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7 Introduction

This section presents information on the clinical procedures performed in MTN-042. The Schedule of Study Visits and Evaluations in Appendix I and II of the protocol indicates when specific clinical and laboratory assessments are to take place. While the protocol dictates the schedule for data capture, the Investigator of Record (IoR) or designee should perform the 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. 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 Medical Records Release/Routine Antenatal and Well-Baby Care

All sites should obtain a signed medical record release (or other documentation which allows for release of medical records), if required by local laws and regulations, as well as antenatal and delivery care provider information at the screening visit in order to contact care providers to obtain available records. For sites that require a medical records release, it is recommended that the following (or similar) language be included: *By signing this release, I provide the [site name] permission to access medical records related to my delivery, including information about my infant at the time of birth. Information from my delivery records may be abstracted by staff and entered into the study database.*

Note that in order to be eligible for the study, participants must be willing and able to provide permission to contact participant's antenatal and postpartum care provider(s) and to obtain copies of antenatal and postpartum care records, including information about the infant at the time of delivery. This permission for the purposes of eligibility determination is documented on the Baseline Behavioral Eligibility Worksheets. All women must also intend to enroll their infant in the study at the time of their enrollment.

Note that it is expected and should be encouraged that mothers continue all their routine antenatal care during their study participation. Similarly, once babies are born, adherence to well-baby care visits should be encouraged. Study visits do not replace routine care provision for mothers or their infants and this should be made clear to participants.

7.2 Maternal Baseline Medical History

Participant baseline medical history and obstetric symptoms are initially collected and documented at the screening visit and then actively reviewed and updated, as necessary, at the enrollment visit. Medical records, including ultrasound results and antenatal care records should also be reviewed when available. Participants should also be encouraged to bring copies of any records in their possession, i.e. antenatal cards or ultrasound reports to the screening and/or enrollment visit.

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)
- Assess and document risk factors other than *in utero* exposures to study products that could contribute to fetal demise, other adverse pregnancy outcomes or congenital malformations.

In order to obtain a complete, accurate, and relevant participant self-reported medical and obstetric history, it will be necessary to ask the participant about significant past medical conditions as well as any current conditions. Previous pregnancy history, including capture of all information on the **Pregnancy History CRF**, as well as history related to her current pregnancy, should be reviewed.

Attention should be paid to evaluate the protocol-specified exclusion criteria related to conditions during the participant's current or previous pregnancies.

It is recommended that sites use the **MTN-042 Baseline Medical and Obstetric History Guide** (available on the MTN-042 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 7.3 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. 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, medication, and obstetric history should be reviewed, including any review of newly available antenatal records or ultrasound reports, and updated, as needed.

7.2.1 Documenting Maternal Baseline Medical Conditions

Details of all relevant conditions identified during the baseline medical and obstetric 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 and/or diagnosed during her current or any past pregnancies. Note that conditions diagnosed during past pregnancies that are not ongoing should be indicated as resolved by marking NO for the question "Is the condition ongoing?".

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 or obstetric exam abnormalities
- Abnormal pelvic exam findings (note: pelvic exam required at enrollment visit, may be conducted if indicated at the screening visit)
- 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 CRF**, 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-042.

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 (i.e. up to the point of randomization) 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 5j 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.

7.3 Maternal Concomitant Medications

The MTN-042 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. Please note vaginal preparations used solely to prepare the vagina for childbirth should be captured on the **Vaginal Practices CRF**, not the **Concomitant Medications CRF** (see Section 7.4).
- Contraceptive medications (if applicable, e.g. at the 6-week PPO visit)
    - 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

Alcohol consumption and recreational drugs should not be reported as concomitant medications on the **Concomitant Medications Log**. Instead, alcohol consumption, defined as any drinking during pregnancy, and any recreational drug use during pregnancy may be considered baseline medical conditions, per site clinician judgment, in which case they should be recorded within the **Baseline Medical History Log.** Consideration should be made to screen out participants who report a history of drinking alcohol or recreational drug use during the current pregnancy based on IoR discretion. If drinking alcohol or recreational drug use is reported during follow-up, these should be captured as AEs on the **AE Log CRF** (see section 8 for guidance on AE reporting terms).

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.

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.

7.4 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 (including practices to prepare for birth/labor). 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 not 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.

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

Prohibited Medications – PEP and PrEP

Concomitant use of medications for PEP and PrEP outside the context of study participation is prohibited. At screening or enrollment, participant-reported use of PrEP or PEP during her current pregnancy is exclusionary. If PEP or PrEP use outside the context of study participation is reported during follow-up, study product should be held (PEP use) or discontinued (PrEP use) and use should be documented on the **Concomitant Medications Log CRF** and PSRT 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 placed on a temporary product hold until prophylaxis regimen is complete. See SSP section 6 for guidance on how to initiate a product hold. Upon completion of PEP use, the study participant may resume study product use per her visit schedule after consultation with PSRT.

While the use of PEP and PrEP is prohibited in the context of trial participation, the MTN-042 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 and also reference the MTN-042 Protocol Counseling Guide available on the MTN-042 website). 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**. Vaginal products used to prepare for childbirth should be captured on the **Vaginal Practices CRF**.

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

- Procedures and resources for referral for 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 Ultrasound Results

Availability of adequate ultrasound results is required for enrollment into MTN-042. If these are not available from medical records at the screening visit, then an ultrasound should be scheduled, and results reviewed at or before the enrollment visit. Per protocol inclusion criteria #2, the ultrasound should be performed no later than the 36th week of gestation for Cohort 1 or the 28th week of gestation for Cohort 2.

Ultrasound measurement of the fetus in the first trimester (up to and including 13 6/7 weeks of gestation) is the most accurate method to establish or confirm gestational age (GA). If adequate records are available from the first trimester, these should be used for eligibility determination. However, it may not be possible to ensure that participants have a first-trimester ultrasound, particularly for Cohorts 1 and 2, given these are not routinely performed in the MTN-042 study countries. As such, the protocol outlines the following maximum gestational ages from which ultrasound results must be available across cohorts. All ultrasounds must be from 8 0/7 weeks GA or later.

Cohort	GA at Enrollment	GA that ultrasound must be available from
1	36 0/7 weeks – 37 6/7 weeks	8 0/7 - 36 6/7 weeks
2	30 0/7 weeks – 35 6/7 weeks	8 0/7 - 28 6/7 weeks
3	12 0/7 weeks – 29 6/7 weeks	8 0/7 weeks - prior to enrollment

In order to have ultrasound results from the acceptable GA range, ultrasounds may occur during prescreening as part of standard of care, especially for Cohorts 1 and 2.

The primary purpose of the ultrasound prior to enrollment is to establish gestational age (see section 7.8 below), and confirm evidence of a viable, intrauterine, singleton pregnancy as part of eligibility determination. Anatomical survey data are to be reported if available. Special note should be made of abnormal findings including assessment of whether the finding impacts participant eligibility.

Ultrasound results that are used to determine participant eligibility should be entered on the **Ultrasound Results CRF** in the Enrollment folder in Medidata RAVE.

Ultrasound results used to confirm eligibility should include, at a minimum, the following:

- Date of scan
- Number of fetuses
- If estimated gestational age is <14 0/7 weeks, a crown-rump length
- If estimated gestational age is 14 0/7 weeks or greater, femur length, abdominal circumference, and biparietal diameter
- Placental location
- Calculated gestational age on the date of the scan or estimated date of delivery

  *NOTE: number of fetuses and placental location are not items that are captured on the **Ultrasound Results CRF**, however, an ultrasound with these elements present is required to evaluate participant eligibility.*

To facilitate obtaining all the required information from the ultrasound scan needed for eligibility determination and completion of the CRF, an optional **Ultrasound Request Form Template** is available on the MTN-042 Study Implementation Tools section of the website. This may be particularly relevant where participants are being referred to external providers to have ultrasounds completed.

During follow-up, if a problem with the pregnancy is suspected, an ultrasound can be ordered, or a referral provided. All ultrasound results obtained during the trial should be entered on an **Ultrasound Results CRF**.

7.8 Calculation of Gestational Age

Calculation and confirmation of gestational age (GA) is required at the screening and enrollment visits. The best obstetric estimate should be used as the measure for gestational age, rather than estimates based on the last menstrual period (LMP) alone. A tool to facilitate gestational age redating is available on the MTN-042 website under study implementation tools.

Sites should use the following online calculator to determine EDD based on LMP:

http://perinatology.com/calculators/Due-Date.htm

Additionally, a calculator to determine the gestational age on a specific date (i.e., the date of enrollment) is available here: https://www.perinatology.com/Reference/Fetal%20development.htm

During the screening visit, sites should calculate the GA using all available information. This may only include the Last Menstrual Period (LMP), if ultrasound results are not yet available. Calculation of the GA at screening is important to ensure that participants are scheduled within the appropriate enrollment window for their cohort.

Once ultrasound results are available, and prior to enrollment, GA should be reviewed and re-dated if necessary.

Gestational age assessment based on measurement of the crown–rump length (CRL) has an accuracy of ±5–7 days in the first trimester. The range of second-trimester gestational ages (14 0/7 weeks to 27 6/7 weeks of gestation) introduces greater variability and complexity, which can affect revision of LMP dating and assignment of a final estimated delivery date (EDD). Table 16 from the MTN-042 protocol includes guidelines for re-dating based on ultrasound.

Table 16. Guidelines for Redating based on Ultrasonography

Gestational Age Range *(based on reported LMP, on the date of ultrasound)*	Discrepancy between Ultrasound Dating and LMP that Supports Redating
≤ 8 6/7 weeks	More than 5 days
9 0/7 weeks to 15 6/7 weeks	More than 7 days
16 0/7 weeks to 21 6/7 weeks	More than 10 days
22 0/7 weeks to 27 6/7 weeks	More than 14 days
28 0/7 weeks and beyond	More than 21 days

If the estimated gestational age by the participant's LMP differs from the ultrasound estimate by more than these accepted variations, the ultrasound estimate of gestational age should be used instead of the participant's LMP estimate.

At the enrollment visit, the **Pregnancy Assessment CRF** should be completed to capture information including the participant's LMP, estimated GA at enrollment, estimated date of delivery (EDD) and information used to determine the EDD.

7.9 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. For Cohorts 1 and 2, the EPDS will be administered at the enrollment visit and the 6-week PPO visit, and as needed at any other timepoint. For cohort 3, the EPDS will be administered at additional timepoints at a frequency of once per trimester.

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-042 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 <u>not</u> 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 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** (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.***

7.10 Follow-up Medical History

An updated participant self-reported medical and obstetric 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 7.2.1 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, including ultrasound results, delivery records, and/or antenatal/postnatal care records should also be reviewed when available. During the first visit following a participant's pregnancy outcome, detailed information about her pregnancy outcome should be obtained (see section 7.10.2 below for details).

Review of the medical and obstetric 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.

7.10.1 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 7.3 above.

7.10.2 Pregnancy Outcome

During the first visit following a participant's pregnancy outcome, detailed information about her pregnancy outcome should be obtained. This will typically occur at the post pregnancy outcome (PPO) visit, which should be completed as soon as possible after the pregnancy outcome, and has a visit window of 14 days from the time of pregnancy outcome. Some initial pregnancy outcome information may also be obtained during the 1-week PPO phone contact, if this visit occurs. If the PPO visit is missed, effort should be made to obtain complete pregnancy outcome information as soon as possible, either during an interim visit or at the 6-week PPO visit. See SSP section 5.5.5.1 for further details regarding missed PPO visits.

When at all possible, efforts should be made to obtain medical records relating to a participant's pregnancy outcomes prior to her PPO visit, such that records can be reviewed by clinical staff in advance of her visit, and any follow-up questions be asked of the participant during her visit.

Effort should be made to capture complete and accurate information as outlined on the **Pregnancy Outcome CRF,** including:

- Outcome date and location

- Pregnancy outcome (full term live birth (≥37 weeks), premature live birth (<37 weeks), stillbirth/intrauterine fetal demise (≥20 weeks), spontaneous abortion <20 weeks, therapeutic/elective abortion, other)
- If "Stillbirth/intrauterine fetal demise", "Spontaneous abortion", or "Therapeutic/elective abortion" a brief narrative of the circumstances
- If "Stillbirth/intrauterine fetal demise", whether fresh, macerated or unknown
- Method of delivery (e.g., caesarian section, vaginal delivery – normal, unassisted, vaginal delivery – assisted (forceps and/or vacuum), other)
- Complications related to pregnancy outcome
- Fetal/infant congenital anomalies

Note that complications related to pregnancy outcome and congenital anomalies are reportable as AEs and/or SAEs; please see section 8 of the SSP as well as AE reporting requirements in the MTN-042 protocol section 8.3 for more details. Sites should be mindful to reconcile reported information on the PO CRF with any reported AEs prior to the mother's study exit (e.g., if an AE is reported for gestational hypertension, this should also be reflected on the PO CRF). Congenital anomalies may also require photographic documentation, if consent has been provided (See SSP Section 7.19.9 below).

Infant information from the time of birth should also be captured on the **Pregnancy Outcome CRF**, including:

- Infant Sex
- Birth Weight
- Birth Length
- Head circumference
- Body temperature
- Pulse
- Rate of respiration
- Oxygen saturation
- Gestational age by best estimation at delivery
    - *Note: GA should be abstracted from review of delivery records and not a new assessment of GA made by the site clinician during the PPO visit*

Information regarding clinical management of enrolled infants is provided in section 7.19 below.

7.11 Maternal Exams

7.11.1 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 required at scheduled follow up exams).

- **General appearance**
- **Weight (see Section 7.11.1.1 for further guidance)**
- **Vital signs:**
    - **Temperature**
    - **Pulse**
    - **Blood pressure (See section 7.11.1.3 for further guidance)**
    - **Respiratory rate**
- Abdomen
- Head, eye, ear, nose and throat (HEENT)

- Height (see section 7.11.1.2 for further guidance)
- Lymph nodes: palpable cervical, axillary and/or inguinal lymph nodes
- 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**.

During follow-up, physical exams are required at the week 4 visits (Cohorts 2-3 only), the PPO Visit, and when clinically indicated. Scheduled follow-up physical exams should include the **bolded** assessments outlined above. Additional assessments may be performed at the discretion of the examining clinician in response to signs, symptoms, or other conditions present at the time of the exam. Furthermore, 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 Event Log (AE) CRF**. See SSP Section 8 regarding AE reporting.

7.11.1.1 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. Calibration records should be maintained in study essential document files. 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.

7.11.1.2 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.

7.11.1.3 Blood Pressure

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

Note: known hypertensive disorder of pregnancy during the current or previous pregnancies are exclusionary and these participants should not be enrolled.

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. For example, if a participant presents with an elevated blood pressure, a repeat blood pressure and urine dipstick should be done to evaluate for preeclampsia, and further management provided through referral to her antenatal care provider as needed. Similarly, should a participant present with symptoms of a UTI and dipstick reveals LE 1+, nitrate neg, 3+ protein, blood pressure should also be done to evaluate for preeclampsia and further referrals to ANC provided as necessary.

Hypertensive disorders of pregnancy should be reported as an AE (see SSP section 8.5) and any medication(s) should be recorded on the **Concomitant Medication Log**. The lowest of repeat blood pressure readings 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.

7.11.2 Obstetric Abdominal Exams

Obstetric abdominal exams are required at all in-clinic visits prior to the PPO Visit (i.e. all visits before pregnancy outcome). Obstetric exams during screening and enrollment should contribute to evaluation of any baseline conditions and potential eligibility status. Exams during follow-up serve the purpose of continued monitoring of the participant's pregnancy, evaluation and management (or referral) of any potential issues, and reporting of AEs, as appropriate.

All obstetric exams will include the following assessments and be documented on the **Obstetric Abdominal Exam CRF**:

- Appearance
- Palpation of abdomen to assess for tenderness
- Fundal height
- Auscultation of fetal heart tones (by Doppler, fetoscope or ultrasound), including rate per minute (not measured if fetus already known to be deceased but has not yet been delivered). If differentiating between maternal and fetal heart rates is difficult, the clinician can check the maternal radial pulse to ensure that the fetal heart rate is truly fetal.

If a problem with the pregnancy is suspected, an ultrasound can be ordered, or a referral will be provided. All ultrasounds conducted during follow-up should be entered on the **Ultrasound Results CRF**.

7.11.3 Pelvic Exams

Pelvic exams are required at the Enrollment visit, and should only be done if indicated at all other visit types, including the screening visit. The pelvic exam during the Enrollment Visit is 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.

Follow-up pelvic exams are only required if indicated. Pelvic exams are considered clinically indicated when new genitourinary complaints outside of the range of normal for pregnant (or recently post-partum) women are present, based on investigator discretion. Investigators should consider referrals for further evaluation as needed, for example, if the participant is experiencing heavy bleeding or potential rupture of membranes that is not within the capacity of the site to evaluate. 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 of this manual.

7.11.3.1 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: All swabs may be self-collected for MTN-042. However, if a speculum exam is being conducted, sites may choose to have the clinician collect any required swabs for that visit to minimize burden on the participant. Similarly, if the participant is uncomfortable collecting the swabs herself, she may request for the clinician to collect them instead (See Section 7.12.5 for more information). If the clinician is collecting swabs, collect specimens in the order listed on the pelvic exam checklist and without a speculum in place (collapsed vaginal walls).

Perform Bimanual Exam/Cervical Check: If indicated, and if within the capacity of site care, after completing all of the above-listed tissue examinations and specimen collection and removing the speculum, perform a bimanual exam/cervical check for adnexal or fundal masses and/or tenderness.

7.11.3.2 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 Result CRF**.

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

- 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
- increased vaginal discharge
- 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.

7.12 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.

7.12.1 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: It is recommended that investigators use their discretion and not enroll participants who screen positive for syphilis. A new diagnosis of syphilis during pregnancy would fall under the purview of an obstetric complication, and a positive antibody test in a previously treated participant would need to be followed to confirm stability and is beyond the time frame of this protocol. Women diagnosed at screening or in follow-up should be provided treatment per site SOPs, as well as referrals for continued management/care

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.

7.12.2 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; otherwise sites are encouraged to use the most appropriate row in the FGGT which most closely resembles the clinical findings (ulceration, for example). Should a participant be newly diagnosed with HSV in follow-up, she should be encouraged to share this information with her obstetric care provider as it may impact delivery planning.

Urinary tract infections (UTIs): UTIs should be diagnosed in MTN-042 based the presence of symptoms and lab results indicative of a UTI (i.e., dipstick and/or urine culture) as per site standard of care. Given that UTI symptoms are often similar to normal conditions experience during pregnancy (e.g. frequent urge to urinate), UTIs should **not** be diagnosed on symptoms alone. See SSP Section 8 for guidance on documenting UTI AEs. Isolated findings of protein or glucose on dipstick, even if noted incidentally while testing for leukocyte esterase and nitrates, should be reported as a laboratory abnormality AE as per SSP section 8.11. In addition, findings of proteinuria should prompt a blood pressure evaluation to rule out preeclampsia.

7.12.3 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. When this is not possible, for example oral fluconazole for the treatment of yeast vaginitis during pregnancy may be contraindicated at certain sites, vaginal medication may be used but should be reported as a protocol deviation. 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-042 but may be recommended for pregnant participants per local guidelines. .

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

7.12.4 Vaginal Discharge

Increased vaginal discharge is a normal occurrence in pregnancy. Physiologic discharge of pregnancy is typically clear to white and homogenous and increases in amount with advancing gestational age. Determining whether a participant's report of increased vaginal discharge merits evaluation is per clinician discretion. Certainly, if the discharge is associated with pruritis, irritation, or odor, it may be worthwhile to assess for symptomatic BV and/or yeast. If the description is consistent with physiologic discharge associated with pregnancy, an evaluation need not be done and no AE should be submitted as this is considered a normal finding (see protocol 8.3.1).

When a participant reports increased vaginal discharge, it will be incumbent on the clinician to ascertain through history whether the discharge might be amniotic fluid in a woman whose amniotic sac spontaneously ruptured. Signs and symptoms which raise the possibility of ruptured membranes rather than physiologic discharge include the following:

- Colorless to slightly yellow thin watery discharge (the consistency of urine)
- An associated gushing or "pop" sensation
- Significant volume to saturate undergarments and clothes

If rupture of membranes is suspected an exam is indicated. The site may elect to perform that evaluation at site, depending on the expertise of the staff, or refer for immediate evaluation to the antenatal clinic.

Similarly, lochia/vaginal discharge within the 6-8 weeks after delivery is considered normal and not reportable as an AE.

Of note, in previous MTN studies, clinicians were asked to distinguish between participant reported and clinician observed discharge. That is not necessary for this study.

7.12.5 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-042. All vaginal swabs can be self-collected, however, clinicians will collect swabs if a pelvic exam is being conducted and/or if this is the preference of the participant. If swabs are being collected by the clinician based on participant preference, this should be documented on the visit checklist and/or chart notes but completion of the pelvic exam checklist, diagrams form, or pelvic exam CRF is NOT required (as this is not considered a pelvic exam). When samples are required because of clinical indications (e.g. wet prep/KOH wet mount), a pelvic exam will be required and therefore a clinician will collect. The ideal order of swab collection is outlined on the visit checklists, as well as reflected in table 7-2 below and the **MTN-042 Swab Order Collection Guide** available on the MTN website.

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

		Swab Type	Visit 1	Visit 2	Cohorts 2-3 only		Bi-weekly Visits After 36th Week	PPO Visit	6-week PPO Visit/SEV/ Early SEV
			SCR	ENR	2-week Visit	4-week Visit(s)			
Pelvic Exam			*	X	*	*	*		*
Pelvic Samples in Order of Collection	NAAT for GC/CT/Trich	Cepheid	X	*	*	*	*	*	X
	Vaginal swabs for microbiota	Dacron (2 swabs)		X	X	X	X		X
	Vaginal pH	Dacron	*	X	*	*	*		X
	Wet prep/KOH wet mount for candidiasis and/or BV	Dacron	*	*	*	*	*	*	*
	Vaginal Gram stain	Dacron		X	X	X	X		X
	Vaginal swab(s) for biomarkers	Dacron		X	X	X	X		X

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

The following should be noted about self-collection of swabs:

- The sample for GC/CT/Trich testing is a collection kit provided by instrument manufacturer (Cephied); if sites switch to another method because of stock outages, the swab type recommended by the manufacturer will be used . All other samples are collected with a Dacron swab. **The most essential element of this process is use of the correct swab type.**

- There is a desired order of collection of swabs shown in table 7-2. This will be followed when the samples are collected by the clinician. Sites will also request participants to follow this order during self-collection, with the understanding that compliance may not be 100%.
- Participants will not be asked to perform vaginal pH or to create gram stain slides. Once these samples are self-collected, they will be given to study staff for vaginal pH and creation of slides.
- Sites may opt to use one sample for GC/CT/Trich or to collect one sample for GC/CT and a separate one for Trich. All tests can be performed from one swab, but collecting two swabs allows for repeat testing in case of issues.

A visual poster outlining the steps for self-collection of a single swab, **MTN-042 Self-Collected Vaginal Swab Instructions**, can be found on the MTN-042 website. Site staff should utilize the poster and review the instructions with the participant when she first collects a swab, and as needed throughout study follow-up. Participants should also be provided guidance on what order to collect swabs in and which type of swab to be used for each test through use of the **MTN-042 Swab Order Collection Guides.** These guides are provided for all visits where more than one swab is expected to be self-collected by the participant. The guides are templates which utilize color-coding to facilitate appropriate swab collection order, and can be adapted to meet site needs. If required locally, sites will submit these materials to local regulatory bodies.

7.13 Postpartum Considerations

After delivery, uterine cramping, perineal pain, and bleeding that is judged by the clinician to be within the range normally anticipated in the postpartum period (approximately 6 weeks following delivery) are not reportable as an AE per protocol. A first or second degree laceration should be considered a normal finding after delivery. It is not necessary to report these as AEs unless there are extenuating circumstances surrounding the tear, such as infection or disproportionate pain. A third and fourth grade tear should prompt AE reporting. Heavy bleeding may be related to infection, retained products of conception, bleeding diathesis, or choriocarcinoma and merits further investigation as well as AE reporting.

Breastfeeding complications may be noted and should reported. 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.

See Section 8.4.1 regarding guidance on AE terminology and grading during the postpartum period.

Sites should have procedures in place for clinical management of breastfeeding complications as well as counseling around breastfeeding topics. This may include in-house expertise for managing maternal and/or infant complications that may be breastfeeding-related, counseling for mothers experiencing challenges related to breastfeeding, resources for addressing questions about introduction of supplemental foods and/or desire to wean, and/or referrals for additional breastfeeding support or clinical management.

7.14 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 of this manual and outlined in the MTN-042 Procedure Guide for HIV Confirmation and Seroconversion, available on the MTN-042 website. **Per protocol, these participants will be followed a minimum of 12 months.** A sample Post-Seroconversion Quarterly Visit Checklist is available on the MTN-042 study website.

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 and PMTCT**, per site SOPs (see also Section 9). 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-042 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 be well positioned to 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.

7.15 Subsequent Pregnancies

In the event of a subsequent pregnancy after pregnancy outcome (e.g., identified through pregnancy testing at 6-week PPO visit), sites are advised to contact the MTN-042 PSRT for PTID-specific guidance. As the product use period will not continue after delivery, no considerations for product holds/discontinuations apply for subsequent pregnancies. Sites should provide clinical management and referrals for antenatal care for subsequent pregnancies per site SOPs.

Note that participants who have a subsequent pregnancy should **not** be considered for enrollment into later cohorts (i.e., cohorts 2-3).

7.16 Management of Laboratory Test Results

Hematology, liver function (AST/ALT), and creatinine testing will be performed at the schedule as outlined in MTN-042 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.

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), 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-042 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.

7.16.1 Creatinine and Creatinine Clearance Rates (Maternal Participants)

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 a sample for Cr is drawn (see protocol section 7.12). To facilitate proper calculation, all sites are encouraged to use the creatinine clearance calculation tool available on Atlas:

> https://atlas.scharp.org/cpas/project/Collaborators/Lab%20Unit%20Conversion%20Tool/begin.view?

Note that the calculator provides results to one decimal point, which is an acceptable level of precision for entry into Medidata RAVE.

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.

Elevated creatinine clearance during pregnancy is expected. As such, high Cr or low CrCl during pregnancy is more concerning in a pregnant woman in the second or third trimester than in a non-pregnant woman, and should be followed up accordingly. Creatinine typically returns to normal levels in the postpartum period. As such, Cr and CrCl will be graded based on absolute values only and not changes from baseline (see protocol section 9.5).

Management of infant creatinine is addressed in section 7.19.3 below.

7.17 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 (Section 9.3), guidance on product hold and discontinuation in response to observed AEs (Section 9.4), and management of other clinical findings (Sections 9.5), HIV infection (Sections 9.6), and early study termination (Section 9.7). Conditions requiring product hold or permanent discontinuation are summarized in Table 7-3 below.

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-042 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.

Participants should be counseled to stop using product when the suspect they are going into labor and/or of if rupture of membranes is suspected. Should labor progress, the **Discontinuation of Study Product CRF** should be completed with indication that the product was discontinued for one of the

protocol-specified scheduled reasons for discontinuation (see * in table below). Product holds for the reason of “suspected onset of labor or rupture of membranes” should only be reported in retrospect, once it is confirmed that labor did not progress and that the participant was clinically eligible to resume product use. For example:

- Participant suspects she is going into labor on 27APR2021 and she stops product use and reports to the hospital. She is admitted and delivers the next day.
    - Complete Discontinuation of Study Product CRF with a reason of “report of admission to care for labor and delivery management” and date study product use ended as 27APR2021.
    - No Product Hold CRF is required

- Participant suspects she is going into labor on 27APR2021 and she stops product use and reports to the hospital. After evaluation they send her home as the labor failed to progress. She notifies the clinic the next day (28APR2021) of the false labor and participant is advised to resume product use. On 30APR2021, she suspects labor again, and this time is admitted and delivers on the same day.
    - Complete Product Hold CRF with a reason of “suspected onset of labor or rupture of membranes”, date of last study product use 27APR2021, date hold was initiated 28APR2021 (date when the site was made aware of the hold), and date study product resumed 28APR2021.
    - Complete Discontinuation of Study Product CRF with a reason of “report of admission to care for labor and delivery management” and date study product use ended as 30APR2021.

Table 7-3 Conditions Requiring Product Hold or Permanent Discontinuation

Condition	Temporary Hold	Permanent Discontinuation
HIV Infection, PrEP or PEP Use		
Positive HIV Rapid Test Result	X	
Confirmed HIV infection		X
Reported use of PrEP for HIV prevention prior to pregnancy outcome.		X
Reported use of PEP for potential HIV exposure	X	
Delivery/Pregnancy Outcome Related		
Report of admission to care for labor and delivery management, including induction of labor and cesarean delivery*		X
Suspected onset of labor or rupture of membranes.	X	
Confirmed labor or rupture of membranes*		X
Pregnancy Loss*		X
Other Conditions/Events Requiring Hold or Discontinuation		
Non-therapeutic injection drug use		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	
Coenrollment (consult PSRT regarding ongoing product use and other potential safety considerations)	X	
Holds/Discontinuations in Response to Adverse Events		
Allergic Reaction to the study product		X
Grade 3 AE **Related** to Study Product Use not in Section 9.5	X	
Grade 4 AE (regardless of relationship to study product)	X	
Conditions Requiring Hold/Discontinuation for **oral Truvada Group** Only:		
Acquisition of hepatitis B infection		X
Initial result of ≥ Grade 2 creatinine clearance	X	
Confirmation of ≥ Grade 2 creatinine clearance after retesting within one week		X
Initial result of ≥ Grade 2 glycosuria or proteinuria	X	
Confirmation of ≥ Grade 2 glycosuria or proteinuria after retesting within one week		X
Conditions Requiring Hold/Discontinuation for **Vaginal Ring** Group Only:		
Superficial epithelial disruption (abrasion/peeling) **which has worsened** after re-evaluation in 3-5 days	X	
Deep epithelial disruption (ulceration)	X	
Symptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) **which has worsened** after re-evaluation in 3-5 days	X	
Asymptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) **which has worsened** after re-evaluation at the next scheduled visit	X	
Generalized erythema or severe edema (area >50% of vulvar surface or combined vaginal and cervical surface)	X	
≥ Grade 2 genital bleeding	X	
Unexpected Grade 1 genital bleeding **due to deep epithelial disruption**	X	
Cervicitis (inflammation and/or friability)	X	
≥ Grade 2 chorioamnionitis (leading to referral for delivery per SOC)		X

*Considered scheduled reason for product discontinuation per protocol and will be mapped accordingly in any reports

7.18 Non-Enrolled Infants

Due to the nature of MTN-042, there may be certain circumstances in which infants are not enrolled in the study (or not enrolled yet). As defined in SSP section 5.5.2, infants must meet the following conditions to be enrolled in MTN-042: (1) born alive and (2) have infant IC provided. Only infants that meet these conditions will be considered 'enrolled' in the study.

For infants who are not enrolled (or not enrolled yet), a limited amount of information related to the infant's status at the time of delivery may be captured from delivery records and/or maternal report and documented in the mother's casebook using the mother's PTID. Written medical records release, if required by local laws/regulations, or other site-specific documentation should specify permission from the mother to capture information related to their infant at birth from their medical records (see section 8.1 above). This includes information on the **Pregnancy Outcome CRF** (pregnancy outcome, congenital anomalies, infant sex, birth weight, length, and other measurements taken at birth). Additionally, any gradable adverse events should be captured on non-enrolled infants as part of the mother's casebook on the **Non-Enrolled Infant AE CRF.** No additional data on non-enrolled infants (e.g. concomitant medications, etc.) should be captured.

Note that use of the **Non-Enrolled Infant AE CRF** may also be relevant when reportable conditions related to the fetus are identified. See section 8.16 for details.

Should a non-enrolled infant be subsequently enrolled, any AEs reported on the **Non-Enrolled Infant AE CRF** should be transferred over to **Infant AE CRF** within the infant casebook for further tracking and management. All **Non-Enrolled Infant AE Log** lines should be deactivated.

7.19 Enrolled Infants

The remainder of this SSP section applies to infants who are enrolled in MTN-042. See SSP section 5.5.2 regarding procedures for infant enrollment.

7.19.1 Infant Medical History, Anthropometry, and Feeding History

If the pregnancy results or resulted in a live-born infant, and consent has been provided for the infant to enroll in MTN-042, then a clinical history of the infant should take place at the PPO visit (scheduled as soon as possible and within 14 days of delivery). This should include review of delivery/well baby medical records as it relates to infant conditions, as well as record of any medication taken or being administered. Clinicians should seek out primary medical records whenever possible, however, if these cannot be obtained, maternal report of any conditions/medications is acceptable.

Assessment of the infant at all visits should include review of the infant's health, anthropometry, and feeding history. To facilitate a thorough assessment, it is recommended that the **Infant Medical/Anthropometry/Feeding History Guide** be used during the initial review of infant medical history (available on the MTN-042 website under Study Implementation Tools). This will most likely occur at the PPO visit, but could occur later depending on whether the PPO visit is missed. Details on breastfeeding exclusivity, weaning, and complementary foods/formula should be captured through administration of the **Feeding Assessment CRF.**

During follow-up, sites should review any previously reported medical conditions for updates and assess any newly reported conditions or symptoms, as appropriate. Detailed review of the Infant Medical/Anthropometry/Feeding History Guide is not required at visits following the initial detailed history-taking.

7.19.2 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.

7.19.3 Creatinine Testing (Infant Participants)

Infant creatinine testing is required at the PPO and 6-week PPO for all infants and if indicated at months 6 and 12 (see Protocol Appendix II). Per protocol, infant creatinine clearance will not be calculated. Absolute values of infant creatinine will be graded based on the protocol specific grading tables outlined in section 8.3.1. At the PPO visit (within 14 days of birth), it is expected that some elevated infant creatine levels may be observed due to maternal lab derangements. These fetal values should typically normalize by the 6-week PPO visit, and no further evaluation is necessary between PPO and the 6-week PPO unless the investigator determines this to be necessary. If elevated creatinine is observed at the 6-week PPO visit, this should be clinically managed and followed to resolution.

7.19.4 Documentation of Infant Medical Conditions

Note that there is no baseline medical history CRF for infants.

Relevant conditions identified through medical history review and infant physical exams should be

source documented in the infant's study records, and as appropriate, infant AEs reported on the **Infant Adverse Event Log**. Note that since infants are exposed to study drug in utero, all conditions will be reported as AEs and not captured as 'pre-existing' conditions. See SSP section 8.16 for infant AE reporting and grading guidance.

7.19.5 Infant Concomitant Medications

Any medications dispensed to the infant from the time of birth should be documented on the **Concomitant Medication Log** in the infant casebook. Please note the start and stop dates of these medications as well as the indication, frequency, dose and route, and whether associated with a reported infant AE.

7.19.6 Infant Physical Exams

As described in protocol section 7.11, clinical evaluation of infants will include the following assessments (including assessment for and documentation of any anomalies, and photograph[s] of the infant if permitted by the mother/guardian – see SSP section 7.19.8 and 7.19.9 for information on assessment of congenital anomalies and photography):

- Vital signs
- Temperature
- Pulse
- Blood pressure *(if indicated)*
- Respirations
- Oxygen Saturation *(if indicated and within capacity of site)*
    - General appearance
    - Weight – *Note: weight should be measured using calibrated infant scales*
    - Length
    - Head circumference – *Note: Position the tape at whatever points on the forehead and occiput give maximal circumference*
    - Anterior fontanel closure/posterior fontanel closure
- 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* *(Present or not)*
- Neck*
- Extremities*
- Skin*
- Neurological* *(Include spine and evaluate for spina bifida or any other abnormalities)*
- Ages and stages assessment *(at 6- and 12-month visits only)*

*May be omitted after the PPO Visit.

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

7.19.7 Assessing Infant Growth

MTN-042 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 7-4 below (also posted on the Study Implementation Tools section of the MTN-042 website). Note that different charts are used for term/preterm infants, at delivery/ all other visits, and for girls/boys.

At birth the intergrowth 21st charts will be used for measuring growth at the appropriate gestational

age at birth, and graded according to the DAIDS FGGT charts. For example, if a parameter is < 3rd PC, it is a grade 3 and should be reported as small for gestational age (SGA) AE. This is relevant for weight, length and HC. For infants with a HC < 3rd PC, evaluation for microcephaly is necessary. For infants with height or weight < 3rd PC a weight-length ratio plot should be done using the appropriate intergrowth chart (term or preterm). Sites are encouraged to consult the PSRT if there are any questions about monitoring infant growth or AE reporting.

After delivery, if the infant is preterm the weight can be plotted according to postmenstrual age according to the intergrowth charts which will accommodate growth according to the postmenstrual age. For term infants after delivery, growth should be plotted against the WHO growth charts using percentiles.

A table with direct links to the appropriate growth charts is provided below. All growth charts are available on the MTN-042 Study website under study implementation tools.

Table 7-4: Growth Charts to Use for MTN-042

GA age at birth	Growth Chart Used at Birth	Growth Chart Used at All Visits after Delivery
Preterm (<37 weeks)	Intergrowth Preterm Boys Intergrowth Preterm Girls	Intergrowth Postnatal Growth Preterm Boys Intergrowth Postnatal Growth Preterm Girls
Term (≥37 weeks)	Intergrowth Newborn Boys Intergrowth Newborn Girls	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. 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?
- 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-042 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.

7.19.8 Assessment of Congenital Anomalies

The European Surveillance of Congenital Anomalies (EUROCAT) Guide 1.4: Instruction for the registration of congenital anomalies (EUROCAT Central Registry, University of Ulster) should be used as the reference which defines minor and major anomalies for MTN-042. Specifically, chapters 3.2 (Minor Anomalies for Exclusion) and 3.3 (EUROCAT Subgroups of Congenital Anomalies) should be referenced:

https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/JRC-EUROCAT-Full-Guide-1-4-version-01-Dec-2020.pdf

Congenital Anomalies may also be considered SAE/EAEs per DAIDS definitions (SSP Section 8.17 regarding reporting congenital anomalies as SAE/EAEs).

Note that all congenital anomalies (minor/major), regardless of whether considered SAE/EAEs, should be reported on the Pregnancy Outcome CRF (if diagnosed through 6-week PPO) and the AE Log CRF (diagnosed at any visit).

All congenital anomaly reports will be reviewed by an external consultant geneticist who confirm a final congenital anomaly determination. As part of this review process, sites will be responsible for completing the following:

- Review infant/delivery medical records for reported congenital anomalies.
    - Certified copies of any relevant medical records from evaluations conducted outside the clinic should be obtained, where possible, and filed in the participant binder.
- For enrolled infants, perform clinical assessments including a physical exam to assess for congenital anomalies and complete a full photo survey as described in section 7.19.9 below (if consented to by mother)

- Document assessment of the congenital anomaly in as much detail as possible on the source documents including:
    - For **enrolled infants** (born alive, infant IC obtained) complete the following in the infant casebook:
        - **Physical Examination CRF**
        - **Pregnancy Outcome CRF** (in maternal casebook, for anomalies identified through the 6-week PPO visit)
        - **AE Log CRF**
        - **EAE Report using Infant PTID** (if DAIDS criteria for EAE/SAE reporting met)
        - **Congenital Anomaly Review CRF**, items "Date of report" through "Are photographs available?" (note: the geneticist will complete items "Date of review" through "Comments")
        - **Photographic Survey CRF** (if photos consented to)
        - **EAE Upload CRF** (if reported to DAIDS as an EAE)
    - For **non-enrolled infants** (not born alive and/or infant IC not provided) complete the following in the maternal casebook:
        - **Pregnancy Outcome CRF** (for anomalies identified through the 6-week PPO visit)
        - **Non-Enrolled Infant AE Log CRF**
        - **EAE Report using Maternal PTID** (if DAIDS criteria for EAE/SAE reporting met)
        - **Congenital Anomaly Review CRF**, items "Date of report" through "Are photographs available?" (note: the geneticist will complete items "Date of review" through "Comments")
        - **EAE Upload CRF** (if reported to DAIDS as an EAE)
- Respond to any clinical queries related to submitted congenital anomalies, as needed:
    - It is possible that after completing their review, the geneticist may request more information from the site in order to make their final determination. Should this be necessary, sites will receive a clinical query from the SCHARP Clinical Safety Associate within Medidata.
- Referrals should be provided as needed for ongoing management of any identified anomalies.

Upload of DAERS EAE Reports to Medidata RAVE

If the congenital anomaly meets DAIDS defined criteria for reporting as an EAE, then a report should be submitted to DAERS (see SSP section 8.17). Report EAE using the infant PTID for enrolled infants. Report EAE using the maternal PTID for non-enrolled infants. All reporting timelines as outlined in the EAE manual should be followed. Once initial comments have been addressed on EAE report, export a PDF of the EAE report for uploading using the **EAE Upload CRF**. If subsequent updates are made to the submitted EAE report, export a copy of the updated report from DAERS. Add a new log line to the **EAE Upload CRF** and upload the updated report. Inactivate the log line with the previous version of the EAE report.

7.19.9 Photographing Congenital Anomalies

It is recommended that the photo survey be completed for all congenital anomalies (minor/major) as long as the mother has consented to this procedure.

Designated staff should first confirm that the mother has provided informed consent to have photographs taken of the child. It is critical that care be taken to provide supportive counseling to the mother regarding the purpose of the photos and to allay any anxiety she may have about her child's condition. As such, suggested counseling messages are provided below for staff to utilize as needed.

Suggested Counseling Messages:

- Provide as much information as possible about the diagnosed or suspected condition—*for example, whether the condition is considered minor or inconsequential to the infant's health, or if more serious, what the options might be for treatment. Reassure the parent(s) that referrals for further counseling and ongoing management of the condition will be provided.*
- Because this is a research study, we may ask to take pictures of conditions even if they are considered minor. The photos are voluntary.
- The photos will help the doctors working on the study evaluate the condition and decide if it is important to your baby's health.

- There is no current evidence to suggest that exposure to the study products caused your baby's condition.
- What questions or concerns do you have?

Note: A woman may change her mind about having photographs taken of her infant. If the woman had previously agreed to the photos, the source documentation must be clear that she is no longer willing to have the photos taken. If she had previously declined but now agrees, she must be re-consented. Making a note in the source records is not adequate documentation in that case. Finally, if a woman has granted permission on the informed consent but is not keen to have all views taken, please obtain whatever images are allowed and document the participant's restrictions in the source records.

In addition to taking specific photos of the anamoly(ies), a complete photo survey of the infant be completed as outlined in the **MTN-042 Infant Photography Guide** (available on the MTN website). Note that the guide includes information on file naming conventions and what views should be captured as part of the photo survey. This will enable the geneticist working with MTN-042 to determine if there are other subtle findings on the physical exam that may not be readily apparent. Having the same geneticist review all cases from each of the participating MTN-042 sites will also provide the team with standardization in assessing congenital anomalies as a primary outcome for the study. As noted above, sites should pursue appropriate referrals and follow up as clinically indicated.

For all congenital anomalies, please include close-up images of the abnormality from as many perspectives as possible (front, rear, left and right lateral, as appropriate). Note that the area of interest should comprise about 75% of the screen, or as much as possible without losing focus. These additional views are requested for all abnormalities noted on the physical exam and are requested even if the abnormality appears in one of the required views.

Any photographs obtained must be stored and managed as part of the infant's medical record as source documents. Digital images should be backed up onto CD (or alternative format) and be signed and dated to show that the CD has been verified as an exact copy of the original photos, having all of the same attributes and information as the original (i.e., no editing occurred before transfer to CD), labeled with the PTID and stored per site SOPs. Note that for confidentiality purposes, cell phone cameras should not be used to capture the photos—a dedicated digital camera that is stored safety and securely should be used. After saving and backup of image files for storage in the participant record is confirmed, image files should be removed/deleted from the camera storage device (e.g., SD card).

7.19.10 Uploading Photographic Documentation

If photos are taken, use the **Photographic Survey CRF** to upload to Medidata RAVE. Select the best photo from each view and upload only one per required view, with the exception of the close-up anomaly images, which should include as many perspectives as possible is requested (front, rear, left and right lateral, as appropriate).

7.19.11 Infant Blood Draws

All enrolled infants will have blood drawn for the protocol-outlined samples as outlined in Appendix II. Babies who are born to mothers with confirmed HIV infection will undergo HIV-1 testing. Blood may be collected by heel stick or by venous puncture, per site SOPs. Details about specimen collection and processing may be found in SSP section 10.

Sites may find Chapter 6 of the WHO guidelines on drawing blood: best practices in phlebotomy useful as a reference for pediatric and neonatal blood draws:
https://www.ncbi.nlm.nih.gov/books/NBK138650/pdf/Bookshelf_NBK138650.pdf

7.19.12 Ages and Stages Assessment

MTN-042 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.

Identifying the Correct Questionnaire to Administer

The ASQ3 questionnaires are available for download on the MTN-042 website under study implementation tools. The appropriate questionnaire based on the infant's age should be administered at the 6-month and 12-month infant visits. While this will typically be the 6-month and the 12-month questionnaire, special cases may necessitate using other versions (2, 4, 6, 8, 9, 10, and 12 month are all available). 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 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:

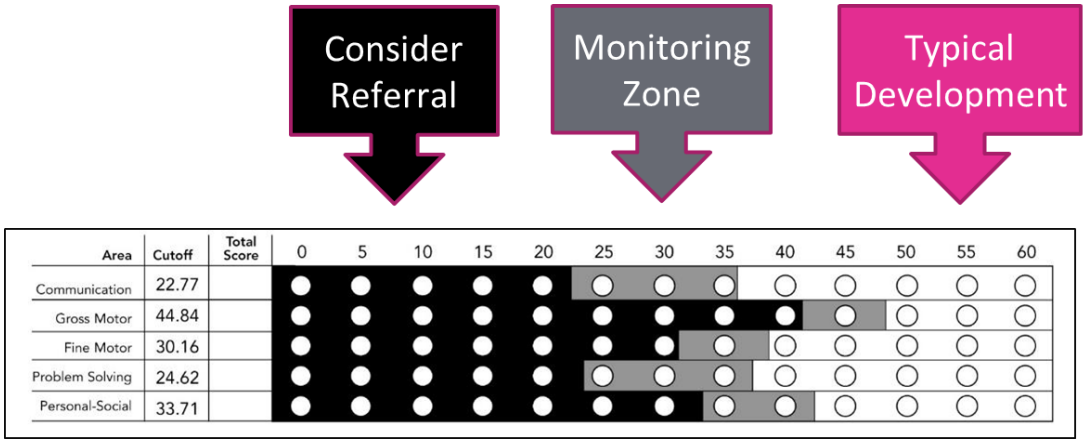
- YES = 10 points
- SOMETIMES = 5 points
- NOT YES = 0 points

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-042 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-042 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.