

Section 10. Clinical Considerations

This section presents information on the clinical procedures performed in MTN 002. 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 History and Ascertainment of Concomitant Medications

A focused baseline medical history is obtained from potential study participants at the Screening and Enrollment Visit. Medications used by the participant also are ascertained and documented at this time. Any updated information is obtained at all follow-up visits. The purpose for obtaining this information during screening and enrollment is to:

- Assess and document participant eligibility for the study
- Assess and document the participants' baseline medical conditions 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 product during the course of the study

10.1.1 Focused Baseline Medical History

The site is encouraged to collect pertinent baseline medical history data (including history of genital symptoms) in their source documentation. 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.

When obtaining a focused baseline medical history for MTN 002, 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 pregnant and probe for the most accurate information available on the participant's current health and pregnancy vis-à-vis the reported history. Several additional guidelines are presented below:

- Review the participant's prenatal record, ultrasound reports and, if indicated, her inpatient chart.
- Record symptoms, illnesses, allergies, and surgeries.
- Record both chronic and acute conditions, as well as both ongoing and resolved conditions.
- Record the number, date, and outcome of each of the participant's prior pregnancies, as well as any gynecologic and obstetrical procedures/surgeries.

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

Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing to elicit complete and accurate history information from study participants.

10.1.2 Initial Ascertainment of Concomitant Medications

The MTN 002 protocol requires documentation of all medications taken by study participants beginning at the Screening and Enrollment Visit and continuing throughout follow-up. Note that for all medications taken up until 24 hours following the administration of study product, the protocol requires that the time of administration be recorded for each medication.

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 intravenous, 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.

It is recommended that study clinicians ascertain participants’ baseline medication information in the context of conducting the baseline medical history. In addition to asking open-ended questions to elicit participant report of current medications, use the information obtained in the medical 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 participant’s baseline medical history information and the Pre-existing Conditions form as appropriate.

Pre-existing Conditions

As noted above, a key purpose of conducting the baseline medical history — as well as the targeted physical and pelvic exam at the Screening and Enrollment visit — is to document participants' baseline medical conditions for comparison with signs, symptoms, and conditions that may be identified or reported at subsequent scheduled or interim study visits. For MTN 002, 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 ongoing conditions observed and/or reported at the Screening and Enrollment Visit should be reported on the Pre-existing Conditions form. This case report form is completed, based on all other screening and enrollment source documents, including the baseline medical history (present in source documents/chart notes), Targeted Physical Exam form, 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 enrollment in the study and are therefore not considered AEs. However, new conditions identified during follow-up that were not present at the time of enrollment, 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 History and Updating of Concomitant Medications

For enrolled participants, an interval medical history and update of concomitant medications are obtained at the Gel Administration Visit. Updates on concomitant medications are also obtained at the 24 Hour Evaluation Visit and the Two Week Phone Call. These procedures are performed at interim visits when clinically indicated. The purpose of these procedures is to determine whether participants have experienced any new illnesses, unexpected symptoms, etc., since the last study visit.

10.2.1 Interval Medical History

At the Gel Administration Visit, retrieve the participant's source documentation with medical history and Pre-existing Conditions forms for reference. When completing the interval history, it is not necessary to actively review/inquire about every body system; 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.

See Section 10.5 below for more information on assessing participant reports of genital bleeding.

Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing to elicit complete and accurate follow-up information from study participants.

10.2.2 Updating of Concomitant Medications Information

At each visit in which concomitant medications information 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 history information, add the condition to her source documentation and Pre-existing Conditions form (if present at enrollment).

Note that for this protocol, the Concomitant Medications Log form includes a place to record the time of administration, which is required for all medications taken up until 24 hours following administration of study gel.

10.3 Targeted Physical Exams

An assessment of vital signs and an abdominal exam are required at the Screening and Enrollment visit, Gel Administration visit, any unscheduled visit and at the 24 hour evaluation visit if indicated. The site clinician 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 targeted physical exam components. Vital signs may be transcribed from the participant's chart if they were taken in the past hour.

Vital signs:

- Oral temperature
- Blood pressure
- Pulse

Clinical assessments of:

- General appearance
- Abdomen
- Other components as indicated by participant symptoms

The Targeted 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 Screening and 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 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 participant's source documentation, and the Pre-existing Conditions form as well, since the condition was present at the time of enrollment.

10.4 Pelvic Exams

Pelvic exams are performed in MTN 002 for purposes of determining eligibility and identifying 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 the Screening and Enrollment Visit, Gel Administration Visit, and if indicated at the 24-Hour Evaluation Visit and unscheduled visits, per protocol Section 7.

Pelvic 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. Pelvic exam procedures must be performed in the order shown on the exam checklist in Section 7 of this manual. When additional exams are performed to assess genital symptoms, only clinically indicated procedures should be performed. As indicated in greater detail below, all exam findings are reported on the Pelvic Exam Diagrams form. Additionally, any abnormal findings are transcribed on to the Pelvic Exam (DataFax) form.

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

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. 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 type and size of speculum and the direction of speculum insertion 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.

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

Documentation of Findings: Document all exam findings — both normal and abnormal — on the Pelvic Exam Diagrams form. Transcribe abnormal findings only on the appropriate Pelvic Exam form case report form. Supplemental information may be recorded on the Pelvic Exam Diagrams form, in chart notes, and/or on other source documents.

10.4.2 Detailed Procedural Instructions

Prior to the Exam: Prepare all required equipment, supplies, and paperwork. Verify that all equipment is in good working order. 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.
- 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.
- Assess for abnormal cervical discharge. Record outcome on the Pelvic Exam Diagrams and on the appropriate pelvic exam form.

- Note all findings (variants of normal and abnormal) on the 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.

Collect Vaginal Sample:

- Collect vaginal fluids via (dry) swab for Trichomonas culture, as required by the visit. Collect fluids from the lateral vaginal wall, away from any apparent abnormalities. Document specimen collection for Trichomonas culture on the appropriate pelvic exam checklist. See Section 12 of this manual for detailed culture preparation and assessment procedures.

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 appropriate pelvic exam checklist. See Section 12 of this manual for further instructions for proper swab handling and storage prior to testing at the MTN Network Laboratory.

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

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 Pelvic Exam Diagrams form is the recommended source documents for recording relevant descriptors and details of abnormal findings; however supplemental information may be recorded on the Pelvic Exam 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.

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.

10.5 Genital Bleeding Assessment

If a 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 unexpected genital bleeding as an AE, clinically appropriate terminology should be used to reflect the cause or source of the bleeding (e.g., "threatened abortion"), and the bleeding itself should be graded according to the "Second/third trimester bleeding", or "Postpartum hemorrhage" row of the Female Genital Toxicity Table as appropriate. Any questions related to genital bleeding assessment or AE reporting for participants should be submitted to the MTN 002 PSRT as described in Section 11.

10.5.1 Participant Reports of Genital Bleeding

As described in Section 10.2, at the Gel Administration Visit, clinicians will obtain interval medical history information from participants. Any reports by participants of genital bleeding will be recorded on baseline and/or interval medical history documents.

10.5.2 Clinician Assessment of Genital Bleeding

Study participants will undergo pelvic exams at the Screening and Enrollment Visit, Gel Administration Visit and if indicated at the 24-Hour Evaluation Visit. Pelvic examinations will be performed and documented as described in Section 10.4.

Reports of genital bleeding should be assessed for whether the bleeding may be related to product use, or whether it may be more likely attributable to another cause. These factors include:

- Complications related to pregnancy
- 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*. Expectedness will be determined based on the participant's baseline medical history (e.g., whether she reports genital bleeding as a pre-existing condition). Lochia 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.

10.5.3 Documentation of Genital Bleeding

Any reports by participants of genital bleeding will be recorded on baseline and/or interval medical history documents. All clinically observed genital blood/bleeding will be documented on the Pelvic Exam Diagrams form and the Pelvic Exam form.

All episodes of unexpected 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.

- Expected genital bleeding should not be reported as an AE.
- Unexpected complications of pregnancy should be reported as an AE according to the Complications of Pregnancy section in the Female Genital Toxicity Table.
- Unexpected genital 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.
- 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 hemorrhage row in the Toxicity 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.

10.6 STI/RTI Management

Clinical and laboratory evaluations are performed at the Screening and Enrollment visit for MTN 002 to diagnose the following sexually transmitted infections and other reproductive tract infections (STIs/RTIs):

- Chlamydia infection
- Gonorrhea infection
- Trichomoniasis

If indicated, the following STIs/RTIs also will be evaluated:

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

- Syphilis infection

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.
Chancroid	The combination of painful ulcer and tender inguinal adenopathy, symptoms occurring in one third patients, suggests a diagnosis of chancroid; 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.

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

10.6.1 STI/RTI Treatment

STIs/RTIs will be treated in accordance with current 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.

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.

CDC Guidelines (2006) can be found at www.cdc.gov/STD/treatment/.

STI/RTI tests of cure are not required in MTN 002; 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. If the participant is otherwise eligible, she may be enrolled after completing treatment and all symptoms have resolved. Please contact the MTN NL with any questions related to testing to confirm treatment effectiveness and/or interpretation of unusual syphilis test results.

10.6.2 Screening and Enrollment Considerations

Potential study participants diagnosed during screening with an STI/RTI per CDC guidelines via laboratory tests will be excluded from enrollment. The only exception to this is women with clinical evidence or laboratory evidence of BV or vulvovaginal candidiasis but who are asymptomatic. If the participant is otherwise eligible, she may be enrolled after completing treatment and all symptoms have resolved.

10.6.3 Adverse Event Reporting Considerations

Per the MTN 002 eligibility criteria, no participant may enter the study with an active STI/RTI diagnosed per CDC guidelines via laboratory tests. 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 002 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 Toxicity 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 enrollment, the infection is considered a pre-existing condition: report on the Pre-existing Conditions form.
- For HPV, genital warts present before enrollment are considered a pre-existing condition: report on the Pre-existing Conditions form.
- Any outbreaks that occur after enrollment are considered AEs, regardless of whether the viral infection was pre-existing before enrollment: report on an Adverse Experience Log form.

10.7 Urinary Tract Infections

Dipstick urinalyses will be performed at unscheduled visits when clinically indicated, to diagnose urinary tract infections (UTI). See Section 12 for details on the required laboratory procedures.

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. The sensitivity test results should be documented in the participant's chart notes. Once a diagnosis has been made, treatment will be provided per site standards of care and applicable site standard operating procedures (SOPs).

10.8 Product Use Management

For this study, in the event that a participant experiences an expedited adverse event that is judged to be definitely, probably, possibly, or probably not related to the study gel, product exposure will be minimized to the extent possible. If clinically appropriate, a physician may conduct a cervicovaginal lavage to minimize exposure. The suspected toxicity will be clinically managed according to the site SOPs. Product use management decisions and actions are undertaken, under the direction of the IoR/PI, as described in Section 11.

10.8.1 Circumstances In Which Study Product May Be Withheld:

- Request by participant to not receive study product
- Decision by the IoR/PI to protect the participant's safety and/or if the participant is unable or unwilling to comply with study procedures

10.8.2 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.