

Section 7. Clinical Considerations

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7. Introduction

This section presents information on clinical procedures performed in MTN-035. The Schedule of Study Visits and Evaluations in Appendix I of the protocol indicates when specific clinical and laboratory assessments are to take place. The Investigator of Record (IoR) or designee should perform symptom-directed examinations at his/her discretion any time during any visit if s/he determines it to be clinically necessary, particularly if there are any ongoing medical or mental health conditions which may require follow-up. The participant’s research record should include documentation of these procedures.

Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in SSP Section 9 (Laboratory Considerations). Instructions for completing data collection forms associated with clinical procedures are provided in SSP Section 12 (Data Collection).

7.1 Baseline Medical History

A participant’s baseline medical and menstrual (if participant can get pregnant) history is initially collected and documented at Screening and then actively reviewed and updated, as necessary, at Enrollment. The purpose of obtaining this information is to:

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

In order to obtain a complete, accurate, and relevant participant self-reported medical and menstrual (if participant can get pregnant) history, it will be necessary to ask the participant about significant past medical conditions as well as any current conditions.

It is recommended that sites use the Baseline Medical History Guide (available on the MTN-035 web page under Study Implementation Materials) in conjunction with the Medical History Log CRF and/or chart notes to guide and document medical history taking. The Medical History Log CRF should be completed based on all Screening source documents including, but not limited to, the Physical Exam CRF, Anorectal Exam CRF, STI Test Result CRF, site-specific lab reports/testing logs and, if applicable, the Genital Exam CRF, Pelvic Exam CRF and Pelvic Exam Diagrams (non-Rave form). Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach to elicit, using probing questions, complete and accurate information from the participant. This is especially important regarding details about severity and frequency of baseline medical conditions.

Details of all relevant conditions identified during the baseline medical history review should be recorded on the Medical History Log CRF. Baseline medical conditions are a subset of a participant's medical history and consist of all ongoing and/or relevant medical conditions, problems, signs, symptoms and abnormal findings that are observed and/or reported at enrollment or before a potential participant is enrolled (randomized). Relevant conditions include (but are not limited to): hospitalizations, surgeries, allergies, conditions requiring prescription or chronic medication (lasting more than two weeks), and any condition(s) currently experienced by the participant. The clinician should record as much information as possible about the severity and frequency of any baseline medical condition in the description field on the Medical History Log CRF to best describe the condition at the time the participant enters the study. In addition to participant-reported conditions, the following should be recorded on the Medical History Log CRF:

- Medically-relevant physical exam abnormalities
- Rectal and if applicable, genital and pelvic exam abnormal findings
- Any identified STIs

Generally, it is not expected that conditions less than grade 1 would be included on the Medical History Log CRF, unless determined to be relevant by the site clinician.

The baseline medical history should explore in detail any medical conditions or medications that are deemed exclusionary for this study.

At Enrollment, a participant's history should be reviewed and updated as needed. Refer to protocol sections 5.2 and 5.3 for a complete listing of study inclusion and exclusion criteria. Information documented on the Medical History Log CRF at Screening must be actively reviewed and updated at Enrollment, especially for those conditions that were ongoing at Screening. This includes a review and update of the condition's description and severity grade. Make sure the "*Is the condition ongoing?*" field is completed/updated for each entry prior to final eligibility confirmation.

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

Chronic Conditions: Chronic conditions should be documented as 'ongoing' at enrollment ("*Is the condition ongoing?*" should be selected as "Yes"), even if the participant is not currently experiencing an acute event (e.g. intermittent headaches). For severity grading, the highest

severity experienced for the condition should be used. In the ‘Description of medical history condition/event’ item, note the typical severity for outbreaks/acute episodes of the condition, and whether the condition is currently being experienced by the participant, or historical. When assessing chronic conditions, it is important to note what, if any, medications a participant may take for reported chronic condition during study participation may result in product discontinuation. For example, if a participant suffers from chronic asthma and uses an anti-inflammatory medication or an immunomodulatory to control his/her condition, site staff are asked to use their discretion with evaluating the eligibility of this participant.

Bleeding Events (for participants that can get pregnant): Note that any menorrhagia, metrorrhagia, or menometrorrhagia events ongoing at the time of randomization should be selected as “not gradable” on the Medical History Log CRF. This is because the Female Genital Grading Table (FGGT) grades these bleeding events relative to each participant’s baseline bleeding pattern. In the “Description of medical condition/event” field, include text similar to what is in the FGGT row to describe the severity and frequency of the condition, and whether it is attributed to a participant’s current contraceptive method. Any past resolved (not ongoing at the time of randomization) menorrhagia, metrorrhagia, or menometrorrhagia events documented on the Medical History Log CRF should be assigned a grade from 1-4, per the FGGT. Infrequent bleeding at baseline should also be captured, using the terms “missed menses”, “oligomenorrhea” or “amnenorrhea,” as appropriate. If infrequent bleeding is explained by contraceptive use, note this in the description field and select ‘not gradable’. If infrequent bleeding is unexplained, assign a severity grade from 1-2, per the FGGT.

Allergic Reactions: If a participant reports having a history of anaphylactic reactions (such as difficulty breathing or severe hives after eating peanuts), even if it has happened only once before, it is still important for the site clinician to document these events as a baseline condition on the Medical History Log CRF. Per the “Acute Allergic Reaction” row of the [DAIDS Toxicity Table for Grading the Severity of Adult and Pediatric Adverse Events](#), an acute anaphylactic event is considered a severity grade 4 as it is by definition a life-threatening reaction. Record the condition/event as “allergic reaction to peanuts” and note symptoms (e.g., “throat swelling” or “shortness of breath”) in the “Description of medical condition/event” field. At Enrollment, select “yes” to the question, “Is the condition ongoing?” and check “no” for the question “Is condition/event gradable?”, as the participant was not experiencing an anaphylaxis event at the time of enrollment/randomization. An AE submission for an anaphylactic reaction is required if this same event occurs after enrollment or during study follow-up. Any acute allergic reaction less than a grade 4 should be documented as a chronic condition.

7.1.1 Follow-up Medical History

It is necessary to update the participant’s medical history at all follow-up visits to determine whether previously reported conditions remain ongoing and whether new symptoms, illnesses, conditions, etc. have occurred since the last medical history was performed. A history should also be performed at interim visits when a participant complains of symptoms or when the purpose of the visit is to re-assess previously-identified AEs. Any symptoms reported by the participant should be further probed and evaluated. Study clinicians should follow up on any ongoing baseline conditions as well as any previously reported adverse events that are continuing.

One purpose of the participant-reported follow-up history is to determine whether previously-documented conditions have changed in severity or frequency. A second purpose is to determine whether new symptoms, illnesses, conditions, etc., have occurred since the medical history was last assessed. The Medical History Log CRF, chart notes or a site-specific tool, if desired, may serve as the source document. All newly-identified participant-reported symptoms and conditions will be considered AEs and documented on the AE Log CRF and other source documents.

For purposes of this study, a “newly-identified” condition is defined as one of the following, referenced against the Medical History Log CRF:

- not present at baseline (enrollment);
- ongoing at baseline but has increased in severity or frequency during follow-up (includes ongoing baseline conditions or AEs that increase in severity or frequency during follow-up);
- ongoing at baseline, resolves during follow-up, and then re-occurs (excludes chronic condition)

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

As an example, follow-up interim history taking could be approached as follows:

- Asking general questions about current health and medications (e.g. How are you feeling today? Any current symptoms or issues since your last visit? Have you been to your doctor or hospital outside the study clinic since the last time we spoke? Changes to any medications you are currently taking?)
- Asking targeted questions about ongoing baseline medical conditions and previously reported AEs (e.g. At your last visit you reported X was ongoing, how are you feeling now? You reported that you occasionally experience X, have you had any recent episodes?)

If, during follow-up, a baseline medical condition resolves or increases in severity or frequency, this should not be updated on the Medical History Log CRF.

- If the condition increases in severity or frequency from baseline, and meets requirements for AE reporting, complete an AE Log CRF to document the new AE (i.e., the baseline condition at an increased severity and/or frequency). The AE Log CRF should be selected “yes” for the question, “Was this AE a worsening of a baseline medical condition?”.
- If a baseline condition resolves during follow-up, and then the same condition recurs during follow-up, document this as an AE but select “no” for the question: “Was this AE a worsening of a baseline medical condition?”. Note the resolution in chart notes but do not update the Medical History Log CRF.

At each follow-up visit, site clinicians will begin the follow-up medical history by reviewing with the participant and eliciting updates (resolution, outcome date, severity grade, etc.) on those symptoms/conditions that were documented as ongoing since the participant’s last visit. Site clinicians should then probe and evaluate for any new onset conditions/symptoms since the participant’s last visit. Clinicians should use their clinical experience and judgment to elicit complete and accurate medical history information from participants.

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

The Medical History Log CRF can be updated with new or corrected information during follow-up, but only in instances when new information related to the participant’s baseline medical history status is obtained after enrollment/randomization. If information is added to the Medical History Log CRF after Enrollment, a chart note explaining the update is required.

7.2 Concomitant Medications

The Concomitant Medications Log CRF is used to document all concomitant medications used by a participant during his/her study participation.

Protocol section 6.7 requires site staff to document all medications taken by study participants beginning at screening and continuing throughout the duration of the study. Medications include the following:

- Prescriptions and “over-the counter” medications and preparations
- Vaccinations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- Contraceptive medications
 - Injectable contraceptive (Depo Provera, NET-EN, Cycloferm, etc.): Record each injection that the participant receives during study participation on a new log line. Enter both the start and stop dates as the date of injection. Indicate the frequency as “once”. Injections of contraceptive medications used before the Screening date are not recorded on the Concomitant Medications Log CRF. This CRF only captures medications used on or after the Screening date.
 - Implants/IUCD: Record each implant/IUCD on a new log line. The start date should be the date of implant or insertion and the stop date should be the date the implant/IUCD is removed, if applicable. Indicate the frequency as “Other” and write “continuous” in the text field. For medical devices with no active medication, such as the copper IUCD, indicate the dose as “1”, the dose unit as “Other”, and indicate “device” in the text field. For IUCD route, select “Other” and write “intrauterine” in the text field. For Implant route, select “Other” and write “sub-dermal” in the text field. If the participant has an implant/IUCD in place at Screening, document this on the Concomitant Medications Log, as well as any other implants or IUCDs they receive during follow-up.
- Oral contraceptive birth control pills:
 - Record each pill pack confirmed by the participant to have been taken on a new log line. Indicate the start date as the date the first pill of the pack was taken and the stop date as the date the last pill of the pack was taken. If the participant is taking birth control pills at Screening, document this pill pack on the Concomitant Medications Log, as well as any other pill packs she begins during follow-up. If a participant misses a pill, this does not need to be recorded on the Concomitant Medications Log CRF.

Use of non-study supplied sexual lubricants as well as any liquid solution (with the exception of water) used to rectally douche should be recorded on the Concomitant Medications Log CRF and selected from the applicable drop-down field on the Discontinuation of Study Product CRF.

Note: Alcohol consumption and recreational drugs should not be reported as concomitant medications on the Concomitant Medications Log. Instead, excessive alcohol consumption (defined as binge drinking [i.e., as defined by the CDC as 4 or more drinks for women and 5 or more drinks for men on a single occasion], heavy drinking [i.e., 7 or more per week for females, 14 or more per week for males] and recreational drug use) may be considered baseline medical conditions, per site clinician judgment, in which case they should be recorded on the Medical History Log CRF.

It is helpful to ascertain the baseline medication information in the context of the baseline medical history. Site staff should ask open-ended questions to elicit participant report of current

medications, and use the information obtained in the medical history to probe for additional medications that the participant may otherwise forget to report.

To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring a list of all medications to study visits.

At each follow-up visit, review the participant's concomitant medications history and document this review by completing the item "Is the participant taking any concomitant medications that have not been previously reported?" on the Follow-up Visit Summary CRF and/or Interim Visit Summary CRF. Ask the participant if s/he has started taking any new medications, and record on the Concomitant Medications Log CRF any new medications s/he reports having started since his/her last medications assessment.

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

7.2.1 Prohibited Medications, Products and Practices

Certain medications and practices are contraindicated during study participation because they may be harmful to the participant, impact product safety parameters, or confound adverse event determination.

Participants will be counseled on avoiding the use of non-study rectal medications or products, including personal lubricants and usual pre-RAI douches containing N-9.

Note: Use of non-study personal lubricants and usual pre-RAI douches that do not contain N-9 are permitted, but must be recorded in the Concomitant Medications Log CRF

Use of any prohibited medications should be recorded on the Concomitant Medications Log CRF as a protocol deviation, if applicable.

7.3 Physical Exam

Protocol Section 7.7 outlines the required physical exam assessments. A comprehensive physical examination is required at Screening. At Screening, during the physical exam, site staff should assess for any other medical condition that would make participation in the study unsafe or interfere with interpreting the study data or achieving the study objectives.

A targeted physical examination (to include assessment of general appearance and vital signs at a minimum) will be done at Enrollment and only if indicated at all other follow-up and interim visits. Site clinicians may use their discretion to determine whether to conduct a more comprehensive physical exam in response to reported symptoms or illnesses present at the time of the exam.

Physical exam assessments should be documented on the Physical Exam and Vital Signs CRFs.

Physical exams may identify additional baseline medical 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 this intermittent chronic condition. In such situations, the clinician should add the information to the Medical History Log CRF as well, since the condition was present at the time of enrollment.

Weight: Participant weight must be measured during the Screening physical exam and additionally when clinically indicated. Weight should be measured in kilograms and should be rounded to the nearest tenth decimal place (e.g., 70.1 kg) Scales should be calibrated at least twice per year, and more frequently if required per local practice standards. Should a site not measure weight using the International System of Units, a site-specific conversion method must be used and documented in the participants' chart to ensure accurate conversion.

Height: Participant height must be measured during the Screening physical exam. It should be measured in centimeters and should be rounded to the nearest tenth decimal place (e.g., 160.4 cm). Should a site not measure height using the International System of Units, a site-specific conversion method must be used and documented in the participants' chart to ensure accurate conversion.

Blood Pressure: Devices are expected to be calibrated regularly per manufacturer's directions.

7.4 Pharyngeal Swab

One swab (pharyngeal) will be collected to test for chlamydia and gonorrhea at Screening and when clinically indicated at all other visits. To collect the swab, the participant should be instructed to open his or her mouth as widely as possible, allowing the clinician to make adequate contact with key areas of the throat (posterior wall, tonsils and uvula). If needed, a tongue depressor may be used. Insert the swab and rub the tonsillar pillars and posterior pharynx (behind the uvula). When removing the swab following collection, carefully ensure that the swab does not touch any area of the mouth (including the tongue, cheeks or teeth) before placing the swab in the appropriate specimen collection tube.

7.5 Anorectal, Genital, and Pelvic Exam Overview

The rectal exam done at Screening and Enrollment is necessary to evaluate protocol exclusion criteria and to collect detailed information on baseline rectal conditions. The exam scheduled during follow-up visits is necessary to assess for safety and collect required laboratory specimens. Pelvic exams and male genital exams are only performed if indicated at all study visits.

Guidance on the conduct of these exams can be found in the remainder of this section.

Exam procedures must be performed in the order shown on the applicable exam checklist and at designated area(s) of the genitalia as noted on the checklist, if specified. The order of specimen collection is critical to ensure that the first specimens collected do not affect subsequent specimens. Collect specimens away from apparent abnormalities and exclude swabbed areas from subsequent examination.

Prior to the exam, prepare all required equipment, supplies, and paperwork; label specimen collection supplies as needed. Review documentation of prior exams and other relevant

documentation from the current visit and prior visits. Explain the procedure to the participant and answer any questions s/he may have.

Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to ensure participant comfort and accurate documentation of exam findings. If not standard of care, consider having an additional person (medical assistant or nurse) present during the examination to ensure participant comfort.

Use clean hand/dirty hand technique, and/or assistants, to avoid contamination. Keep extra gloves available as two hands may be needed at different time points during the exam.

7.6 Detailed Procedural Instructions for Pelvic Exams

7.6.1 Procedures for Participants Who Can get Pregnant

Pelvic exams are only conducted if clinically indicated at all study visits. Pelvic exams should ideally not be performed and pelvic samples should ideally not be collected if the participant is experiencing menstrual-like bleeding, as this may interfere with visualization of the vagina and complicate interpretation of lab assays. Below is guidance on what to do in the event a participant is experiencing menses or any vaginal bleeding at the time of an exam:

- During Screening and/or Enrollment, if the participant is experiencing or reports any vaginal bleeding, reschedule the exam and associated sample collection to be completed within the 45-day screening window.
- During a scheduled follow-up visit, the conduct of the pelvic exam and associated sample collection should still be completed as long as bleeding is no greater than mild spotting and the participant is comfortable. If she is experiencing greater than mild bleeding, perform other protocol-specified procedures at the visit and schedule the participant to return for sample collection as soon as possible after bleeding subsides, within the visit window.
- If a participant who can get pregnant presents for an interim visit complaining of genital symptoms, perform a pelvic exam to evaluate her symptoms at that time. If the participant is not comfortable with completing an exam, a visit should be scheduled to complete the pelvic exam as soon as possible after vaginal bleeding stops.

General Technique:

- 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. Record the type and size of the speculum used on the Pelvic Exam Diagrams form. Prior to insertion, ensure that the speculum functions properly and has no rough edges.

Position the Participant:

- Drape the participant and establish a comfortable examination position that allows for appropriate examination of the genitalia such as dorsal lithotomy with or without use of stirrups; the position should allow for the perineum and vulva to be inspected. Make all necessary adjustments to the equipment and room to ensure the participant's comfort (e.g., adjust stirrups and back elevation as needed).

Examine the External Genitalia

- For pelvic exams, a visual exam (i.e. a naked eye examination) should be performed of the external genitalia including the perineum, and perianal area. Palpate the inguinal lymph nodes to assess for enlargement and/or tenderness. Assessment of Inguinal lymph nodes should be done at Screening and at other visits only if indicated. Do not insert the speculum before examining the external genitalia.

Examine the Internal Genitalia (Cervix and Vagina)

- If clinically indicated, a speculum exam may be performed. The speculum may be lubricated with warm water only, 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 to avoid trauma while enabling visualization of the cervical face and upper vagina. If the cervix is poorly visualized, to avoid iatrogenic injury, remove the speculum and use a gloved finger (lubricated with warm water if needed) to establish the position of the cervix. Then re-insert the speculum. Perform naked eye exam of the cervix and vagina, noting any abnormal findings.
- 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.
- Removal of visual obstruction: After collection of vaginal and endocervical specimens, any obstruction (e.g., mucus, cellular debris) may be removed using a large saline-moistened swab (scopette) in a gentle dabbing fashion to remove the obstruction. Avoid twisting or rolling the swab over the surface of epithelium. Do not use a dry swab to remove any obstruction at any time, as this may cause trauma to the epithelium. If saline is not available, a swab moistened with water will also suffice.

Perform Bimanual Exam

- A bimanual examination may be performed at Screening and when clinically indicated. After completing all the above-listed tissue examinations and specimen collection and removing the speculum, perform a bimanual exam for adnexal or fundal masses and/or tenderness.

7.6.2 Pelvic Specimen Collection

Clinicians should collect pelvic specimens without a speculum in place.

Chlamydia trachomatis (CT)/ Neisseria gonorrhoea (GC)/ Trichomonas (TV):

Collection of the two vaginal swabs for NAAT for GC/CT/TV will be done at Screening and all other visits if clinically indicated. The clinician will perform this collection using the Gen Probe APTIMA, Cepheid GeneXpert kit or another method approved by the MTN LC in the local or regional laboratory. The clinician/assistant will use the collection swab provided. The clinician/assistant will open the peel pouch containing the swab. Insert the swab 1½ inches into vagina and rotate 360° against lateral vaginal wall. After specimen collection, put the swab in the transport medium and break the shaft at the breakpoint. Re-cap tube securely by snapping the cap into place.

7.6.3 Documenting Pelvic Exam Findings

In the event a pelvic exam is performed, all findings (normal and abnormal) should be documented using the Pelvic Exam Diagrams form. If an exam is conducted at baseline, abnormal findings will be documented on the Pelvic Exam CRF and the Medical History Log CRF. When an exam is conducted during follow up, all abnormal findings identified will be documented on the Pelvic Exam CRF and Adverse Event Log CRF, as appropriate. Supplemental information may also be recorded in chart notes or on other designated source documents as needed.

Note: All pelvic exam findings consistent with the “grade 0” column of the FGGT are considered normal. The following also are considered normal:

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

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

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

7.7 Detailed Procedural Instructions for Genital Exams

7.7.1 Procedures for Individuals with a Penis or Neopenis

Male genital exams are only conducted if clinically indicated at all study visits. The participant should be asked to stand with feet about shoulder width apart with the clinician sitting in front of the participant. If the participant is not able to stand, s/he may lie in a supine position on the exam table (i.e. lying horizontally with the face and torso facing upwards).

A general inspection of the entire penile surface (internal and external foreskin [if present], shaft, glans and urethral meatus), scrotum and inguinal lymph nodes should be performed, via naked eye examination and use of a hand-held magnifying glass. When evaluating the penile surface, the clinician should assess any abnormalities on the skin (retracting foreskin, if present). The shaft should be palpated to assess any irregularities. When inspecting the scrotum, the clinician should inspect the skin for any scars. The urethral meatus should be examined for any discharge, inflammation, lesions, etc. The clinician should also lift and palpate the scrotum to assess any bulging in the inguinal area as well as any penile or scrotal abnormalities.

7.7.2 Documenting Genital Exam Findings

In the event a genital exam is performed, all findings (normal and abnormal) should be documented using the Genital Exam CRF. If an exam is conducted at baseline, abnormal findings will be documented on the Genital Exam CRF and the Medical History Log CRF. When an exam is conducted during follow up, all abnormal findings identified will be documented on the Genital Exam CRF and Adverse Event Log CRF, as appropriate. Supplemental information may also be recorded in chart notes or on other designated source documents as needed.

Genital exam findings should be documented using terminology corresponding to the Male Genital Grading Table (MGGT) and the Genital Exam CRF. For findings where the finding term marked on the Genital Exam CRF is more specific than the corresponding term on the MGGT, use the more specific term.

7.8 Detailed Procedural Instructions for Anorectal Exams

Rectal exams are required at all study visits, except for Product Switch visits (Visits 4 and 6) and the Final/Early Termination Visit, at which rectal exams should only be done if clinically indicated.

Position the Participant

- Position the participant in the left lateral decubitus position (fetal position) with both legs flexed allowing a full view of the anus, perianus and buttocks.

Examine perianal genitalia

- A visual perianal exam should also be performed during routine scheduled rectal exams. With gloved hands, the clinician should separate the participant's buttocks as far apart as is comfortable for him/her. Perform a naked eye examination of the perianal area and evaluate any abnormalities including but not limited to hemorrhoids, lesions, lumps, or rashes.

Digital Rectal Examination

- This examination is performed prior to the insertion of the anoscope. This examination is intended to relax the anal sphincter around the opening of the anus in preparation for the subsequent anoscopy. In addition, the examination enables the clinician to assess potential findings such as lumps/areas of discomfort. The clinician will lubricate a gloved finger with *Good Clean Love* lubricant. The clinician will then gently and slowly insert a gloved index finger (palmar surface down) into the anus. The clinician should sweep the finger circumferentially around the entire anal/distal rectal surface. Any abnormal findings or unexpected discomfort should be noted. It is not required for this exam to assess the prostate gland.
- Potential participants identified at Screening with abnormalities of the rectal mucosa, or anorectal symptoms that represent a contraindication to study participation are not eligible for the study. For participants who enroll in the study, abnormal anorectal exam findings (that are not exclusionary) identified at Screening and Enrollment should be recorded as a baseline medical condition.

7.8.1 Rectal Specimen Collection

Swab Collection for HSV Detection

For site with capacity, the HSV 1/2 swab should be collected after visual examination of the perianal area and **prior** to the digital examination. The swab for detection of HSV 1/2 is

only done if clinically indicated (i.e. the presence of shallow perianal ulceration or vesicle crops).

***Chlamydia trachomatis* (CT)/*Neisseria gonorrhoea* (GC)**

Collection of the rectal swab for NAAT for GC/CT is done using the collection kit specific to Gen-Probe Aptima, Cepheid GeneXpert NAAT or method approved by the MTN LC in the local or regional laboratory. The clinician/assistant will open the peel pouch containing the swab. Slowly insert rectal swab from collection kit. Insert the swab approximately 2-4 cm, per kit instructions, into the rectum, past the anal sphincter, and rotate it 360 degrees against the rectal wall several times. Carefully remove the swab and insert the swab into the appropriate transport tube, breaking the shaft at the breakpoint. Re-cap tube securely by snapping the cap into place. Always follow package collection kit instructions.

Examine rectum/anal canal

At screening and enrollment, an anoscopy should be performed. Using study-provided lubricant (Good Clean Love lubricant), the clinician should sparingly lubricate the anoscope prior to insertion. With one hand, separate and hold the buttocks; use the other hand to insert the anoscope. Slowly and steadily push the anoscope into the anus until it is fully inserted. Hold the obturator in place while doing this. The anoscope with obturator should then be inserted into the anal canal until the anoscope 'wings' touch the anal verge. The clinician should maintain pressure on flange to ensure continued placement of the anoscope and then remove the obturator. Using a lighted instrument (e.g. otoscope or torch) to illuminate the rectum after removing the obturator, the rectal lumen should be visible at the end of the anoscope. The clinician should visually assess the rectal mucosa after the anoscope is in place. When exam of the anal canal is complete, withdraw the anoscope, assessing the anal canal as the anoscope is withdrawn.

7.8.2 Documentation of Rectal Exam Findings

All rectal exam findings should be documented using the Anorectal Exam CRF.

All abnormal findings must be thoroughly documented and include location and severity of the finding to ensure an appropriate assessment can be made during subsequent examinations. Supplemental information may also be recorded in chart notes or on other designated source documents, as needed.

As previously mentioned, all abnormal non-exclusionary findings identified at Screening and Enrollment will be documented as baseline medical conditions on the Medical History Log CRF as well.

Any abnormal findings identified during follow-up will be documented on the Anorectal Exam CRF, as appropriate and as an adverse event, if applicable, on the Adverse Event Log CRF. Any unexpected discomfort should also be noted in chart notes.

Per protocol section 8.3.1, fecal urgency, bloating, flatulence and bleeding associated with rectal procedures deemed to be within the range of what is normally expected will not be reportable as AEs. Bleeding of greater quantity or longer duration than what is typical, per clinician assessment, should be reported as an AE.

The results of laboratory tests performed using specimens collected during follow-up rectal exams should be recorded on the STI Tests Results CRF.

7.9 STI/RTI/UTI Evaluation, Management and Treatment

Clinical and laboratory evaluations are performed in MTN-035 to diagnose the following STIs and RTIs:

- Chlamydia infection
- Gonorrhea infection
- Trichomonas
- Syphilis infection
- HIV 1/2
- Herpes simplex virus (HSV1/2 detection, at sites with capacity)

All participants diagnosed with an active sexually transmitted or reproductive tract infection (STI/RTI) or UTI (based on the presence of symptoms suggestive of a UTI including but not limited to dysuria, urgency, frequency) should be provided treatment and or referral for treatment per site standard of care and applicable site standard operating procedures (SOPs). STIs/RTIs will be treated in accordance with current World Health Organization (WHO) guidelines which can be accessed at: <http://www.who.int/hiv/pub/sti/pub6/en/>.

Potential participants presenting with an infection requiring treatment at Screening or Enrollment, may be treated and re-tested during the screening process and, if treatment is completed and symptoms have resolved within the screening window, enrollment may proceed. Per current WHO guidelines, the following symptomatic infections require treatment and are exclusionary: *Neisseria gonorrhoea* (GC), *Chlamydia trachomatis* (CT), syphilis, active herpes simplex virus (HSV) lesions, anogenital sores or ulcers, or symptomatic genital warts, chancroid, pelvic inflammatory disease (PID), symptomatic bacterial vaginosis (BV), symptomatic vaginal candidiasis, and trichomoniasis.

Infections should be considered “symptomatic” when a participant self-reports or complains of symptoms associated with the infection. Symptoms should not be confused with “signs” of infection that may be observed during clinical examinations performed by study staff.

Please note:

- HSV-1 or HSV-2 seropositive diagnosis with no active lesions is permitted since treatment is not required.

Urinary Tract Infections (UTIs): Suspected UTIs may be clinically managed based solely on the presence of symptoms indicative of a possible UTI or other method of diagnosis (i.e., urine culture or dipstick) as per site standard of care.

The following symptoms are considered indicative of a possible UTI:

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

A urine dipstick may be performed per site SOP; however, sites are expected to send a urine culture for definitive diagnosis when a UTI is suspected. The results of the urine culture do not need to be returned before presumptive treatment, but the results of the culture will influence how the AE is captured. When the participant initially reports symptoms suggestive of a urinary tract infection, capture each symptom as a separate AE. If urine culture results are positive, update the AE Log CRFs to reflect a single AE for grade 2 Urinary Tract Infection per UTI criteria defined in the FGGT or the MGGT, as

applicable. If the urine culture is negative, the AE (s) will remain reported as symptoms only. Record the results of any dipsticks performed and urine culture results in chart notes and/or other site-specific source documents.

Note that urine dipstick testing is only performed if clinically indicated. At Screening, positive dipstick results do not directly impact eligibility, but abnormal protein and glucose parameters should prompt further evaluation or consideration, pending IoR review. Abnormal protein and glucose discovered at Screening should be captured on the Medical History Log CRF. In follow-up, findings of abnormal protein and glucose on the dipstick should be reported on the AE log CRF as indicated. Grade the severity of the urine glucose value according to the "Proteinuria, random collection" row of the DAIDS Toxicity Table. Note that findings of LE/nitrites are not gradable per the toxicity table, and like other non-gradable labs, should not be reported as baseline medical conditions or AEs.

When clinically appropriate, investigators should use oral or parenteral medications when possible to avoid intravaginal or rectally-administered medication use. Observed single dose treatment should be provided whenever possible, per clinician discretion.

Per protocol section 8.3.1, asymptomatic bacterial vaginosis (BV) does not require treatment per current WHO guidelines. Asymptomatic vaginal candidiasis also should not be treated. During screening, these asymptomatic infections are not exclusionary and during follow-up these asymptomatic infections are not considered AEs; however, they will be captured on the STI Test Results CRF.

7.10 HIV Testing

At Screening and/or Enrollment (prior to randomization), all participants will undergo HIV testing. At Enrollment, sites will perform HIV rapid test (s) to screen for HIV and must ensure results are returned prior to randomization. If one or both rapid HIV tests are positive or discordant, this alone does not render a participant ineligible for enrollment. Participants must undergo confirmatory testing to confirm HIV status prior to enrollment. See SSP Section 9.6.2 for more information.

If at Screening and/or Enrollment a potential participant has signs and/or symptoms consistent with acute HIV infection, s/h is not eligible for enrollment. Acute HIV infection is defined as the period of rapid viral replication that immediately follows the initial establishment of infection with HIV. Symptoms of acute HIV infection may be indistinguishable from a typical viral syndrome, as well as from COVID-19, and may include a combination of the following:

- fever
- fatigue
- headache
- myalgia
- weight loss
- pharyngitis or sore throat
- lymphadenopathy
- rash
- diarrhea

Clinicians should assess the possible causes of these symptoms, the length of time the participant has been experiencing them, and their severity grade. Symptoms should be managed clinically, per site standards of care. The participant will not be eligible for study participation.

Participants who fail screening due to concern for acute HIV infection should have repeat HIV testing for study purposes no earlier than two months following the prior negative HIV test. If the HIV antibody test is negative at that point, and the participant no longer has symptoms suggestive of acute viral infection, the participant may undergo a second

screening attempt for the study, assuming no other interim contraindications are noted. If an alternative diagnosis for the symptoms is identified (e.g., malaria or influenza) then a second screening attempt may be scheduled two months following the initial attempt, once all symptoms have been resolved. If symptoms are not adequately resolved by the time of second screening attempt, and HIV testing is negative, assess for additional possible causes for the symptoms and refer the participant for further evaluation, if necessary. If during the second screening attempt other contraindications for eligibility are present, the participant is not eligible for study participation.

For any participant in follow-up whose HIV test is reactive, study product and study participation must be temporarily held and confirmatory HIV testing should be done. In addition, if a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV exposure, HIV testing should be performed immediately.

For any participant found to have confirmed HIV infection after Enrollment, product use and study participation must be permanently discontinued and terminated from the study. All participants with confirmed HIV infection will be counseled and referred to available resources for medical and psychosocial care and support. All referrals, outcomes, and follow-up plans and actions must be fully documented in participant study records.

Protocol-specified examinations and laboratory tests will provide information upon which appropriate clinical care decisions can be made. Study staff must refer participants to non-study HIV care providers. Study staff should provide and explain all study examination findings and test results to participants. They should also provide copies of laboratory results to participants and their non-study providers (if the participant grants approval). Study investigators should be available to consult with non-study providers on optimal clinical care and treatment decisions for participants.

Plasma storage is required for further MTN LC testing (HIV RNA, HIV drug resistance) when the additional sample (e.g. sample 2) is collected at a site's local laboratory to confirm a participant's HIV status. Refer to SSP Section 9.6.2 for more information.

7.11 Syphilis testing

Prior to enrollment in the study, appropriate clinical management action (as noted below) is required with any positive syphilis test and confirmation found at screening. Action required prior to enrollment depends on the current health status of the participant and the availability of medical records documenting prior infection, as follows:

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

If syphilis is diagnosed during screening, 'syphilis seropositivity' should be recorded within the Medical History Log CRF, and the screening RPR titer included ("RPR titer: 1 to X"). A baseline medical history condition of syphilis seropositivity should be documented on the "ongoing at time of assessment" at baseline. A test of cure (i.e., four-fold decrease in titer) is not required prior to enrollment; however, repeat serology is expected after treatment for clinical management purposes.

7.12 Clinical and Product Use Management

Protocol section 9 provides detailed guidance on clinical and product use management, including general criteria for product discontinuation (section 9.3), guidance on product discontinuation in response to observed AEs (section 9.4), STIs/RTIs (section 9.5), HIV-1/2 Infection (section 9.6), pregnancy (section 9.7), and early study termination (section 9.8).

All specifications of protocol sections 6 and 9 must be followed; IoRs are encouraged to consult the PSRT with any questions related to proper interpretation of the protocol and, in particular, proper management of study product use. Conditions requiring permanent discontinuation are summarized in Figure 6-1 below.

The protocol mandates, per section 9.3, permanent product discontinuation when a participant reports prohibited medication use. When possible, treatment options that are not prohibited per protocol should be pursued; however, clinical management of the participant should be prioritized if alternative treatment is not available. If prohibited medications other than those listed in protocol section 9.3 are used, sites should consult the PSRT.

All clinical and product use management must be fully documented in participant study records. When the PSRT is consulted in relation to clinical and product use management, completed PSRT query forms (including a response from the PSRT) must be printed and filed in participant study records. Unless otherwise specified in protocol section 9, the IoR/designee should immediately consult the PSRT for any product discontinuations. Product discontinuations must be communicated to site pharmacy staff using the Study Product Request Slip as described in SSP Section 5 (Study Product Considerations). Product discontinuations also must be documented on the Treatment Discontinuation CRF.

Figure 7-1
Conditions Requiring Temporary or Permanent Discontinuation

Condition	Permanent Discontinuation	Temporary Discontinuation
Reported use of non-study rectal medications or products, including personal lubricants and usual pre-RAI douches containing N-9.	X	
Unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee.	X	
Anorectal STIs		X
Reactive HIV testing pending confirmation		X
Acquisition of confirmed HIV infection	X	
Pregnancy	X	
Grade 3 or 4 AE	[X]	[X]

[X] Study product must be held and the IoR must consult with PSRT regarding continued use of study product and progression to other study product