

Section 10. Clinical Considerations

This section presents information on clinical procedures performed in MTN-007. 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 and Menstrual History

The participant's baseline medical and menstrual (if female) history is initially collected and documented at the screening visit. It is then actively reviewed and updated, as necessary, at the enrollment visit. After the enrollment visit, the baseline medical and menstrual history should not be updated unless the participant recalls information at a later visit related to his/her medical history at baseline.

The baseline medical and menstrual history will ascertain a participant's medical history by major body systems, a participant's alcohol and drug use history, as well as specific rectal/GI symptoms a person may have experienced. The form will also be used to explore any medical conditions or medications that are deemed exclusionary for this study. The purpose of obtaining this information during screening and enrollment 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
- Monitor any potential adverse events associated with the use of the study product during the course of the study

The non-DataFax Participant-Reported Baseline Medical and Menstrual History form is a recommended source document for collecting baseline medical and menstrual history information; however, alternative site-specific history forms may be used. That is, a site may create its own source documentation.

When obtaining the baseline medical and menstrual history, it is not necessary to document the participant's lifetime medical history; rather, site staff should ask the participant to answer questions/describe conditions based on the time since he/she has become sexually active. "Sexually active" refers to the time point that the participant first had vaginal or anal sexual intercourse with another partner (this does not include oral sex). Additional guidelines to collecting the baseline medical and menstrual history are listed below:

- Use the list of body systems and conditions on pages 1-3 of the Participant-reported Baseline Medical and Menstrual History form as guide to probe for history related to each system and condition. For conditions that are not associated with the listed systems, record relevant history in the "other medical problem" section on page 6.
- Record symptoms, illnesses, allergies, and surgeries
- Record both chronic and acute conditions, and both ongoing and resolved conditions

- Document whether each condition is currently ongoing; for enrolled participants, conditions that are ongoing at the time of enrollment/randomization are transcribed onto the Pre-existing Conditions form. For ongoing recurrent conditions that are expected to be experienced during follow-up (e.g. headaches), the condition need not be present on the day of enrollment to be considered ongoing at the time of enrollment.
- For all ongoing conditions, assess and record the current severity of the condition per the DAIDS Toxicity Table, Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies). See Section 11 of this manual for further clarifications, guidelines, and tips for severity grading in MTN-007.
- Record information on the participant's use of alcohol and recreational drugs, including the specific substances used and dates and frequency of use (page 4 of the Participant-reported Baseline Medical and Menstrual History form). If the participant reports any diagnosed conditions associated with alcohol or drug use that are not recorded elsewhere, record the conditions and relevant details, including date of diagnosis and severity grade.
- If the participant has a known history of STI or RTI, these may be recorded in the "STI/RTI" items on page 4 of the Participant-reported Baseline Medical and Menstrual History form.
- For anal/colorectal/GI symptoms, each symptom listed on pages 5 and 6 of the Participant-reported Baseline Medical and Menstrual History form should be read aloud to the participant to actively ask him/her about each one.
- Record whether the participant has experienced any type of sexual assault; if so, document relevant details on page 6 of the Participant-reported Baseline Medical and Menstrual History form.
- Record any other obstetric (women only), gynecologic (women only), or reproductive problems and/or procedures, and relevant details (including severity grade for any ongoing conditions or problems) on page 6 of the Participant-reported Baseline Medical and Menstrual History form.
- *Women only:* For menstrual history information, including menstrual symptoms, non-menstrual genital bleeding, and description of usual menstrual cycle, complete all items on page 7 of the Participant-reported Baseline Medical and Menstrual History form.
- *Women only:* For pregnancy history (page 8 of the Participant-reported Baseline Medical and Menstrual History form), record the outcome, outcome date, and type of delivery for each pregnancy. Also record any congenital anomalies or other problems associated with each pregnancy, as well as the current vital status (alive or deceased) of all children born alive.
- *Women only:* For contraceptive history (page 7 of the Participant-reported Baseline Medical and Menstrual History form), record all contraceptive methods ever used by the participant and approximate dates of use for each method. Document any problems experienced with use of each method and any other relevant details. Current contraceptive methods should be transcribed onto the Concomitant Medications Log form.

- Document medications currently taken for all ongoing conditions on the Concomitant Medications Log form (or other site-specific source document) as described in Section 10.4.

10.2 Follow-up Medical and Menstrual History

It is necessary to update the participant's medical history at each follow-up clinic visit (and any interim visit) in order to determine whether previously reported conditions remain ongoing and whether new symptoms, illnesses, conditions, etc. have occurred since the last medical and menstrual history was performed. The non-DataFax form Participant-reported Follow-up Medical and Menstrual History form can be used to gather this information. At each post-enrollment visit it is only necessary to record information that has occurred or changed since the previous visit.

10.3 Pre-existing Conditions

A key purpose of conducting the baseline medical and menstrual history, as well as the physical and rectal exams (described below), is to document participants' baseline medical conditions, for comparison with signs, symptoms and conditions that may be identified or reported during follow-up. All ongoing medical conditions, problems, signs, symptoms and abnormal findings that are observed and/or reported *at or before enrollment* are considered pre-existing conditions.

For all participants enrolled in the study, all ongoing conditions recorded as pre-existing are to be thoroughly source documented and transcribed onto the Pre-existing Conditions case report form. This form is to be completed at the Screening Visit and reviewed/updated at the Enrollment Visit based on all screening and enrollment source documents including, but not limited to, the Baseline Medical and Menstrual History form, Physical Exam form, Rectal Exam form, Anoscopy and Sigmoidoscopy Results form, Laboratory Results form, and STI Laboratory Results form.

All pre-existing conditions noted at screening and enrollment must be graded though they are not considered to be adverse events. The purpose of grading a pre-existing condition is because the Pre-existing Conditions form serves as the "starting point" from which study clinicians must determine whether abnormal conditions, symptoms, signs and findings identified during follow-up are adverse events (AEs). By definition, pre-existing conditions are present prior to enrollment/randomization and are, therefore, not considered AEs. However, new conditions identified during follow-up that were not present at enrollment/randomization, and pre-existing conditions that increase in severity (increases to a higher grade) or frequency during follow-up, are considered AEs. Therefore, the clinician should record as much information as possible about the severity and frequency of any pre-existing condition in source documents as well as in the comments field of the Pre-existing Conditions form to best describe the condition at study entry. This allows for greater objectiveness in noting any grade increase of the pre-existing condition.

10.4 Concomitant Medications

The MTN-007 protocol requires site staff to document all medications taken by study participants beginning at screening and continuing throughout the duration of the study. This includes any prescriptions, over-the-counter preparations, vitamins and nutritional supplements, recreational drugs and herbal and naturopathic preparations. All medications, drugs, supplements and preparations will be recorded on the Concomitant Medications Log.

It is helpful to ascertain the baseline medication information in the context of the baseline medical/menstrual history. Site staff should ask open-ended questions to elicit participant report of current medications, and use the information obtained in the medical/menstrual history to probe for additional medications that the participant may otherwise forget to report. For example, if the participant reports headaches as part of her medical history, but does not spontaneously list any medications taken for headaches; ask if she takes any medications for headaches. Similarly, if a participant reports taking a medication for a condition that he inadvertently did not report when providing medical history information, add the condition to the baseline medical/menstrual history source document.

At each follow-up clinic visit, retrieve the participant's previously completed Concomitant Medications Log form, record any new medications provided to the participant by study staff, and actively ask the participant whether he/she is still taking all previously-recorded medications, at the same dose and frequency. Also actively ask whether the participant has taken any new medications since the last medical/menstrual history was taken. To further probe for updates, if the participant reports any intercurrent illnesses, symptoms, etc. since his/her last medical history, ask whether he/she took any medications for those. Add all new information to the form in log fashion, using additional form pages as needed. If a participant reports taking a new medication for a condition that he/she inadvertently did not report when providing follow-up medical/menstrual history information, add the condition to his/her follow-up medical/menstrual history source document. To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring all medications to all study visits.

10.5 Prohibited Medications and Products

For MTN-007 the following medications are prohibited from use during the study:

- Heparin (including Lovenox)
- Warfarin
- Plavix (clopidogrel bisulfate)
- Rectally administered medications (including over-the-counter preparations)
- Aspirin
- NSAIDS*
- Post-exposure prophylaxis
- Systemic immunomodulatory medications
- Rectally administered products containing N-9
- Any drug associated with the increase likelihood of bleeding after mucosal biopsy
- Any other investigational drug

* If use of NSAIDS is reported by a participant prior to a study visit in which endoscopic examinations and/or biopsies are obtained, the study visit should be rescheduled. If the event this is not able to occur, the determination of action would be decided by an urgent PSRT consultation. Study product use may be discontinued at the discretion of the IoR/clinician in consultation with the PRST.

If a participant reports using a prohibited medication during the study, this must be recorded on the Concomitant Medications Log. Should a participant report using any of the above listed medications or products, study staff should consult the PSRT regarding product use.

10.5 Physical Exam

A physical exam is completed at the Screening, Enrollment, Treatment 1 and Final Clinic Visits. It should only be performed at the Treatment 2 Visit if it is clinically indicated. At all scheduled time points, physical exams should include the assessments listed in protocol section 7.11 and repeated below. Site clinicians may use their discretion to determine whether or not to conduct a more complete physical exam in response to reported symptoms or illnesses present at the time of the exam.

Following is a list of required physical exam components:

- Height (may be omitted after the Screening visit)
- Weight
- Vital Signs
 - Temperature
 - Pulse
 - Blood pressure
- General appearance
- Abdomen
- Other components as indicated by participant symptoms

The non-DataFax Physical Exam form is a recommended source document for recording physical exam findings.

For participants who enroll in the study, abnormal physical exam findings (that are not exclusionary) identified at the Screening and Enrollment Visits should be recorded on the Pre-existing Conditions form. Abnormal findings found during physical exams performed during follow-up should be documented and/or reported as described in Section 11.

Physical exams may identify additional baseline medical 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 and the Pre-existing Conditions form as well, since the condition was present at the time of enrollment.

10.6 Rectal Exams

Rectal exams are required at the Screening, Enrollment, Treatment 1, and the Final Clinic Visits. A rectal exam is performed at the Treatment 2 Visit only if clinically indicated. A basic rectal exam consists of a digital examination of the rectum as well as a visual inspection of the anus and surrounding area. In most cases, when a rectal exam is performed, rectal samples (swabs, sponges, etc.) are also collected.

Rectal exams must be performed in the order shown on the rectal exam Checklists. These checklists are in Section 7 of this SSP. Detailed procedural and documentation instructions are provided below.

Potential participants identified at screening with abnormalities of the colorectal mucosa, or colorectal symptoms that represent a contraindication to biopsy (in the opinion of the clinician) are not eligible for the study. For participants who enroll in the study, abnormal rectal exam findings (that are not exclusionary) identified at the Screening and Enrollment Visits should be recorded on the Pre-existing Conditions form. Abnormal findings found during rectal exams performed during follow-up should be documented and/or reported as described in Section 11.

10.6.1 Anorectal Visual Inspection

Anorectal examinations are undertaken in a private examination room with a curtain drawn between the participant and the entrance door. Explain all procedures to the participant before and while performing them.

The participant should be undressed from the waist down, lying in the left lateral (decubitus/fetal) position on top of the examination table with the anal area exposed and at the lower edge of the table.

The anal and perianal area is visually examined and any abnormal finding(s) noted on the Rectal Exam CRF as well in chart notes.

10.6.2 Digital Rectal Exam

The clinician performs a digital rectal exam with Pre® Personal lubricant prior to the insertion of the anoscope to relax the anal sphincter and rule out gross obstructions or malformations that may prohibit anoscopy.

The right buttock is gently raised to allow visualization of the anus (the participant may do this if they wish). A lubricated (Pre® Personal lubricant) gloved finger is gently inserted and swept around the entire internal anal circumference. Any abnormal finding or unexpected discomfort should be noted on the Rectal Exam CRF as well in chart notes.

Note: In order to reduce the amount of mucosal trauma, this is an anal canal exam only and is not a full digital rectal exam with examination of the prostate.

10.6.3 Specimen Collection

Perform rectal specimen collection in the sequence specified on the rectal exam checklists in Section 7. Additional details are included below. For more information on specimen collection, processing and testing of rectal specimens, see SSP section 12.

Anorectal Swabs

Swabs will be collected for both GC and CT using the GenProbe Aptima detection system and rectal microflora using a port-a-cult.

A lubricated (Pre® Personal lubricant) anoscope is inserted into the anal canal until the anoscope ‘wings’ touch the anal verge. After removing the obturator, the GC/CT swab will be inserted into the rectal lumen that is visible at the end of the anoscope and rotated through 360 degrees and removed. The rectal microflora swab will be taken after the swab for GC/CT using the same technique.

Rectal Sponge

Rectal Sponge Preparation

Approximately 45 minutes before the collection of the rectal sponge specimen through the anoscope, a clinician or staff member should prepare the materials (the insertion tube) as follows:

1. Obtain a disposable transfer pipette and cut off the end approximately 1 inch from the tip
2. Insert the stem of the sponge into the end of the pipette
3. Make sure that the stem of the sponge will fit the pipette snugly and will not dislodge during insertion or extraction from the rectal cavity.

Figure 10-1: Disposable Transfer Pipette Extension with Rectal Sponge



Using study provided lubricant (Pre® Personal lubricant), site clinician should lubricate the anoscope prior to insertion. The anoscope should then be inserted into the anal canal until the anoscope ‘wings’ touch the anal verge, then remove the obturator. After removing the obturator, place the sponge (attached to the pipette extension) through the anoscope into the rectum and hold (or leave) it against the rectal wall for 5 minutes. Remove the sponge, disengage the sponge with plastic stick from the plastic holder, and place the sponge into the appropriate tube. Note: The plastic holder refers to the transfer pipette used to make the stick longer and easier to manipulate. At visits when both swab(s) and sponge are collected, they may be taken sequentially with the GC/CT swab taken first during the same anoscopic examination.

Rectal Lavage

Rectal Lavage is a procedure in which involves instilling a solution to wash the rectum. The effluent is collected for analyses, such as inspection for any epithelial cells that may have sloughed off of the rectal mucosa.

With the participant in the left lateral position, insert the lubricated (Pre® Personal lubricant) nozzle of the 120ml enema bottle containing Normasol into the rectum. When the nozzle is fully inserted, squeeze the bottle to instill the solution into the rectum. Ask the participant to hold the fluid for at least 3-5 minutes, then ask the participant to use the restroom and dispel the fluid and stool into the collection ‘hat’, taking care not to urinate or place paper in the ‘hat’.

Samples of effluent (for lavage studies) and stool (for measurement of fecal calprotectin) will be taken from the ‘hat’.

10.6.4 Sigmoidoscopy

- Check to ensure the sigmoidoscope is switched on, suction is on, and air flow is working.
- With the participant in the left lateral decubitus position, the sigmoidoscope tip is lubricated with Pre® Personal lubricant and gently inserted to 15 cm from the anal verge.
- Introduce endoscopic ‘jumbo’ forceps into the sigmoidoscope channel and commence mucosal specimen collection at between 12-15 cm from the anal verge. The forceps need to be carefully washed in water between every biopsy.

- Biopsy 1: Shake the biopsy into a 10% formalin tube for histology
 - Biopsy 2: Shake the biopsy into a labeled RNA later tube for gene expression determination
 - Biopsy 3 and 4: Shake each biopsy into a labeled RNA later tube for cytokine determination
 - Biopsy 5, 6 and 7: Shake each biopsy into a RPM tube for T cell phenotype
- Remove the sigmoidoscope.

10.6.5 Anoscopy

- Ensure the high-resolution anoscope is switched on, height adjusted so that the circular field of light has the anal opening centered, and magnification is set to x 16.
- A clear plastic anoscope is inserted as described above.
- Using the same endoscopic biopsy forceps used for sigmoidoscopic biopsies, 7 rectal biopsies are taken by sampling the most dependent area first to avoid blood obscuring the field.
- Biopsy number and tube placements are as above for sigmoidoscopic biopsies, and again forceps are washed between each biopsy in water.
- Rectal blood is mopped using proctoswabs after the biopsies have been taken, and the anoscope is removed. Excess lubricant is wiped from the anal margin.
- Vital signs are re-taken are obtained and documented in chart notes.