Section 7. Clinical Considerations

7 Introduction

This section presents information on the clinical procedures performed in MTN-043. The Table of Visits and Study Procedures in Appendix I and II of the protocol indicates when specific clinical and laboratory assessments are to take place for mothers and infants, respectively. While the protocol dictates the schedule for data capture, the Investigator of Record (IoR) or designee should perform a symptom-directed examination at his/her discretion during any visit if s/he determines it to be clinically necessary, particularly if there are any on-going medical or mental health conditions that require closer follow-up. The participant's research record should include documentation of these procedures. Throughout the SSP, the term 'clinician' will refer to a study doctor or a nurse in settings where nursing training, scope of practice, and delegation, permit nurses to perform clinician activities under doctor supervision.

Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 8 of this SSP. Information on performing laboratory procedures is described in Section 10. Instructions for completing data collection forms associated with clinical procedures are provided in Section 11 and within the CRF completion guidelines (CCGs).

7.1 Maternal Baseline Medical History

Participant baseline medical history is initially collected and documented at the screening visit and then actively reviewed and updated, as necessary, at the enrollment visit. Medical records may also be reviewed when available.
The purpose of obtaining baseline medical history 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 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 **MTN-043 Baseline Medical History Question Sheet** (available on the MTN-043 web page under Study Implementation Materials) in conjunction with the **Baseline Medical History Log CRF** and/or chart notes to guide and document medical history taking. Medications and vaginal products used by the participant also are ascertained and documented at this time (see Section 7.2 below). Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit complete and accurate information from the participant. This is especially important with regard to details about severity and frequency of baseline medical history conditions (i.e. up to the point of randomization). Any related referrals for ongoing conditions should be managed according to clinical judgment and local standard of care, and documented appropriately in the chart.

At the enrollment visit, a participant's medical and medication history should be reviewed and updated, as needed.

7.1.1 Documenting Maternal Baseline Medical Conditions

Details of all relevant conditions identified during the baseline medical history taking should be recorded within the **Baseline Medical History Log CRF**. Relevant conditions include (but are not limited to): hospitalizations; surgeries; allergies; conditions requiring prescription or chronic medication (lasting for more than 2 weeks); and, any condition(s) currently experienced by the participant.

In addition to participant-reported conditions, record the following on the **Baseline Medical History Log CRF**:

- Grade 1 and higher lab values
- Medically-relevant physical exam abnormalities
- Abnormal pelvic exam findings
- Any identified STIs

The clinician should record as much information as possible about the severity and frequency of any baseline medical condition in the description field within the **Baseline Medical History Log CRF** to best describe the condition at the time the participant enters the study. Severity of each baseline medical condition should be assessed per the DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT) Addendum 1 dated November 2007. If the condition is not listed in the Female Genital Grading Table for Use in Microbicide Studies, refer to the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017 (hereafter referred to as the "DAIDS Toxicity Table"). Generally, it is not expected that conditions less than Grade 1 would be included on the Baseline Medical History Log, unless determined to be relevant by the site clinician. Examples of conditions that are not gradable but could be determined to be relevant include asymptomatic BV or previous surgeries. See Section 8 for further clarifications, guidelines, and tips for severity grading in MTN-043.

The purpose of grading the baseline medical condition is to determine whether abnormal signs, symptoms, and/or conditions identified during follow-up are adverse events (AE). By definition,

baseline medical conditions that are present prior to or at enrollment are not considered AEs. New untoward medical conditions identified during follow-up that were not present at enrollment, and baseline medical conditions that increase in severity (increase to a higher grade per the DAIDS toxicity table) or frequency during follow-up, are considered AEs.

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. It should be noted that any significant obstetrical complications and any *uncontrolled* active or chronic conditions as outlined in protocol eligibility criteria 8 are exclusionary.

During screening, if a participant reports having a history of anaphylactic reactions (such as acute anaphylaxis after eating peanuts), even if it has happened only once before in their lifetime, it is still important for the site clinician to document these events as a pre-existing condition on the Baseline Medical History CRF. Per the "acute allergic reaction" row of the DAIDS Toxicity Table, 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 types of symptoms (e.g., "throat swelling" or "shortness of breath") and indicate the severity grade 4 in the "Description of medical condition/event" field. At the Enrollment Visit, check "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.

Information documented on the **Baseline Medical History Log CRF** at the Screening Visit must be actively reviewed and updated at the Enrollment Visit, especially for those conditions that were ongoing at the Screening Visit. 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, update the date the condition or event resolved. 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 selected "no." If a baseline medical condition first identified at the Screening Visit is ongoing at the Enrollment Visit, assess the severity at the Enrollment Visit and update the severity grade (up or down) as applicable to reflect the severity at the time of enrollment/ randomization.

7.2 Maternal Concomitant Medications

The MTN-043 protocol requires documentation of all medications taken by study participants beginning at the Screening Visit and continuing throughout follow-up. The **Concomitant Medications Log CRF** is used to document all concomitant medications used by a given participant during her study participation. Medications include the following:

- Prescription and "over-the counter" medications and preparations
- Vaccinations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations, including vaginal formulations, which are intended to function as medication.
- Contraceptive medications
    - Injectable contraceptive (Depo, NET-EN, Cyclofem, 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".
    - 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 a participant misses a pill, this outage does not need to be recorded on the Concomitant Medications Log CRF

- Implants/IUD: Record each implant/IUD 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/IUD is removed. Indicate the frequency as "Other" and write "continuous" in the text field. For medical devices with no active medication, such as the copper IUD, indicate the dose as "1", the dose unit as "Other", and indicate "device" in the text field. For IUD route, select "Other" and write "intrauterine" in the text field. For Implant route, select "Other' and write "sub-dermal" in the text field

Excessive alcohol consumption and use of recreational drugs should not be reported as concomitant medications on the **Concomitant Medications Log CRF**. Instead, these may be considered baseline medical conditions, per site clinician judgment, in which case they should be recorded within the **Baseline Medical History Log CRF.** Consideration should be made to screen out participants who report a history of drinking alcohol or recreational drug use during the most recent pregnancy based on IoR discretion. If drinking excessive alcohol or recreational drug use is reported during follow-up, these should be captured as AEs on the AE log as "excessive alcohol use during breastfeeding" or "drug exposure during breastfeeding," .

Study staff should use the information obtained during the review of the medical and obstetric history to probe for additional medications that the participant may have forgotten to report.

It is preferable to record the trade or generic name of the medication based on exactly what the participant is taking within the CRF. A combination medication can be recorded as one entry using the generic name. If a combination medication does not have a generic name or the generic name is unknown, each active ingredient must be reported as a separate entry in order to be accurately identified at SCHARP.

If a participant is unable to provide the exact name of a medication, record the type or class of medication as the medication's name with the text "name unknown". For example, if the participant knows she takes a blood thinner, but cannot provide the exact name, use "anti-coagulant – name unknown" for the medication name field. Participants should then make every effort to contact the study site with the name of the medication or bring the medication, at her next scheduled visit, so that this information can be reconciled in the Con Med CRF.

Medication history information documented within the Concomitant Medications Log at the Screening Visit must be actively reviewed and updated at the Enrollment Visit. Review the information within the CRF with the participant at the Enrollment Visit and update as applicable.

7.3 Feeding Assessment

An infant feeding assessment is required at Screening, Enrollment, and every follow-up visit except the SEV. At Screening and Enrollment, the primary purpose of this assessment is to ascertain eligibility for the study and ensure that all infants who enroll in the study are exclusively breastfed by the infant's mother. The clinician should use the **Feeding Assessment-Screening and Enrollment CRF** to ascertain what the baby has been fed in the past seven days. Note that if the infant has received any foods or liquids other than the mother's breast milk, he/she should not be enrolled in the study (The eligibility criteria for the study also require that the mother is breastfeeding only one infant. If the mother indicates there are other children she is also nursing, she should be screened out of the study. This information will be based on self-report and documented on the Screening Behavioral Eligibility Worksheet and the Enrollment Behavioral Eligibility Worksheet, depending on the visit). In instances where the infant has received non-breast milk foods or liquids, additional counseling and information about appropriate infant feeding practices may be necessary and referrals for outside care may also be warranted. Sites are encouraged to make use of any locally available or study-specific resources about infant feeding, as needed (See Section 9.3 for more information). Mothers of infants who are exclusively breastfed should be asked about how long they intend to continue exclusive breastfeeding and provide the average number of times they nurse (or provide expressed milk) each day (24 hours). While there is not a study-defined minimum number of times each day a mother must breastfeed in order to be eligible for the study, additional probing about breastfeeding practices may be warranted if a mother indicates that she nurses her infant fewer than 6 times each day. To be

eligible for the study, mothers should intend to continue exclusive breastfeeding for at least 3 more months. Study staff should check answers provided on the **Feeding Assessment – Screening and Enrollment CRF** against answers provided on the Screening Behavioral Eligibility Worksheet and Enrollment Behavioral Eligibility Worksheet to make sure that no responses during either assessment would be exclusionary. Per standard of care or clinical discretion, additional questions may be incorporated into the feeding assessment and recorded in chart notes. Clinicians may ask about any breastfeeding challenges or successes and should address any questions the participant may have. An observed feeding may be incorporated into the feeding assessment, if deemed necessary by the clinician or if requested by the participant.

During follow-up visits when a feeding assessment is required, the **Feeding Assessment – Follow Up CRF** should be used to assess frequency of breastfeeding (or breast milk feeding) and will be used to document whether the infant has received any foods or liquids other than the mother's breast milk since the last study visit. When completing the **Feeding Assessment CRF**, site staff should try to confirm that infants who are breastfeeding received the mother's own breast milk. In rare circumstances, the study site may become aware of an infant who is receiving breast milk from someone other than the participant mother. If anything other than the mother's own breast milk has been provided, a **Feeding Inventory CRF** will be required to document what was given, when, and why. Note that a separate **Feeding Inventory CRF** should be completed for each type food or liquid the infant received other than the mother's milk.

If a mother reports that she has completely weaned her baby, she will continue to receive study product and both she and her infant will continue with all regularly scheduled study visits. For the purposes of this study, weaning will be defined as at least one week without providing any breast milk to the baby and no intention of providing it in the future. Some mothers may not consider comfort nursing to help soothe a crying baby or get a baby to sleep as providing breast milk, but since there is the possibility of milk transfer, all nursing or suckling at the breast should be considered breastfeeding.

7.4 Vaginal Practices

Vaginal practices will be assessed at each study visit and recorded on the **Vaginal Practices CRF**. At the screening visit, all participants should be administered the **Vaginal Practices CRF** to assess whether the participant reports any listed practices in the past 30 days. The CRF prompts for specific practices, e.g. insertion of water, water plus soap, or materials such as paper, cloth, or cotton wool, ashes or powders, or fingers to clean or insert something. The CRF also has a response option for "Other" which should be used to capture any vaginal practices reported but not listed. Note: All ***medicated*** vaginal products (including prescription medications, over-the-counter preparations, vitamins and nutritional supplements, and herbal preparations) should be recorded on the **Concomitant Medications Log** as noted in section 7.3 above and <u>not</u> on the **Vaginal Practices CRF**.

At all visits after screening, staff will assess whether the participant has inserted anything in her vagina since her last visit. If yes, a new **Vaginal Practices CRF** should be completed. Note that use of vaginal medication(s) or other vaginal products within five days prior to Enrollment is exclusionary (with day of enrollment counted as "Day 0").

At any point during the study, counseling on healthy vaginal practices/hygiene should be provided per standard of care, as needed.

7.5 Prohibited Medications, Products, and Practices

<u>Prohibited Medications – PEP and PrEP</u>

Concomitant use of medications for PEP and PrEP outside the context of study participation is prohibited. Additionally, at screening or enrollment, participant-reported use of PEP within 6 months prior to Enrollment is exclusionary. If PEP or PrEP use outside the context of study participation is reported during follow-up, study product should permanently discontinued. Use should be documented on the **Concomitant Medications Log CRF** and PSRT should be notified. Note: only PrEP use *outside* of the context study participation should be documented as a concomitant medication.

Although use of PEP is prohibited per protocol, in the event a participant reports possible exposure HIV, she should be provided or referred for PEP as soon as possible, ideally within 24-72 hours. If a participant initiates PEP, she will be permanently discontinued from product use but she and her infant may remain in study follow-up with modified procedures until their originally scheduled study exit date . See SSP section 6 for guidance on how to initiate a product discontinuation.

While the use of PEP and PrEP is prohibited in the context of trial participation, the MTN-043 study team is committed to provision of the highest standards of HIV prevention. Sites should outline in SOPs their procedures for PrEP provision and referrals, should a participant not want to join the study (or discontinue participation in the study) and instead access PrEP from locally available sources, as applicable. SOPs should also address circumstances and procedures for provision and referrals for PEP to potential or enrolled study participants. Please see further details outlined in section 7.6 below regarding SOP requirements for PrEP and PEP.

Prohibited Vaginal Products and Practices

Per protocol, concomitant use of vaginal products, including, spermicides, lubricants, contraceptive VRs, douches, vaginal medications, etc., is prohibited at any time during study follow-up.

Additionally, the following practices are prohibited in the 24 hours prior to each clinic visit:

- receptive sexual activity (including penile-vaginal intercourse, anal intercourse, receptive oral intercourse, finger stimulation)
- inserting any non-study objects into the vagina (including tampons, pessaries, sex toys, female condoms, diaphragms, menstrual cups, cervical caps or any other vaginal barrier method, etc.)

Participants will receive protocol counseling on what vaginal products and practices to avoid during all in-clinic visits starting at the enrollment visit (see SSP section 9.2). During the screening visit, prohibited practices and products are reviewed during the administration of informed consent. Healthy vaginal practices should be encouraged by clinic staff. For example, women should be advised against the use of douches, soaps, or other detergents to clean inside the vagina, as well as herbs or other materials to dry or tighten the vagina.

Should prohibited vaginal practices or products be reported, this should be documented on the **Vaginal Practices CRF**, unless the product is a vaginal medication (including prescription medications, over-the-counter preparations, vitamins, nutritional supplements, and herbal preparations which are intended to function as medication), in which case this should be documented on the **Concomitant Medications Log**. If prohibited vaginal practices or products are reported, study product use may continue, and counseling should be reinforced about what practices/products should be avoided during study participation.

7.6 SOPs for PrEP and PEP Provision and Referrals

As part of study activation, all sites are required to have in place site-specific procedures in place for training staff on current local guidelines, PrEP counseling, and as applicable, PrEP provision and referrals. Provision of PEP should also be addressed in site SOPs (either within this same SOP, or separately). The following information should be addressed within site SOPs:

- Current National PrEP-specific Guidelines/Policies
- Information for participants on PrEP
- Guidelines and Tools for providers, such as:
  - Indications for PrEP use

- Eligibility for/Contraindications to PrEP
- If applicable, procedures for on-site PrEP provision including:
    - Staff Training and certification
    - Procedures for initiation of PrEP, including required baseline evaluations and counseling
    - Ongoing safety monitoring and management, including conditions for stopping PrEP

- Plan for post-trial access of PrEP, if available
- Procedures and resources for referral for PEP (may be addressed in separate SOP, if preferred by site).

PrEP SOPs should be routinely reviewed and updated based on changes in local guidelines/policies and availability/accessibility of PrEP. The following are a list of resources for current information on PrEP:

- http://www.prepwatch.org/
- http://www.who.int/hiv/topics/prep/en/
- http://www.cdc.gov/hiv/risk/prep/index.html

7.7 Edinburgh Postnatal Depression Screening (EPDS) Tool

The EPDS will be utilized as a screening tool to help identify depressive symptoms and other mental health issues in maternal participants. The EPDS will be administered at Enrollment, Month 1, Month 2, and PUEV.

During the enrollment visit, the EPDS should be administered prior to randomization of the participant, such that any potential mental health conditions can be appropriately captured as pre-existing conditions on the **Baseline Medical History Log**.

> *NOTE: Scores of 10+ relate to possible depression and 13+ probable depression, however scores in isolation should never be used in eligibility determination—investigator judgement should always be used to determine need for further evaluation/referrals (or first line support if/when site has capacity to offer). In some cases, participants with elevated EPDS scores and/or clinically diagnosed depression may still be good candidates for participation in the study. If, however, an investigator feels that a participant's mental health status falls into the category of an "uncontrolled chronic condition" he/she may decide the participant is ineligible to join the study.*

The EPDS is a 10-item questionnaire that is available in all local languages for MTN-043 as a CRF. The questionnaire may be administered by any study staff member who has been trained in questionnaire administration and associated site SOPs as referenced below. Further guidance on administration of the EPDS is as follows:

- Read the introductory statement at the beginning of the questionnaire, highlighting that the questions on this form ask about how the participant has felt over the course of the past seven days.
- Read each numbered statement (1-10) to the participant word-for-word; after reading each statement, read the response categories for that statement word-for word. Note that the response categories differ for each statement.
- As needed, repeat the numbered statements and/or response categories (repeat probe) to help the participant understand the statements and the response categories she is asked to choose from. If needed, other types of probes may also be used to help the participant choose the response category that best matches how she has felt in the past seven days.
- Do not read the last item on the form (regarding referral) to the participant. Record "yes" or "no" for this item based on whether referrals were subsequently made. "Yes" should be recorded

whenever referrals to relevant services or resources available within the study site or external to the study site. All referrals should be further source documented in participant study records.

- For this study, the EPDS is not intended to be — and should not be — used for diagnostic purposes. **Medidata RAVE will automatically calculate the total score based on the participant responses.**
- A score of 10 or higher indicates possible depression, scores of 13 or higher indicate probable depression. Both should prompt discussion with the participant on reported symptoms and assessment of whether the participant may require additional support, evaluations, and/or treatment for possible depression or other mental health issues. If the participant expresses suicidal thoughts (item 10), immediate referral and possible hospital evaluation should be pursued. Specifically, responses of "Yes, quite often," "Sometimes", or "Hardly Ever" all require further evaluation and referral. It is recommended that enrollment procedures be discontinued on this day for these participants. The only exception to this is if a participant answers "hardly ever" and after further evaluation by the investigator, it is determined that they had only very fleeting suicidal thoughts, without the slightest hint of plan or intent. In this case, the investigator may use their discretion to proceed with enrollment. If the investigator has any doubt, it is recommended that enrollment be delayed until further evaluation or consultation (e.g. with the PSRT) can be obtained. All conversations with the participant about her response to this question as well as decisions made regarding enrollment and additional support/referrals should be clearly documented in the participant record.

- Follow site-specific SOPs with respect to further evaluation, treatment, documentation, and/or reporting of symptoms of depression.
- Any diagnosed conditions that meet criteria for entry into **Baseline Medical History Log CRF** (during enrollment) or **AE Log CRFs** (during follow-up) should be reported on these forms, respectively.

  Note: It is not generally expected that there will be a one-to-one correspondence between elevated scores and entries into Adverse Event eCRFs; clinical judgement and further evaluation is required to determine whether a participant has experienced an adverse event and whether any such adverse event meets protocol criteria for entry into AE Log CRFs.

7.8 Follow-up Medical History

An updated participant self-reported medical history is required at each scheduled visit during follow-up. 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.

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 applicable CRFs itself, 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 in the participant chart.

For purposes of this study, a "newly-identified" condition is defined as one of the following:

- 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 which should be reported in accordance SSP Section 7.1.2 above)

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**.

If, during follow-up, a baseline medical condition resolves or increases in severity or frequency from baseline, this is not updated on the **Baseline 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?". For example, a participant has a Grade 1 hemoglobin at Screening. At Visit 3, her laboratory test shows that the condition has resolved. Note the resolution in chart notes but do not update the Baseline Medical History Log CRF. At her 6-week PPO visit, her laboratory results show a Grade 1 hemoglobin result again. This Grade 1 event should be documented as an AE but it should not be considered a "worsening of condition" since her baseline result has previously resolved.

Any newly available medical records should also be reviewed when available.

Review of the medical history must be documented; this can be done in chart notes or in a site-specific tool if desired. If no new symptoms, illnesses, conditions etc., are reported, and if ongoing conditions remain unchanged, the participant chart should reflect this.

During follow-up, if a condition is identified as being present at baseline and the participant inadvertently did not report it in her baseline medical history, the clinician should add the newly-identified information to the **Baseline Medical History Log CRF**. A chart note should also be documented to explain why the newly-identified information is recorded on the **Baseline Medical History Log CRF** retrospectively.

7.8.1 Review of Medications History

At each follow-up visit, review the participant's concomitant medications history and document this review by completing the Concomitant Medications Log CRFs. Ask the participant if she has started taking any new medications, and record on the Concomitant Medications Log CRF any new medications she reports having started since her last medications assessment. In addition, review all previous entries that do not have a "*Date Stopped*" entered and ask the participant whether she 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 CRF** 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. For guidance on recording contraceptive methods as concomitant medications, refer to section 7.2 above.

7.9 Maternal Exams

7.9.1 Physical Exams

The goal of the Screening physical exam is to collect detailed information on baseline conditions, as well as to evaluate eligibility. All abnormal signs/symptoms/diagnoses identified during the screening physical exam should be recorded within the **Baseline Medical History Log CRF** and followed up on at the Enrollment visit.

A complete physical exam will be conducted at the screening visit and a targeted (abbreviated) physical exam for all subsequent scheduled exams. Per protocol Section 7.11, the following assessments are all required at the Screening physical exam (only bolded assessments are also required at scheduled follow up exams).

- **Vital signs:**
  - **Temperature**
  - **Pulse**

- **Blood pressure (See section 7.9.1.3 for further guidance)**
- **Respiratory rate**

- **General appearance**
- **Weight**
- Height
- Abdomen
- Head, eye, ear, nose and throat (HEENT)
- Lymph nodes: palpable cervical, axillary and/or inguinal lymph nodes
- **Breasts**
- Neck
- Heart: rate, rhythm, murmurs
- Lungs: observation of character of respirations, auscultation
- Extremities
- Skin: rashes, scars, bruising, needle tracks, jaundice
- Neurological

The organ system/body part evaluation as part of the physical exam assessment is documented within the **Physical Exam CRF**. The vital signs, weight, and height assessments are documented within the **Vital Signs CRF**.

After the full physical at screening, targeted physical exams are required at Enrollment, PUEV, and any Early Termination visits. Scheduled follow-up physical exams should include the bolded assessments outlined above, as well as any additional assessments deemed appropriate by the examining clinician.

If-indicated physical exams may be conducted at any time based on the discretion of the study clinician and in response to signs, symptoms, or other conditions present at the time of the visit. There are no required elements to these if-indicated exams, other than what the examining clinician deems necessary. Vitals may be routinely collected at any visit per site practice/standard of care.

Physical exams performed during follow-up (including unscheduled exams that are clinically indicated) are documented using the **Physical Exam CRF** and the **Vital Signs CRF**. Abnormal physical exam findings newly-identified during follow-up are recorded and tracked using the **Adverse Experience Log (AE) CRF**. See SSP Section 8 regarding AE reporting.

7.9.1.1 Weight

Weight should be measured in kilograms and should be rounded to the nearest tenth decimal place, if applicable (e.g., 54.7 kg). Scales must be calibrated at a frequency per the manufacture's recommendations or any local regulations, whichever is more stringent. It is recommended that scales be calibrated at least annually. At each site, consistent weighing procedures should be followed for all participants. Each site may choose to consistently weigh participants fully clothed or wearing clinic gowns.

7.9.1.2 Height

Height should be measured in centimeters and should be rounded to the nearest whole number, as applicable (e.g., 160 cm). For participants with hairstyles that could affect height measurements, a tongue depressor or other device should be held horizontally to the wall chart at the top of the participant's head (not at the top of her hairstyle) to obtain accurate measurements.

7.9.1.3 Blood Pressure

Blood pressure devices are expected to be calibrated regularly per manufacturer's directions.

If the participant develops hypertension during study follow-up, it is recommended that study sites evaluate and counsel the participant and refer the participant per site SOPs for further treatment and management. Antihypertensives, including thiazide diuretics and angiotensin converting enzyme (ACE) inhibitors, are not contraindicated in MTN-043. Any medication(s) should be recorded on the

Con Meds Log. The most recent blood pressure reading that is used for clinical management should be recorded on the Vital Signs CRF. For further guidance on completing blood pressure entries into Medidata, please see Vital Signs CRF Completion Guidelines.

7.9.1.4 Breast Exam

Breast exams should be completed at screening and as part of scheduled targeted exams after screening, including at the enrollment visit. The Enrollment breast exam should be done prior to final determination of eligibility and randomization. At Screening or Enrollment, any abnormal breast exam findings that are grade 2 or higher are exclusionary.

During the exam, the clinician should check the entire breast, underarm, and collarbone area for any abnormalities. The clinician should do a manual exam of one breast and then the other, making sure to also check the lymph nodes near the breast to see if they are enlarged. Clinicians should check the appearance of both breasts, making sure the appearance is normal, and the skin on the areolas and nipples is intact. As noted above, grade 2 or breast exam findings at screening or enrollment are exclusionary; during follow-up, the following conditions warrant intervention but not discontinuation of breastfeeding.

- Nipple pain: Common, normal at onset of breastfeeding, check latch and skin integrity.
- Nipple Thrush: Check infant oral cavity. Report infant AE (oral Candidiasis) as well as maternal, as appropriate.
- Mastitis: Breast pain/tenderness, red, wedge-shaped area
- Breast abscess: Firm, very tender breast, overlying erythema, fluctuant swelling
- Breast engorgement: Engorgement is breast fullness caused by edema with onset of lactation after birth, or at other times due to accumulation of excess milk
- Galactostasis/Mammary duct obstruction: Plugged ducts are areas of milk stasis within ducts that cause distended breast tissue.

During follow-up, all abnormal findings should be documented in the participant chart and on the **AE Log CRF**, if applicable. All prescription medications and over-the-counter preparations should be documented on the **Concomitant Medications Log.**

In addition to the scheduled breast exams required per protocol, breast exams may be performed any time they are clinically indicated during follow-up. Note that maternal *or* infant conditions could be an indication to perform a breast exam for the mother. Possible reasons for clinically indicated breast exams include, but are not limited to:

- Follow-up on previously reported AEs
- New participant report of pain/discomfort during or between feedings or other self-reported participant concerns
- Infant failing to gain weight as expected

All sites should have an SOP that includes information on the management of breastfeeding complications. At a minimum, this SOP should include information on the following:

- Clinical procedures and in-house expertise for managing maternal and/or infant complications that may be breastfeeding-related.
- Counseling for mothers who
    - are experiencing clinical challenges related to breastfeeding
    - are planning to or already have introduced supplemental foods to their infants
    - express desire to or have already weaned their babies from breastfeeding
- Referrals for additional breastfeeding support, if needed

7.9.2 Breast Milk Sample Collection

Participants will provide breast milk samples at all visits starting at Week 1. All Milk Samples must be frozen within 24 hours of collection.

A breast milk sample to confirm an adequate supply is not required at screening or enrollment since a mother must be exclusively breastfeeding to be eligible for the study. However, it is important to assess a participant's willingness and ability to provide breast milk samples during follow-up as part of the informed consent process. Information gleaned during the feeding assessments and physical exams (including the breast exam) should also be used to ensure the participant will be able to comply with protocol-required breast milk sample collection without any negative consequences for her or her baby.

While breast milk sample collection is an essential study procedure, sites should always prioritize women feeding their infants over providing the study-required breast milk samples. This is especially important for women who may be struggling with breast milk supply and infants who are not growing adequately or are sick. During a visit, if an infant is hungry, the participant should first feed her baby and then provide her breast milk sample. In some cases, this may mean that sample collection needs to be delayed until later in the visit than originally planned or that the full volume is unable to be collected.

Mothers will have the option to hand express their milk or use a site-provided manual breast pump. Women who have a personal pump (manual or electric) will also be permitted to use them for study purposes. Participants should be given a clean, quiet, and private space to express their milk. The **Breast Milk Expression Guide for MTN-043/B-PROTECTED** is available on the MTN-043 website and can be provided to participants who may need assistance learning how to express their milk. Indicate whether the breastmilk sample was collected via hand expression, breast pump, or both when it is recorded in the **Specimen Storage CRF.**

A minimum of 8 mls is required for study testing purposes. To obtain this sample, the participant should empty all milk from at least one breast into the study-provided collection container. Once the milk flow from the first breast has stopped, the site or participant should evaluate the volume collected. If at least 8 mls have been collected, milk collection should be considered complete. If less than 8 mls have been collected, the participant should proceed with expressing all milk from the second breast as well. If milk is collected from both breasts, it should be combined into one container. If a participant has expressed milk for 20 minutes and the breast is not empty and/or the minimum milk volume has not yet been collected, site staff may advise the participant to discontinue efforts at that time.

Once milk has been collected, a designated study staff member should follow the steps outlined in Section 10.9 to remove the aliquots required for testing purposes. Excess milk that is left over from sample collection may be returned to the participant, if desired, or poured down a sink drain. In cases where the participant wishes to keep the excess milk, site staff should review the **Feeding Expressed Breast Milk in MTN-043/B-PROTECTED** factsheet to make sure participants understand the storage guidelines and feeding techniques associated with expressed milk.

Milk collection is permitted off site, when needed. If this will happen as part of an off-site visit, site staff should take any equipment with them that might be needed. Aliquoting may take place at the off-site visit or, if the participant does not wish to keep excess expressed milk, the entire sample may be transferred back to the study lab for aliquoting. If milk collection during a regularly scheduled clinic visit is missed for any reason, this may also be made up by asking the participant to collect milk off site as soon as possible within the visit window. The site should provide a milk collection container to the participant, though any clean plastic vessel can be used if this is missed. Arrangements should be made for the participant to return her sample to the clinic or for clinic staff to retrieve the sample from the participant. The sample may be refrigerated or stored at room temperature until it can be returned to the clinic lab for processing. The temperature of the transported samples must not exceed 25^{o}C; cold packs can be used as needed.

7.9.2.1 Breast Pump Cleaning and Storage

Breast pumps must not be shared between participants. If using a personal pump (not study-provided) for milk collection in the study, participants should follow manufacturer's instructions for cleaning of pumps, If not specified in these instructions, do not use bleach or organic solvents. Make sure that if the participant is using soap to clean her pump, any soap residue is completely removed after use as this can affect eventual testing.

Study-provided breast pumps should be cleaned by site staff and stored on site in between study visits. Pumps can be cleaned by disassembling and placing all parts in boiling water for five minutes. Pump parts should be thoroughly air dried before storing for the participant until her next visit. Sites should clearly label each pump storage container with the participant's PTID so it can be easily identified at her next clinic visit.

7.9.3 Pelvic Exams

Pelvic exams are required at the Screening and Enrollment visits, PUEV, and Early Termination. They should be done if indicated at all other visit types. The pelvic exams during Screening and Enrollment are necessary to evaluate protocol exclusion criteria and to collect detailed information on baseline genital/genitourinary conditions. The Enrollment pelvic exam should be done prior to final determination of eligibility and randomization. At Screening or Enrollment, any abnormal pelvic exam findings that are grade 2 or higher are exclusionary. Note that cervical bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal by the IoR/designee is not exclusionary, nor considered an AE.

Additional pelvic exams may be performed if indicated. Pelvic exams are considered clinically indicated when new genitourinary complaints are present, based on investigator discretion. Investigators should consider referrals for further evaluation as needed and all new symptoms, regardless of resolution date and whether or not a pelvic exam was conducted, should be reported as adverse events per section 8.10 of this manual.

7.9.3.1 Pelvic Exam Procedures

Pelvic examinations will be conducted per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at https://apps.who.int/iris/bitstream/handle/10665/69748/WHO_RHR_04.02_eng.pdf;jsessionid=9291A4A28F8951CC188B1F61DB46C8DA?sequence=1

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 ensure 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 at different time points during the exam. Use a speculum of appropriate type and size to permit adequate visualization of the vagina and cervix.

Prior to the Exam: Prepare all required equipment, supplies, and paperwork; label specimen collection supplies as needed. Verify that all equipment is in good working order. Review documentation of prior exams (as applicable) and other relevant documentation from the current visit and prior visits. While the participant is clothed, explain the procedure to her and answer any questions she may have.

Examine the External Genitalia:

- Do not insert the speculum before examining the external genitalia.
- Relax 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, and perianal area.

Examine the Cervix and Vagina:

- A speculum exam is required during enrollment pelvic exams, and only if indicated during other exams. 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 of the cervix, if applicable, and vagina.

Removal of Visual Obstruction: Any obstruction (e.g., mucus, cellular debris) may be removed with 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.

Complete Examination of the Cervix and Vagina: To complete the naked eye examination 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.

Collect Specimens: If the clinician is collecting swabs, collect specimens in the order listed on the pelvic exam checklist and after the speculum is removed (collapsed vaginal walls).

Perform Bimanual Exam: If indicated, after completing all of the above-listed tissue examinations and specimen collection and removing the speculum, perform a bimanual exam for adnexal or fundal masses and/or tenderness and to confirm normal involution of the uterus during the postpartum period.

7.9.3.2 Documenting Pelvic Exam Findings

All exam findings (normal and abnormal) should be documented on the site-designated source document, as specified in the site's Source Documentation SOP. All abnormal findings must be thoroughly documented (e.g., to include type, size, anatomical location, and severity grade) on the **Pelvic Exam CRF**, and any other relevant source documents as desired, to ensure appropriate assessment can be provided during the next pelvic exam.

All abnormal findings observed during the Screening and Enrollment Visits will be documented on the **Pelvic Exam CRF** and the **Baseline Medical History Log CRF**. All abnormal findings identified during follow-up will be documented on the Pelvic Exam CRF. All newly-identified abnormal pelvic exam findings will be documented on an AE Log CRF. The results of site local laboratory test results performed using specimens collected during pelvic exams are recorded on the **STI Test Results CRF.**

All pelvic exam findings consistent with the "grade 0" column of the FGGT are considered normal. For the purposes of this study, 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
- cervical ectopy

- expected bleeding
- edema
- vulvar varicosities

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 often but not always deep)

Color:

- Normal
- Slightly red
- Red
- White
- Other (includes “pale”)

Blood Vessels

Integrity:

- Intact
- Disrupted

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

Table 7-1 below provides further information to guide and standardize terminology used to describe abnormal pelvic exam findings.

Table 7-1: 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. May be sharp or diffuse.	
Edema	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 often but not always deep.

Refer to Protocol Section 7 and Appendix I for a listing of when clinical and laboratory evaluations for gonorrhea, chlamydia, syphilis, hepatitis B, and trichomonas are required. Bacterial vaginosis (BV) and candidiasis should also be evaluated if indicated based on participant symptoms.

7.10 STI/RTI/UTI

Refer to Protocol Section 7 and Appendix I for a listing of when clinical and laboratory evaluations for gonorrhea, chlamydia, syphilis, hepatitis B, and trichomonas are required. Bacterial vaginosis (BV) and candidiasis should also be evaluated if indicated.

7.10.1 Considerations at Screening/Enrollment

Participants diagnosed during screening with an STI/RTI/UTI requiring treatment may be enrolled in the study after treatment is complete provided all symptoms have resolved and the 35 day screening window is still open. Test of cure for STI/RTI/UTIs after treatment is NOT required before a participant is enrolled. Results of all STI testing should be documented on the **STI Test Results CRF**. UTI testing (dipstick/urinalysis) should be documented on the **Urine Test Results CRF.**

Syphilis: If a reactive RPR is identified during screening, a confirmatory test (MHA-TP or TPHA) result must be received, and appropriate clinical management action taken, prior to enrollment in the study. Action required prior to enrollment depends on the current health status of the participant and the availability of medical records documenting her prior infection, as follows:

- If the participant has clinical signs or symptoms of syphilis, she must be treated prior to enrollment. If the participant is otherwise eligible for the study, enrollment may proceed immediately following completion of treatment and resolution of signs and symptoms.

- If the participant has no clinical signs or symptoms of syphilis, but credible medical records are not 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 Baseline 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 or cure (i.e., four-fold decrease in titer) is not

required prior to enrollment; however, repeat serology is expected 6 months after treatment for clinical management purposes.

Genital warts: Genital warts requiring treatment must be treated prior to enrollment. Genital warts requiring treatment include those that cause an undue burden of discomfort to the participant, e.g., due to bulky size, unacceptable appearance, and/or physical discomfort (equivalent to a Grade 2 or 3 finding on the DAIDS FGGT). Documentation of improved participant symptoms to Grade 1 or 0 must be present before the participant is considered eligible for participation.

Vaginal candidiasis: Participants diagnosed with symptomatic vaginal candidiasis during screening are eligible once they have completed treatment and symptoms have resolved.

7.10.2 STI/RTI/UTI Diagnosis

If an STI, RTI, or UTI is identified during follow-up, it should be documented as an AE. 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.

Genital HSV: No laboratory testing is required for herpes simplex virus (HSV-1 or HSV-2) during the study but may be done if indicated and per local standard of care. Per the FGGT, the term 'genital herpes' may only be used for adverse event reporting if laboratory testing is conducted to confirm HSV; otherwise sites are encouraged to use the most appropriate row in the FGGT which most closely resembles the clinical findings (ulceration, for example).

Urinary tract infections (UTIs): UTIs may be diagnosed in MTN-034 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. See SSP Section 8 for guidance on documenting UTI AEs based on symptoms or culture.
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

7.10.3 STI/RTI/UTI Management

Treatment: All participants diagnosed with a UTI should be provided treatment per site standard of care and applicable site SOPs. All STIs/RTIs should be managed per current WHO guidelines, site standard of care and applicable site SOPs. When clinically appropriate, investigators should use oral or parenteral medications to avoid intravaginal medication use. Observed single dose treatment should be provided whenever possible, per clinician discretion.

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.**

Syndromic Management: Syndromic management of STIs is acceptable per site SOP and local standard of care; however, a thorough laboratory evaluation is expected in the context of this research study so that a specific diagnosis might be uncovered.

Test of Cure: STI/RTI tests of cure are not required in MTN-043 but may be recommended for pregnant participants per local guidelines. .

Partner Referrals: Participants' partners should be offered treatment, or referrals, as per sites' SOPs.

7.10.4 Vaginal Discharge

Both participant complaints and clinical findings of abnormal vaginal discharge are common in microbicide studies. While the evaluation of abnormal vaginal discharge may not differ between the

two, whether treatment is offered and how the abnormality is reported may. Abnormal vaginal discharge may be associated with yeast and/or BV among other conditions. Site clinicians are encouraged to thoroughly evaluate complaints and/or findings of abnormal vaginal discharge as per their discretion. Whether to treat the underlying cause of the abnormal vaginal discharge will depend on:

1. What the underlying diagnosis is; and,

2. Whether the participant is symptomatic.

If the evaluation reveals an underlying STI such as trichomoniasis, the participant and her partner(s) should be offered treatment regardless of symptoms. If the evaluation reveals BV or yeast, the participant should be offered treatment only if she is symptomatic. Sites should prescribe non-vaginal treatment when possible.

SSP Section 8 details the reporting of vaginal discharge adverse events.

7.10.5 Collection of Vaginal Swabs

Table 7-2 below outlines schedule of pelvic exams and vaginal swab samples, as well as the swab type required for each test, for MTN-043. All vaginal swabs will be clinician collected during the pelvic exam (either required or if-indicated). The ideal order of swab collection is outlined on the visit checklists, as well as reflected in table 7- below.

Table 7-2. Schedule of Pelvic Exams and Vaginal Swab Samples

		Swab Type	SCR	ENR, PUEV, & Early Term
Pelvic Samples in Order of Collection	NAAT for GC/CT/Trich	Cepheid	X	*
	Vaginal swab(s) for microbiota	Dacron		X
	Vaginal pH	Dacron	*	*
	Wet prep/KOH wet mount for candidiasis and/or BV	Dacron	*	*
	Vaginal Gram stain	Dacron		X
	Vaginal swab(s) for biomarkers	Dacron		X

X = Required; * = If indicated and/or per local standard of care

7.11 Postpartum Cconsiderations

Vaginal bleeding judged by the clinician to be within the range of normally anticipated in the postnatal period should not be reported as an AE. Vaginal bleeding, uterine cramping, and perineal pain present at the time of screening or enrollment should be captured on the **Baseline Medical History Log CRF** so resolution or worsening of symptoms during follow-up can be accurately captured. Heavy bleeding may be related to infection, retained products of conception, bleeding diathesis, or choriocarcinoma and merits further investigation as well as AE reporting.

See Section 8.3 regarding guidance on AE terminology and grading during the postpartum period.

7.12 Care and Support for Seroconverters

During follow-up, HIV testing will be performed as described in Section 10 of this manual and participants who become infected with HIV will have modified study procedures/visit schedule as described in Section 5.6.2 of this manual and outlined in the MTN-043 Procedure Guide for HIV Confirmation and Seroconversion, available on the MTN-043 website. Sites are encouraged to use a modified visit checklist for these visits to ensure only study procedures permissible for a seroconverter are performed.

All participants with confirmed HIV infection will be counseled and actively referred to available sources of medical and psychosocial care and support, **including immediate referral for ART treatment with or without cessation of breastfeeding**, per site SOPs (see also Section 9) and local standards of care. The potential of infant prophylaxis will also be discussed if applicable. Infants whose mothers have seroconverted will have an additional visit 12 weeks after maternal seroconversion is diagnosed. See Section 5.X for more information on these visits.

Site staff must actively follow-up on all referrals on a weekly basis until care is established to determine if the participant actually sought the care to which she was referred, the outcome of the referral, and whether additional referrals are needed. All referrals, outcomes, and follow-up plans and actions must be fully documented in participant study records.

While MTN-043 cannot provide clinical care and treatment for HIV infection, protocol-specified examinations and laboratory tests will provide information upon which appropriate clinical care decisions can be made. In particular, the studies will provide information on participants' stage of HIV disease, HIV RNA PCR, CD4+ T cell count, and information on HIV drug resistance.

Given the above, study staff must refer participants to non-study HIV care providers for initiation of antiretroviral therapy (ART), or for additional care and management for those who may be experiencing a drug-related toxicity, or may need to consider changing ART regimens due to resistance. Study staff will provide and explain all study examination findings and test results to participants. They also will provide copies of laboratory test result reports to participants and their non-study providers. Study investigators will be available to consult with non-study providers on optimal clinical care and treatment decisions for participants.

Routine resistance testing will be completed for every participant who has a confirmed positive HIV test after enrollment. Resistance testing will take place at the Virology Core (VC) lab (Pittsburgh) and results will be provided from the VC to site IoRs as they become available. This information should be filed in the participant binder and shared with the participant and her HIV care provider. The participant should be counseled accordingly, members of the LC and VC will be available to site leadership to talk through all resistance results. If there are any questions related to clinical next steps, the IoR should contact the PSRT for further guidance.

7.13 Pregnancies

In the event of a participant pregnancy, follow procedures outlined in Section 5.7 of this manual.

7.14 Management of Laboratory Test Results

Hematology, liver function (AST/ALT), and creatinine testing will be performed at the schedule as outlined in MTN-043 protocol appendix I. For each study participant, the IoR or designee is responsible for monitoring these test results over time and for ensuring appropriate clinical management of all results. All reviews of laboratory test results should be documented on the lab results printout (provided by the lab to the clinic) and/or in chart notes.

Document all abnormal Screening Visit lab values (i.e., severity grade 1 and higher), regardless of grade, on the **Baseline Medical History Log CRF**. During Follow-up, all abnormal lab results, not otherwise associated with a reported clinical AE and that were not present at baseline, will be reported on the **AE log**.

All sites must establish SOPs for reporting and managing critical laboratory values. At a minimum, all test results of severity grade 3 and higher, and all results requiring product hold (see protocol section

9.3-9.4), should be considered critical and urgently reported to a study clinician; lower grade results also may be considered critical at the discretion of the IoR.

The IoR or designee should routinely review MTN-043 participant study records to ensure proper monitoring and clinical management of laboratory test results, and documentation thereof. All reviews performed by the IoR or designee should be documented in participant study records.

7.14.1 Calculating Creatinine Clearance Rates

Each time a participant's serum creatinine level (Cr) is tested, her creatinine clearance (CCr) rate must be calculated, using the Cockcroft Gault formula, which applies to all participants regardless of age per the protocol. Note the participant serum creatinine value and weight is required for this formula. As such, weight should be measured each time sample for Cr is drawn. To facilitate proper calculation, all sites should use the MTN-043 Creatinine Clearance Calculator, which is available on the MTN-043 website. The worksheet will calculate the creatine clearance rate and percent change from baseline. After completing the Excel worksheet, a copy should be printed, initialed and dated, and filed in the participant's chart.

Should a site not want to use the calculator and instead use local laboratory calculated CrCl values available on lab reports, this must receive prior approval by the MTN LC.

7.15 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for product hold and discontinuation, guidance on product hold and discontinuation in response to observed AEs, and management of other clinical findings, HIV infection, and early study termination. Conditions requiring product hold or permanent discontinuation are summarized in Figure 7-3 below. Note that if an AE is reported in retrospect that would have required a product hold and PSRT consultation prior to resumption, these processes must be followed, even if the AE has since lessened in severity.

All specifications in Protocol Sections 9 must be followed. IoRs are encouraged to consult the PSRT with any questions related to proper interpretation of the protocol and proper management of study product use.

Flow sheets outlining product management procedures can be found on the MTN-043 Study Implementation Materials webpage. 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.

All product holds and discontinuations must be communicated to site pharmacy staff using the Study Product Request Slip, as described in SSP Section 6. Product holds and discontinuations also must be documented within the **Product Hold Log** and/or **Discontinuation of Study Product CRFs**, as appropriate.

Table 7-3 Conditions Requiring Product Hold or Permanent Discontinuation

Condition	Temporary Hold	Permanent Discontinuation
Positive HIV Rapid Test Result	X	
Confirmed HIV infection		X
Acquisition of hepatitis B infection (for Truvada group only)		X
Initial result of ≥ Grade 2 creatinine clearance (for Truvada group only)	X	
Confirmation of ≥ Grade 2 creatinine clearance after retesting within one week (for Truvada group only)		X
Initial result of ≥ Grade 2 glycosuria or proteinuria (for Truvada group only)	X	

Confirmation of ≥ Grade 2 glycosuria or proteinuria (for Truvada group only) after retesting within one week.		**X**
Allergic Reaction to the study product		**X**
Reported use of PrEP for HIV prevention outside of the study		**X**
Reported use of PEP for potential HIV exposure		**X**
Non-therapeutic injection drug use		**X**
Pregnancy		**X**
Unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their/their infant's safety and well-being by continuing product use, according to the judgment of the IoR/designee.	**X**	
Grade 3 maternal AE **Related** to Study Product Use	**X**	
Grade 4 maternal AE (regardless of relationship to study product)	**X**	
Grade 3 or 4 infant AE (regardless of relationship to study product)	**X**	
Deep epithelial disruption (ulceration)	**X**	
Coenrollment (consult PSRT regarding ongoing product use and other potential safety considerations)	**X**	

7.16 Clinical Management of Infants

7.16.1 Medical Records Release

All sites should obtain a signed medical record release and pediatric care provider information at the screening visit, if required by local laws and regulations to allow the study site to obtain copies of pediatric care records throughout study participation. Sites should ensure the medical records release includes the following (or similar) language: *As the legal guardian of [insert infant's name], I provide the [site name] permission to access his/her pediatric care records. Information from these records may be abstracted by staff and entered into the study database.*

Since the medical records release is only signed at the screening visit, site teams may want to encourage potential participants to bring any available pediatric care records with them to the screening visit so these can be evaluated by study staff and included in participant charts, as appropriate. Once a signed medical release is on file, staff should reach out to pediatric care providers following the screening visit to obtain any additional records that might be available. These should be reviewed and evaluated between screening and enrollment, if possible. Any records that are newly available at the time of enrollment must also be reviewed to help confirm infant eligibility.

Note that study visits do not replace routine care provision for mothers or their infants and this should be made clear to participants. Adherence to any post-partum care visits for mothers and well-baby care visits for infants should be encouraged and facilitated, if needed, by the study staff.

7.16.2 Infant Care

Globally, most common immediate causes for early childhood mortality include infectious conditions, e.g., diarrhea, respiratory infections, malaria, and measles. Per the WHO ETAT guidelines, the following emergency signs in infants should prompt immediate action:

- Obstructed or absent breathing
- Severe respiratory distress
- Central cyanosis
- Signs of shock (cold extremities with capillary refill time >3 seconds and a weak, fast pulse)
- Coma (or seriously reduced level of consciousness)
- Seizures

- Signs of severe dehydration in a child with diarrhea with any two of these signs: lethargy or unconscious, sunken eyes, very slow return after pinching the skin

There are a number of conditions that are common within the first year of an infant's life which are summarized in this section. Close attention and appropriate clinical management and/or prompt referrals should be made whenever infant AEs are identified.

- **Rash**: seborrheic dermatitis common in the first month; after three months of age commonly atopic dermatitis.
- **Thrush (oral candida infection):** Thrush may develop as early as 7 to 10 days of age and appears often within the first year of life. In the healthy newborn, thrush is a self-limited infection, but it usually should be treated to avoid feeding problems. Infants with recurrent or persistent thrush should be tested for HIV.
- **Undernutrition, stunting, and wasting:** Because of rapid growth and increased vulnerability to infection, children <2 years of age are most at risk groups for undernutrition. Severe acute malnutrition (SAM) is diagnosed by using the weight-for-length z score (WLZ) and graded using the underweight row (<2 years of age) in the DAIDS tox table. In infants <6 months, SAM is defined by a very low weight-for-length or the presence of bilateral pitting edema.
- **Infant vomiting:** Can be hard to tell if infant is spitting up or vomiting because some infants reflux forcefully or in large amounts. In infants <3 months old, forceful vomiting always requires further evaluation. Potential causes in these infants include narrowing of stomach (pyloric stenosis) or blockage of intestines (intestinal obstruction). Infants can also vomit because of infections
- **Serious bacterial infection:** Pneumonia is one of the leading causes of childhood deaths. Clinical diagnosis and treatment of pneumonia a challenge, especially in neonates and young infants <2 months of age. Fast breathing (⩾60 breaths/min.) in infants up to 59 days a sign of pneumonia (small proportion of healthy young infants breathe faster than 60 breaths per minute).
- **Lower Respiratory Tract Infection:** Characterized in infants by poor feeding, irritability and lethargy, gruting/cyanosis, fever, cough/wheeze, chest in drawing.

  Treating these illnesses maybe outside of the site's clinical capacity in which case the expectation is that site staff will facilitate prompt referral to an appropriate health care facility.

7.16.3 Infant Medical History and Concomitant Medications

As with mother participants, as full medical and medications history of the infant should take place at the screening visit and be actively reviewed at all subsequent visits. Medical records should be reviewed when available.

In order to obtain a complete, accurate, and relevant participant self-reported medical history, it will be necessary to ask the infant's mother about significant past medical conditions as well as any current conditions the infant is experiencing.

It is recommended that sites use the **MTN-043 Infant Medical History Assessment** (available on the MTN-043 web page under Study Implementation Materials) in conjunction with the **Baseline Medical History Log CRF** in the infant's casebook and/or chart notes to guide and document medical history taking. Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit complete and accurate information from the participant. During follow-up, sites should review any previously reported medical conditions for updates as appropriate. Infant AEs should be captured in the infant's casebook using the **Adverse Event Log.**

Medications used by the infant also are ascertained at screening and all subsequent study visits. Medication use should be documented on the **Concomitant Medications Log** within the infant's casebook**.** Documentation should include the start and stop dates of these medications as well as the indication, frequency, dose and route. During follow-up, also record whether the medication was taken to treat a reported AE.

7.16.4 Infant Physical Exams

A complete physical exam will be conducted at the screening visit and a targeted (abbreviated) physical exam for all subsequent scheduled exams. Per protocol Section 7.11, the following assessments are required at the Screening physical exam (bolded assessments are also conducted at scheduled follow up exams).

- **Vital signs**
  - **Temperature**
  - **Pulse**
  - **Blood pressure**
  - **Respirations**
- **General appearance**
- **Weight**
- **Length**
- **Head circumference**
- **Heart**
- **Lungs**
- Abdomen *Note: Abdominal examination should include examination of the genitals, specifically noting whether genitalia are female/male/intersex; for males whether testes are descended and whether any hypospadias is noted, or any other abnormalities*
- Head, eye, ear, nose and throat (HEENT)*
- Lymph nodes
- Neck
- Extremities
- Skin
- Neurological
- **Ages and Stages® assessment (at Enrollment and PUEV only)**

After the full physical at screening, targeted physical exams are required at Enrollment, PUEV, and any Early Termination visits. Scheduled follow-up physical exams should include the bolded assessments outlined above, as well as any additional assessments deemed appropriate by the examining clinician.

If-indicated physical exams may be conducted at any time based on the discretion of the study clinician and in response to signs, symptoms, or other conditions present at the time of the visit. There are no required elements to these if-indicated exams, other than what the examining clinician deems necessary.

Infant exams should be documented on the **Physical Exam** and **Infant Vital Sign CRFs**.

7.16.5 Assessing Infant Growth

MTN-043 uses the intergrowth 21st and WHO growth standards to monitor growth (weight, length, and head circumference (HC)) for infants up to one year of age). Site staff should access these growth charts via the links provided in Table 7-3 below (also posted on the Study Implementation Tools section of the MTN-043 website). Note that different charts are used for term/preterm infants, and for girls/boys. If the infant was preterm, the weight should be plotted according to postmenstrual age according to the intergrowth charts. For term infants, growth should be plotted against the WHO growth charts using percentiles. Note that per protocol, infants with a birth weight <2000 grams should be excluded.

A table with direct links to the appropriate growth charts is provided below. All growth charts are available on the MTN-043 Study website under study implementation tools.

Table 7-3: Growth Charts to Use for MTN-043

GA age at birth	Growth Chart Used at All Visits =
Preterm (<37 weeks)	Intergrowth Postnatal Growth Preterm Boys Intergrowth Postnatal Growth Preterm Girls
Term (≥37 weeks)	WHO growth Charts: Boys Weight for Age 0-2 Years Boys Length for Age 0-2 Years Boys Head Circumference for Age 0-2 Years Girls Weight for Age 0-2 Years Girls Length for Age 0-2 Years Girls Head Circumference for Age 0-2 Years

Precise weight and length measurements are critical for accurate growth assessments and interpretations. At each visit, study staff should plot the infant's weight, length and head circumference on the appropriate growth chart. If weight and/or length measurements taken prior to screening are available in infant medical records, these should be plotted on the appropriate growth chart along with measurements taken by the study team. The same chart should be used from visit to visit so changes over time can be easily tracked. Staff initials and dates should be recorded either on the chart itself next to each point or on the back of the form. Individual points should be connected with a single line so the growth curve can be seen. The positions of individual points on the plot are less important than this overall trajectory and growth over time.

Major percentile curves on the growth charts lie at the 3, 15, 50, 85, 97th percentiles. If the plotted point is on or near the percentile line (either just above or below), the infant is described as being at that percentile.

Growth charts are not intended for use as diagnostic instruments, but should be used as screening tools that contribute to forming an overall clinical impression for the child being measured. Healthy children typically follow the same growth trajectory over time. A normal growth curve is between the 3rd and 97th percentile and parallels the 50th percentile growth line. Weight should be proportional to length.

Questions to consider when evaluating a child's growth include the following:

- Does the child's growth follow a consistent pattern, i.e., percentile assessments are trending positively along the same trajectory?
- Is growth between the 3rd and 97th percentiles?
- Are there health issues or factors from the additional information gathered during the medical history that may be impacting growth, e.g., illness and/or decreased appetite?
- What did the mother report during the feeding assessment? Are there any challenges with breastfeeding that could explain the growth trajectory? Has the infant been exposed to any foods or liquids besides breast milk that might be impacting growth?
- How does the infant appear on physical exam? How is his/her strength/color/alertness/, etc.? Are there any unusual features that could suggest a syndrome or genetic abnormality?

The growth curve trajectory over time should be evaluated while the infant is still in the clinic, keeping in mind that clinical referral with documented action plans or an interim visit for re-checking growth may need to be scheduled if growth concerns arise.

Further investigation may be warranted based on growth charts showing any of the following:

- An upwards or downwards trend over a short period of time where a child crosses 1 major

percentile curve, sustained on 2 occasions, particularly for weight-for-age.
- Growth consistently below the 3rd percentile or > 97th percentile
- Flat growth curve trend, i.e., when infant is not gaining weight between visits. Infants are expected to regain birth weight by two weeks of age and then gain about 0.5 to 1 ounce (15-30 grams) per day through the first few months of life, Double birth weight by 5-6 months, triple by 1 year. Any period of not gaining weight after two weeks of age needs to be followed closely with interim visits (e.g., 1 month follow-up weight check) and referral to a dietician if the weight is not improving.

Clinicians should consider potential cause(s) of growth abnormalities/disturbances, such as poor nutritional intake due to challenges with breastfeeding or improper mixing of formula, tuberculosis, protein energy malnutrition, or chronic illness. Refer to a pediatrician (if a pediatrician is not listed on the MTN-043 Delegation of Duties log) and/or a dietician for assessment and treatment plan as soon as possible, preferably within one week. It is also highly recommended that the site schedule an interim infant visit(s) within an appropriate period for follow-up to assess progress. Weight and length should be plotted on the growth chart during any interim visits scheduled to follow-up on infant growth.

7.16.6 Infant Blood Draws

All enrolled infants will have blood drawn for the protocol-outlined samples as outlined in Appendix II. Blood may be collected by heel stick, or by using a 23gauge butterfly needle for venous puncture, per site SOPs. Details about specimen collection and processing may be found in SSP section 10.7.

7.16.7 Ages and Stages Assessment

MTN-043 will use the Ages & Stages Questionnaires (**https://agesandstages.com/**) to track developmental progress and identify infants who may need referral for developmental or social-emotional evaluation. The ASQ3 screens 5 domains—Gross Motor, Fine Motor, Communication, Problem Solving, and Personal Social.

The ASQ3 questionnaires are available for download on the MTN-043 website under study implementation tools. The appropriate questionnaire based on the infant's age should be administered at Screening, Enrollment, PUEV, and Early Termination. Depending on infant age, it may be necessary to use the ASQ 2 Month, 4 Month, or 6 Month questionnaire. The ASQ-3 Age Calculator (www.agesandstages.com/age-calculator/) should be used to help select the correct questionnaire. Sites should select the administration date (visit date), child's date of birth, and indicate how many "weeks premature" the infant was born. To determine weeks premature, subtract the child's gestational age when born from **37 weeks**. For example, if the child was born at 36 weeks, enter "1 week" in the "weeks premature" field, if born at 35 weeks enter "2 weeks" in the "weeks premature" field. Click 'calculate' to determine the appropriate questionnaire to administer.

Questionnaire Administration

The ASQ3 questionnaires should be administered by a clinical staff member who has received training on the assessment. Questionnaires are only available in English, but should be discussed in the language that the participant is most comfortable with. Alternatively, if the mother is literate in English, the questionnaire may be provided to her to complete and then reviewed with a staff member before the end of the visit. Note that staff should make cultural substitutions (e.g. say 'rice' instead of 'applesauce') or adapt questions as needed (e.g. if culturally inappropriate to look in a mirror, use a cell phone camera instead) to elicit the most accurate response to each item.

Mothers should be reassured that this is a screening tool and that her baby may not be able to do everything being asked yet. It can be explained that the tool is used to identify social-emotional or developmental strengths, as well as concerns. Some example language that may be used when introducing the questionnaire is below.

> *"ASQ-3 provides a quick check of your child's development."*
>
> *"Your answers will show your child's strengths and any areas in which your child may need more help or practice."*

"The information you provide will be helpful in determining whether your child needs further assessment."

"Your child may be able to do some, but not all, of the items."

Sites should have available any materials that may be needed for infants to try any activities, as needed (e.g. small toy, ball, string, mirror, book, crayon, paper, small box, cloth). Familiar toys or objects should be used when possible. Babies should be rested and fed—it can help to make it a game. Explain the response items to the mother before administering the questionnaire:

- **Yes** = child is performing the skill
- **Sometimes** = child is just beginning to perform or does on occasion
- **Not Yet** = child is not yet performing skill

Obtaining the most accurate information should come from having the child try each activity (if feasible in clinic) and discussion with the mother. Mothers should be advised to answer questions based on the babies on usual behavior. Note: It is not required that each activity be "performed" in front of clinic staff member in order to respond "yes" or "sometimes"– discussion with mother about what is typical should be used to elicit the most accurate response.

Documentation and Scoring

Items on the questionnaire that are not relevant to a research population (e.g. all of page 1, and identifying information on the Information Summary Page) should be lined through, initialed and dated. PTID, visit date, and staff initials and date should be added to each page of the questionnaire.

The ASQ3 should be scored after administration and total scores for each domain calculated. Scores are calculated as follows:

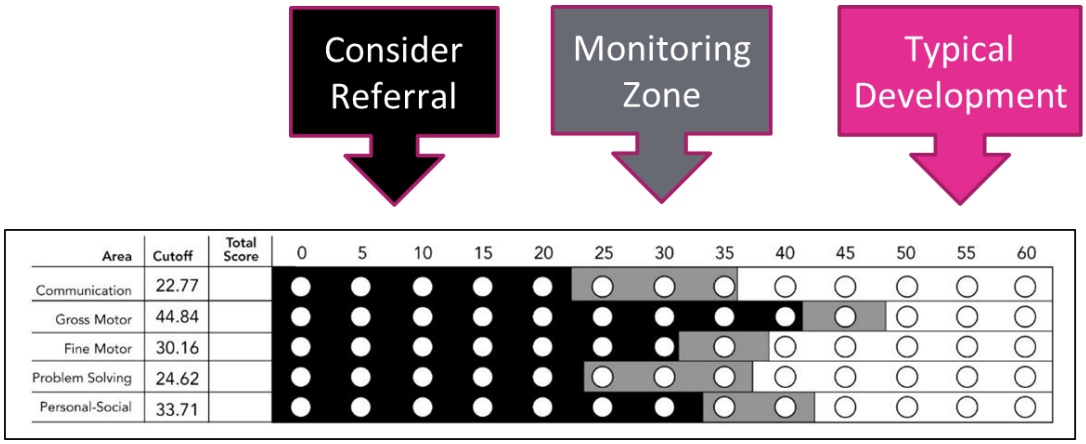
- YES = 10 points
- SOMETIMES = 5 points
- NOT YES = 0 points

It is anticipated that the questionnaire will be administered in the clinic and no response items will be missing. However, if 1 or 2 items are missing, an adjusted score should be calculated using the following online tool: https://agesandstages.com/free-resources/asq-calculator/ If three or more items are missing, do not score the area—screening results may not be accurate.

Total the points in each of the five developmental areas and record the scores on the **Information Summary Page** (final page of the questionnaire) and **Infant Ages and Stages Assessment CRF**—and compare results to the area cutoffs. Also refer to the YES and NO responses and notes from the Overall section so that they can be considered alongside scores for decision-making.

Monitoring, Referrals and Follow-up

The **Information Summary Page** provides the area cutoffs that may indicate a need for referrals (black shaded area) or monitoring (grey shaded area). An example from one of the ASQ questionnaires is provided below.



It is recommended that parents of infants with scores in the monitoring zone be provided age-appropriate learning activities to support the child's development. Ideas for learning activities by age group that staff can review with parents are available on the MTN-043 website under Study Implementation Tools. Staff can also consider rescreening infants that fall in the monitoring zone earlier than scheduled per protocol (e.g. within 2-3 months, during an interim visit). Staff may also use their discretion to provide referrals for further evaluation for infants in the monitoring zone.

Scores below the area cutoffs should be assessed along with any relevant clinical findings and discussion with the mother about any concerns, to determine if referral for further evaluation of any developmental or social-emotional issues is warranted. If the child's scores are close to the area cutoff, staff may decide to provide learning activities and rescreen in shorter timeframe instead of pursuing immediate referrals.

Regardless of child's scores, if concerns are noted in the overall section (the free text section of the questionnaire), they should be discussed with parent. Refer to the **Guide for Using the ASQ-3 Overall Questions** available on the MTN-043 website as a resource for making potential referrals in different developmental areas.

All referrals should be made per site SOPs and documented in the participant record. Should further evaluation result in a diagnosed condition, sites should report on the Infant AE Log CRF and update the Infant Ages and Stages Assessment CRF to indicate that an AE has been reported.