ Request to withdraw participant from the study
- ☐ Request to unblind participant's gel assignment
- ☐ Other, specify:

Is this query a request for the PSRT to consult on an adverse event (AE)?
☐ Yes → continue completing this page
☐ No → skip to Comments on page 2

Primary AE of concern:

AE onset date (dd-MMM-yy): **AE severity grade at onset:**

Relatedness to study gel:
☐ Definitely related
☐ Probably related
☐ Possibly related
☐ Probably not related
☐ Definitely not related

Current study gel administration:
☐ No change
☐ On hold
☐ Permanently discontinued
☐ Not applicable

Has this AE been reported on a SCHARP AE Log form?
☐ Yes
☐ No

Has this AE been reported as an EAE?
☐ Yes
☐ No

Has this AE been assessed more than once?
☐ Yes
☐ No → skip to Comments on page 2

Date of most recent assessment (dd-MMM-yy):

Status of AE at most recent assessment:
☐ Continuing, stabilized (severity grade unchanged)
☐ Continuing, improving → severity grade decreased to
☐ Continuing, worsening → severity grade increased to
☐ Resolved

Comments: Provide additional details relevant to this query. If gel use has been held, include date of last reported gel application prior to the hold (per participant report).

End of Form for Site Staff. Email completed form to the HPTN 059 Protocol Safety Physicians (brynah@uic.edu **and** nconnolly@mail.magee.edu). If an email response is not received from the PSRT within 3 business days, re-contact the Protocol Safety Physicians and/or HPTN CORE Protocol Specialist (ecyrus@fhi.org) for assistance.

FOR PSRT USE ONLY — PROVIDE RESPONSE TO QUERY HERE

PSRT Responding Member:
PSRT Response Date (dd-MMM-yy):

Query Outcome:
☐ Approved
☐ Not approved
☐ Not applicable

PSRT Comments: