Section 8. Adverse Event Reporting and Safety Monitoring

8 Introduction 8-1
8.1 Definitions 8-2
8.1.1 Adverse Event (AE) 8-2
8.1.2 Serious Adverse Events (SAEs) / Expedited Adverse Events (EAEs) 8-3
8.2 Reporting EAEs 8-4
8.2.1 Updating EAE Reports 8-5
8.3 Reportable Adverse Events and Terminology 8-5
8.4 Reporting Considerations for Pregnant Participants 8-7
Table 8-1 Adverse Event Reporting During Pregnancy by Gestational Age 8-7
Figure 8-1 Overview of Assessment and Reporting Procedures for Genital Bleeding in a Pregnant Participant; Beginning with Participant Report of Blood/Bleeding 8-9
8.4.1 Reporting Considerations During the Postpartum Period 8-9
8.4.2 Adverse Event Association with Pregnancy 8-9
8.5 Protocol Specific Grading Scales and Secondary Outcome Definitions 8-10
Table 8-2 Protocol Specific Grading Tables 8-10
8.6 Reporting Genital, Genitourinary, and Reproductive System AEs 8-13
8.7 Reporting Abdominal Pain as an AE 8-15
8.8 Reporting Weight Loss as an AE 8-15
8.9 Reporting Terminology Considerations for Additional Adverse Events 8-15
8.10 Reporting Pelvic Examination Findings as AEs 8-16
8.11 Reporting Laboratory Abnormalities as AEs 8-16
8.12 AEs Involving Hospitalizations/ Surgical Procedures 8-17
8.12.1 Reporting Guidance for Cesarean Sections 8-17
8.12.2 Reporting Guidance For Preterm Delivery 8-17
8.13 Reporting HIV Infection Illness 8-17
8.14 Reporting Sexual Assault 8-18
8.15 Reporting alcohol or drug use during pregnancy 8-18
8.16 Infant/Fetal AE Reporting 8-19
8.16.1 Common Infant Conditions AE Reporting Guidance 8-20
8.17 Reporting Congenital Anomalies 8-22
8.18 Adverse Event Severity Grading 8-23
8.19 Reporting Maternal or Infant Deaths 8-24
8.20 Adverse Event Relationship to Study Product 8-24
8.20.1 Dapivirine Ring: Relationship to Drug or Device 8-25
8.21 Adverse Event Outcomes and Follow-Up Information: During the Study 8-25
8.22 Adverse Event Outcomes and Follow-Up Information: After Study Termination 8-26
8.23 Reporting Recurrent Adverse Events 8-26
8.24 Social Harms (Social Impacts) 8-27
8.25 Reports of Intimate Partner Violence (IPV) 8-28
8.26 MTN-042 Safety Monitoring, Review, and Oversight 8-28
8.27 Safety Distributions from DAIDS 8-29
Appendix 8-1 MTN-042 Protocol Safety Review Team Plan 8-29

8 Introduction

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-042. Please also refer to Protocol Section 8 and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.1 dated July 2017, including:

- Addendum 1: Female Genital Grading Table for Use in Microbicide Studies (FGGT), November 2007

- Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, Jan 2010)
- DAIDS Adverse Experience Reporting System (DAERS) Reference Guide for Site Reporters and Study Physicians
- Investigator's Brochure for Dapivirine Ring
- Package Insert for FTC/TDF Tablet

8.1 Definitions

8.1.1 Adverse Event (AE)

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines an AE as any untoward medical occurrence in a clinical research participant administered an investigational product and that does not necessarily have a causal relationship with the investigational product. As such, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

For MTN-042, the ICH-E6 definition is applied to all participants, beginning at the time a maternal participant is enrolled (i.e. randomized) through when the mother and the infant terminate from the study, respectively. Study staff must document within the **Adverse Event (AE) Log CRF** all reportable AEs reported by or observed in study participants, regardless of severity and presumed relationship to study product.

The AE CRF may be used as source documentation for the following AE information:

- Date reported to site
- AE term/diagnosis
- Onset date
- SAE/EAE onset date
- Severity grade
- Relationship to study product (related or not related), and for DVR relatedness to device or drug
- Association with pregnancy
- Study product administration as related to the AE
- Outcome status
- Outcome date (or ongoing at time of termination)
- AE treatment
- Whether the AE is serious per ICH guidance (see Section 8.1.2)
    - If SAE, onset date and ICH criteria for SAE
- Whether the AE meets expedited AE reporting requirements (see Section 8.1.2)
- Whether the AE is a worsening of a baseline medical history condition
- Additional comments/details related to the AE

For maternal participants, relevant medical conditions, problems, signs, symptoms, and findings identified prior to enrollment are documented within the **Baseline Medical History Log** (whether they are ongoing at enrollment or not). If this condition worsens (increases in severity or frequency per the DAIDS grading table) after enrollment, the worsened condition is considered an AE. If a baseline medical history condition resolves after enrollment, but then recurs at a later date, the recurrence is considered an AE.

Note that since infants are exposed to study drug in utero, all conditions identified and birth and beyond will be reported as AEs and not captured as 'pre-existing' conditions. Further information about reporting AEs on the fetus/infant is outlined in section 8.15 below.

Per protocol, the following AEs **<u>are not reportable</u>** in MTN-042:

- Asymptomatic BV and asymptomatic candida.
- Bleeding at the time of speculum insertion/removal or cervicovaginal specimen collection that is judged by the clinician to be within the range normally anticipated for that procedure; however, bleeding of greater quantity or longer duration than typical will still be reported.
- Uterine cramping that is judged by the clinician to be within the range normally anticipated post-delivery.
- Perineal pain that is judged by the clinician to be within the range normally anticipated post-delivery.
- Lower extremity edema that is judged by the clinician to be within the range normally anticipated during pregnancy.
- Decreased fetal movement; however, AEs identified in the course of clinical evaluation of decreased fetal movement will be captured
- Findings on electronic fetal monitoring strips; however, AEs identified in the course of clinical evaluation of concerning electronic fetal monitoring will be captured
- Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths); however, untoward maternal conditions that either result in or result from fetal losses are reported as AEs.
    - NOTE: All fetal losses will be reported by sites on pregnancy outcome CRFs to the SDMC and will be considered during safety reviews conducted by the SDMC, the DAIDS MO, the NICHD MO, PSRT, and IRP.
- Physiologic discharge associated with pregnancy.
- Lochia judged to be within the range of normal experienced in the post-partum period
- Vaginal bleeding that is judged by the clinician to be within the range normally anticipated in the postnatal period.

8.1.2 Serious Adverse Events (SAEs) / Expedited Adverse Events (EAEs)

ICH-E6 defines a serious adverse event (SAE) as an AE following any exposure to study product which:

- Results in death,
- Is life-threatening,
    - ***NOTE:*** *The term "life threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. A Grade 4 severity grading on the DAIDS Grading Table does not necessarily mean that an event is life-threatening. When determining whether a Grade 4 event meets the ICH definition of "life threatening", consider the event in the context of any related symptoms the participant may have experienced.*
- Requires in-patient hospitalization or prolongs an existing hospitalization,
    - *The following types of hospitalizations are not considered Adverse Events, serious or otherwise:*
        - *Any admission unrelated to an AE (e.g., for labor/delivery, including cesarean section)*
        - *Admission for diagnosis or therapy of a condition that existed before enrollment AND has not increased in severity per the DAIDS Grading Table since baseline.*
- Results in persistent or significant disability/incapacity, or

- Is a congenital anomaly/birth defect *(see SSP section 7.19.8 for detailed information regarding assessment of congenital anomalies)*
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above.

ICH guidance (E2A) also states that medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious.

SAEs are a subset of all reportable AEs. For each AE identified in MTN-042, an authorized study clinician must determine whether the AE meets the ICH definition of "serious". The AE Log CRF includes a specific question to record this determination.

When assessing whether an AE meets the definition of serious, note that seriousness is not the same as severity, which is based on the intensity of the AE (see Section 8.4 for more information on severity grading).

All AEs that meet the definition of "serious" (SAEs), regardless of relationship to study product, are expedited adverse events (EAE). Seriousness is the only consideration in determining whether an AE meets the definition of an EAE. EAEs require additional reporting for rapid review and assessment by DAIDS (see section 8.2). In some cases, DAIDS may be required to report an EAE to the US FDA.

8.2 Reporting EAEs

EAEs should be reported per the *Manual for Expedited Reporting of Adverse Events to DAIDS, version 2.0; January 2010*. Reporting guidelines outlined in SSP Section 2.1 and Appendix A should be followed.

For MTN-042 the "SAE (Serious Adverse Event) Reporting Category" will be used to report EAEs.

If DAERS cannot be accessed (e.g., due to poor internet connectivity), paper-based EAE reporting should be used, per instructions provided in the *Manual for Expedited Reporting of Adverse Events to DAIDS*. Completed paper EAE Forms may be faxed or digitally scanned and emailed to the DAIDS RSC via email. The EAE Form and form completion instructions are available on the DAIDS RSC web site (http://rsc.tech-res.com). Contact details for submission of EAE Forms to the RSC are provided in the *Manual for Expedited Reporting of Adverse Events to DAIDS*.

All EAEs, including congenital anomalies and birth defects identified among infants of study participants, must also be reported within the appropriate AE Log CRFs (Maternal AE Log, Non-Enrolled Infant AE Log, or Infant AE Log), with the EAE specified.

If the fetus experiences an EAE after the mother enrollment into the study, then the EAE should be reported under the maternal PTID in DAERS, if the EAE meets the criteria for expedited reporting to DAIDS. After birth, if the infant is enrolled, all EAEs reported to DAIDS should be reported under the infant PTID.

If an EAE has been reported in DAERS under the mother PTID (before infant enrollment) and later the infant enrolls, then the original EAE under the mother PTID needs to be withdrawn from DAERS by DAIDS RSC Safety office and the site needs to enter a NEW EAE under the infant PTID.

When completing AE Log CRFs and EAE reports, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness, and consistency.

All AE descriptions and details (e.g., onset date, severity grade, relationship to study product, SAE criteria) should be recorded consistently across all documents when possible. In cases where one EAE involves several AEs (a motor vehicle accident, for example), ensure consistency between the EAE and associated AE Log CRFs as much as possible.

All EAE reports received at the DAIDS RSC will be compared with AE Log CRFs received at the MTN SDMC to ensure that all reports that should have been received by both the DAIDS RSC and the SDMC have been received and that the details recorded on each form are consistent.

If an EAE that was previously reported to the DAIDS RSC resolves and then later recurs at a level requiring expedited reporting, the second occurrence must be reported as a new EAE report (and a new AE Log CRF, if not already completed).

8.2.1 Updating EAE Reports

For each EAE reported to DAIDS, sites are required to submit an updated report to DAIDS as soon as significant additional information becomes available. Note that updates made to EAE reports should also be made to the corresponding AE Log CRF, as applicable. Similarly, any updates made to an AE Log CRF should also be made to the corresponding EAE report, as applicable. EAE follow-up information should be reported to the DAIDS RSC, using the update function in DAERS, under the following circumstances:

- Requests from DAIDS for additional information
- A change in the relationship between the AE and study product by the study physician
- Additional significant information that becomes available for a previously reported AE (this is particularly important for new information addressing cause of death if the initial assignment was "pending")
- Any change in the assessment of the severity grade of the AE
- An update including the final or stable outcome, unless the initial SAE submitted had a final or stable outcome noted already
- Results of re-challenge with the study product, if performed

Note that although assessment of a change in the severity grade between the AE and the study product does not require a new EAE form it must be reported as a new AE Log CRF to the SDMC (as described previously).

In MTN-042, re-challenge with study product may occur in the context of study product use having been held in response to an EAE, but then resumed after resolution or stabilization of the EAE. In such a case, site staff should provide follow-up information to the DAIDS RSC describing the participant's condition after resuming product use. Follow-up reports should be submitted approximately one month after resuming product use, unless safety concerns are identified before one month has elapsed. In that case, the follow-up report should be submitted as soon as possible after the safety concern is identified.

8.3 Reportable Adverse Events and Terminology

The AE Log CRFs (AE Log CRFs in the respective maternal and infant casebooks, as well as the Non-Enrolled Infant AE Log CRF within the maternal casebook) are used to report all AEs, reported by or observed in enrolled study participants, to the MTN SDMC. A site-specific tracker may be used for documentation and tracking purposes.

Study staff must assign a term or description to all AEs identified in MTN-042 ("Adverse Event (AE)" term item on the AE log CRFs). The guidance below should be followed when assigning AE terms/descriptions:

- Whenever possible, use a diagnosis as the AE term. Document associated signs and/or symptoms related to a diagnosis in the comments section of the AE CRF.
- When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, report each individual sign and symptom as an AE.
- Include anatomical location when applicable, and use a specific location term (e.g., "vaginal" instead of "genital")
- Use medical terms (e.g., "ulcers" instead of "sores")
- Use correct spelling
- Do not use abbreviations. Abbreviations for the following laboratory findings are acceptable:
    - WBC
    - MCV

- Hgb
- Hct
- ALT or SGPT
- AST or SGOT

Any lab value that is severity Grade 1 or higher according to the DAIDS Grading Table, regardless of where the testing took place, should be reported as an AE and documented within the AE Log CRF. Lab results from outside sources should be filed in participant charts as source documentation, if they are available. Even when source documentation from an outside lab is not immediately available, self-reported lab-based AEs (for example, a participant was told by an outside health care provider that she tested positive for gonorrhea) should be captured within the AE Log CRF (and confirmed by on-site testing as soon as possible). In contrast, CRFs that capture local laboratory results should only be used to document lab results from protocol-specified tests run at site-approved labs.

Procedures per se should not be reported as AE; rather the underlying condition, which leads to a procedure, may be considered an AE. Any associated procedures may be considered treatments for the AE. For example, while “dilation and curettage” for a retained placenta would not be considered an AE, “retained placenta” would, with “dilation and curettage” documented as a treatment provided for the AE. In addition, any event that occurs because of a study related procedure should be recorded as an AE. Specify in the AE text description if the AE is related to a procedure (iatrogenic). For example, if a participant experiences dizziness from a blood draw, then “dizziness due to blood draw” should be submitted as an AE.

When completing the AE text description, do not include information on relatedness to study product or timing of study product use in the AE term/description. Limit the AE text to the medical description and anatomical location, when needed. Including such text affects the way the AE is MedDRA-coded, and thus, how it will appear in safety reports.

However, when reporting AEs which are **due to the act of ring removal or insertion**, specifically, please follow the guidance below:

- If the AE is **due to the act** of study ring insertion or removal, include this information in the AE text. For example, use AE text of “pelvic pain due to ring removal” or “vulvar laceration due to ring insertion” rather than just “pelvic pain” or “vulvar laceration.”

It is important to clearly identify AEs that are due to the act of study ring insertion or removal because these AEs are assigned unique coding terms within the standardized MedDRA coding system.

If the AE is **not** due to the act of study ring insertion or removal, do not include mention of the ring in the AE text.

- If text is present in the “Comments” field that the AE is due to the act of ring insertion or removal, this same text needs to be in AE term item. If not, this may result in a Safety Query asking that this information be added to the AE term item in order to accurately and completely describe this AE.

Sites must include text in the “Comments” field to provide the rationale or alternative etiology for why each AE has been judged “related” or “not related" Within the “Relationship to Study Product” item.

Source documentation requirements for AEs are listed in SSP Section 8.1.1.

Sites should check local IRB/EC and drug regulatory bodies' requirements regarding the reporting of AEs and ensure that expectedness is also captured for these AEs if required by local regulatory entities.

Site-specific delegation of duties documentation should designate study staff authorized by the IoR to complete AE Log CRFs. Regardless of who initially completes these forms, a clinician listed on the site’s FDA Form 1572 should review them to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

Additional guidance for reporting certain types of AEs in MTN-042 is provided below. Please see the **MTN-042 AE Text Guidance document** available on the MTN-042 website under study implementation tools for further AE term guidance. Further guidance on severity grading for each of these is provided in SSP Section 8.5.

8.4 Reporting Considerations for Pregnant Participants

AEs that are deemed related to the pregnancy, worsened by the pregnancy, or require changes in clinical management of the pregnancy should be reported, as clinically indicated, using the appropriate pregnancy related terms or indicating the AE is during pregnancy by adding 'antepartum' or 'postpartum' when describing the AE diagnosis on the AE Log CRF. Some events are inherently related to pregnancy (e.g., eclampsia); there is no need to add "antepartum" or "postpartum" to these AE descriptions. Please see the MTN-042 AE Text Guidance document available on the MTN-042 website under study implementation tools for further AE term guidance

Fetal losses (of any kind) are not reportable AEs. However, **maternal complications or side effects associated with fetal loss** that would otherwise be reported as an AE are considered AEs, and should be reported. For example:

- vaginal bleeding associated with miscarriage
- pelvic pain associated with miscarriage

Bleeding and pelvic pain or contractions are common complaints in pregnancy and may accompany a fetal loss. Depending on the circumstances, pain and bleeding experienced during pregnancy may be reported as AEs. In general, bleeding associated with delivery (intrapartum and/or post partum) is not considered an AE, provided the bleeding does not exceed the expected amount. Likewise, contractions at term are considered normal and should not be reported as an AE. Pain during pregnancy, with the exception of term contractions, should be captured as an AE. Bleeding prior to the onset of labor (and not associated with delivery) should also be captured as an AE. "Intrapartum hemorrhage" should be used to describe bleeding that occurs during labor, but not at delivery or after delivery. For example, a participant in labor with a placental abruption or a previa who presents with bleeding, should be considered to have an "intrapartum hemorrhage." Should it be difficult to ascertain whether the bleeding occurred "intrapartum" or "post partum" from the record, but it is clear that there was excessive bleeding at the time of delivery, record "post partum hemorrhage."

See Table 8-1 for more guidance on reporting AEs **during pregnancy**. Events classified as "NOT AE" in the table below are not recorded on either AE Log CRFs, but should be documented on alternative source documents (e.g. in the chart notes).

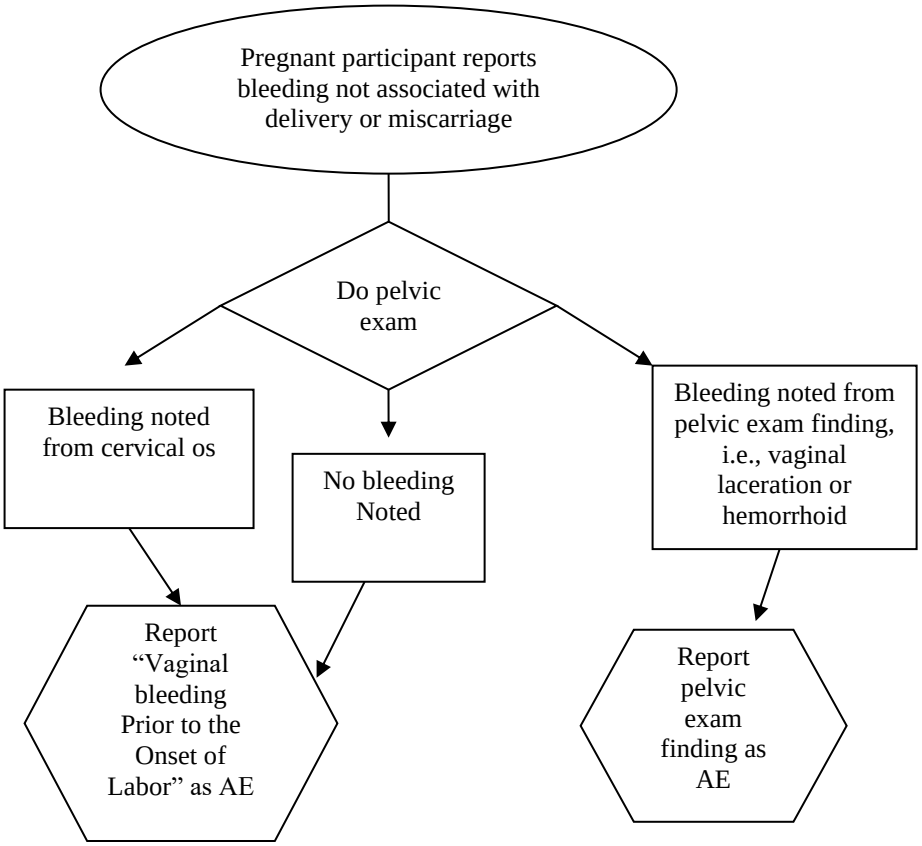
Table 8-1 Adverse Event Reporting During Pregnancy by Gestational Age

	Table 8-1 **Adverse Event Reporting During Pregnancy** **by Gestational Age**			
		0 to<20 weeks	**20 to<37 weeks**	**Term** **≥37 weeks**
Not Associated with Pregnancy Loss or Delivery	**Painful Cramping/** **Uterine Contractions**	Pelvic Pain, antepartum (Grade per Pain row of FGGT)	Preterm Contractions (Grade per Preterm Contraction row in FGGT)	**NOT AE**
	Vaginal Bleeding	Bleeding Prior to Onset of Labor (Grade per protocol specific grading table for "Bleeding during pregnancy, prior to the onset of labor" – see section 8.5 below)		

Associated with Pregnancy Loss or Delivery	**Painful Cramping/ Uterine Contractions**	Pelvic Pain, antepartum associated with miscarriage (grade per Pain row in FGGT)	Preterm Contractions (grade per Preterm Contraction row in FGGT)	**NOT AE**
	Vaginal Bleeding	Vaginal Bleeding Associated with Miscarriage (Grade per protocol specific grading table for "Bleeding during pregnancy, prior to the onset of labor" – see section 8.5 below)	**NOT AE** unless EBL is greater than WNL at any point in delivery If EBL >WNL, record Intrapartum Hemorrhage or Post-Partum Hemorrhage and grade per protocol specific grading table for Intrapartum Hemorrhage or Post-Partum Hemorrhage – see section 8.5 below	**NOT AE** unless EBL is greater than WNL at any point in delivery If EBL >WNL, record Post-Partum Hemorrhage and grade per protocol specific grading table for Post-Partum Hemorrhage – see section 8.5 below
	Fetal Loss	**NOT AE**	**NOT AE**	**NOT AE**
		Miscarriage	**Delivery**	
EBL= estimated blood loss; WNL=within normal limits				

If a pregnant participant reports bleeding (not associated with delivery) study staff should investigate the source of the bleeding. If a pelvic exam finding such as a vaginal laceration, a cervical polyp, or hemorrhoids, is identified as the source of the bleeding, the finding should be recorded as the AE and an explanation provided in the comments section of the AE Log CRF that the finding was associated with bleeding. Figure 8-1 is intended to clarify this point:

Figure 8-1 Overview of Assessment and Reporting Procedures for Genital Bleeding in a Pregnant Participant; Beginning with Participant Report of Blood/Bleeding



8.4.1 Reporting Considerations During the Postpartum Period

The postpartum period (approximately 6-12 weeks following delivery) is a period of physiologic transition where some adverse events are considered normal and not reportable as AEs. **After delivery**, uterine cramping and perineal pain that is judged by the clinician to be within the range normally anticipated in the postpartum period are not reportable as an AE per protocol. As specified in protocol 8.3.1, vaginal bleeding and discharge associated with pregnancy/postpartum period (lochia) within the range of normal for the postpartum period are also considered expected and not reported as AEs. Additionally, the DAIDS toxicity table excludes weight loss during the postpartum period as a reportable condition.

Outside of the conditions specified in the protocol as "not reportable" during the postpartum period, other new or worsening postpartum conditions (or, conditions listed above but judged to be outside of the range of what the investigator would consider "normal") identified during follow-up should be reported as adverse events. Breastfeeding-related AEs may be observed in the postpartum period and should be reported and graded using the "estimating severity grade" row of the DAIDS Toxicity Table. Fatigue due to sleep disturbances, while expected, is also considered an AE and should be reported.

8.4.2 Adverse Event Association with Pregnancy

Unique to MTN-042 is an ancillary question on the AE Log CRF, "AE is associated with pregnancy." Clinicians are asked to consider each AE separately and select the checkbox if deemed related to pregnancy. For example, if a participant reports reflux, and it is the clinician's assessment that the reflux is due to pregnancy, the checkbox should be selected. If a participant is in a motor vehicle accident while pregnant and experiences a broken arm, the checkbox will not be selected.

"Associated" in this situation does not refer to temporal association, but etiologic association. Only AEs for which pregnancy may be a contributing factor should be marked. Furthermore, AEs uncovered in the post-partum period that are presumed to be associated with the postpartum state should be marked. An example of this might be "fatigue."

Please note that the answer to the question of pregnancy association and the question regarding relatedness to study product are not mutually exclusive. That is, the clinician may consider that a particular AE is related to study product and also associated with pregnancy. For example, a participant reports baseline nausea, Grade 1. After starting oral product, her nausea increases to Grade 2. It would be reasonable to mark that the AE is associated with pregnancy and also "related" to study product.

Importantly, the answer to the "associated with pregnancy" AE will not be queried by SCHARP. SCHARP will review the AE term and the comments section to assign the appropriate term for the AE database.

8.5 Protocol Specific Grading Scales and Secondary Outcome Definitions

Protocol-specific grading scales will be used for the following AEs as outlined in Table 8-2 below. All conditions that are grade 1 or higher should be reported as AEs using the appropriate terms. **Conditions which are also indicated as secondary endpoints should be noted as a complication of pregnancy on the Pregnancy Outcome CRF**.

Table 8-2 Protocol Specific Grading Tables

PARAMETER	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	Grade 4 POTENTIALLY LIFE-THREATENING
Bleeding during pregnancy, prior to the onset of labor	Spotting or bleeding less than menses	Bleeding like menses*or heavier, no intervention indicated *note: "menses like" refers to several days of moderate bleeding	Profuse bleeding with dizziness or orthostatic hypotension, transfusion	Potentially life-threatening profuse bleeding and/or shock
Hypertensive disorders of pregnancy	Pregnancy-induced hypertension	Mild preeclampsia	Severe preeclampsia	HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, eclampsia, or life-threatening sequelae of preeclampsia (e.g., pulmonary edema)
Gestational diabetes	Diet-controlled, no or minimal interference with usual social and functional activities	Medication prescribed	Evidence of adverse effects on pregnancy secondary to diabetes	N/A

Chorioamnionitis	Fever of 38°C – 38.4°C (or 100.4°F - 100.9°F) with more than one of the following: FHR > 160 BPM, maternal HR > 120, uterine tenderness between contractions, purulent AF, or preterm labor	Grade 1 plus fever of 38.5°C -40°C (or 101°F - 104°F)	Grade 2 plus fetal distress or fever > 40°C (or 104°F)	Grade 3 plus fetal demise or maternal symptoms of shock
Puerperal sepsis and endometritis	Low grade fever and uterine tenderness, resolved with oral antibiotics	Moderate symptoms, treated by ⩽ 3 days of parenteral antibiotics	Severe symptoms treated with > 3 days of IV antibiotics or addition of heparin	Severe infection or infection for which operative intervention is indicated
Preterm premature rupture of membranes (PPROM)	N/A	Preterm rupture with hospitalization but not resulting in delivery at less than 37 weeks' gestation	Delivery at 33-36 weeks' gestation or 1501-2500 grams birth weight	Delivery < 33 weeks' gestation or ⩽ 1500 grams birth weight

PARAMETER	**Grade 0 NORMAL**	**Grade 1 MILD**	**Grade 2 MODERATE**	**Grade 3 SEVERE**	**Grade 4 POTENTIALLY LIFE-THREATENING**
Postpartum hemorrhage	Estimated blood loss (EBL) < 500 mL for vaginal delivery or < 1000 mL after caesarian section (CS) or reported as normal	EBL 500-1000 mL for vaginal delivery or 1000-1500 mL for CS or reported as slightly increased	EBL > 1000 mL or vaginal delivery or > 1500 mL for CS, with or without mild dizziness, no transfusion required	Hemorrhage at a level for which transfusion of 1-2 units of packed cells, but no other blood products indicated	Hemorrhage with shock or coagulopathy, for which transfusion of > 2 units of packed cells or any amount of other blood components is indicated

Note that the following table was developed based on the post partum hemorrhage row and should be used to grade intrapartum hemorrhage:

PARAMETER	**Grade 0 NORMAL**	**Grade 1 MILD**	**Grade 2 MODERATE**	**Grade 3 SEVERE**	**Grade 4**

					POTENTIALLY LIFE-THREATENING
Intrapartum hemorrhage	Within the anticipated amount	N/A	Above the anticipated amount but not requiring transfusion	Hemorrhage at a level for which transfusion of 1-2 units of packed cells, but no other blood products indicated	Hemorrhage with shock or coagulopathy, for which transfusion of > 2 units of packed cells or any amount of other blood components is indicated

Note that if the verbatim term for the protocol-outlined secondary outcome is not documented in the medical record, but a condition is presumed based on review of information by the site clinician, this should still be reported on the **Pregnancy Outcome CRF**. The following definitions should be followed when reporting hypertensive disorders of pregnancy[1] presumed based on chart review:

Gestational hypertension (i.e. pregnancy-induced hypertension, grade 1): Pregnancy >20 weeks and NEW diagnosis of hypertension (⩾140 mmHg systolic and/or ⩾ 90mmHg) WITHOUT severe features of pre-eclampsia or proteinuria

Pre-eclampsia WITHOUT severe features (i.e. mild pre-eclampsia, grade 2): Pregnancy >20 weeks and NEW diagnosis of hypertension (⩾140 mmHg systolic and/or ⩾ 90mmHg) AND proteinuria BUT **NO** severe features which include:

- Severely elevated blood pressures, with systolic blood pressure ⩾160 mmHg and/or diastolic blood pressure ⩾110 mmHg, which is confirmed after only minutes (to facilitate timely antihypertensive treatment)
- Development of a severe headache (which can be diffuse, frontal, temporal or occipital) that generally does not improve with over the counter pain medications (such as acetaminophen/paracetamol)
- Development of visual changes (including photopsia, scotomata, cortical blindness)
- Eclampsia, or new-onset grand mal seizures in a patient with preeclampsia, without other provoking factors (such as evidence of cerebral malaria or preexisting seizure disorder). Seizures are often preceded by headaches, visual changes or altered mental status
- New onset thrombocytopenia, with platelet count <100,000/μL
- New onset of nausea, vomiting, epigastric pain
- Transaminitis (AST and ALT elevated to twice the upper limit of normal)
- Liver capsular hemorrhage or liver rupture
- Worsening renal function, as evidenced by serum creatinine level greater than 1.1 mg/dL or a doubling of the serum creatinine (absent other renal disease)
- Oliguria (urine output <500 mL/24 h)
- Pulmonary edema (confirmed on clinical exam or imaging)

Pre-eclampsia WITH severe features (i.e. severe pre-eclampsia, grade 3**)**: Pregnancy >20 weeks and NEW diagnosis of hypertension (⩾140 mmHg systolic and/or ⩾ 90mmHg) AND severe features as listed above.

[1] Rouse CE, et al. Hypertensive disorders of pregnancy: Case definitions & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016 Dec 1;34(49):6069-6076. doi: 10.1016/j.vaccine.2016.03.038. Epub 2016 Jul 15

8.6 Reporting Genital, Genitourinary, and Reproductive System AEs

The category of genital, genitourinary, and reproductive system AEs includes AEs involving the vulva, vagina, cervix, uterus, fallopian tubes, ovaries, breasts, anus, rectum, kidneys, ureters, urethra, and bladder. All AEs associated with abnormal pelvic exam findings, STIs, UTIs, and RTIs fall in this category.

Vaginal Discharge: Increased vaginal discharge is considered a normal occurrence during pregnancy and is not reportable as an AE if description is consistent with physiologic discharge associated with pregnancy (or the postpartum period, i.e. lochia). If discharge is associated with pruritis, irritation, or odor, and follow up evaluations reveal a diagnosis of symptomatic BV and/or yeast or other STI, then the appropriate STI/RTI term should be used to report the AE.

Vaginal odor: Per the FGGT, odor is listed as a symptom and should be documented as an AE if different from baseline and not due to a larger diagnosis. This is based on participant report of the symptom only and grading based on the participant's perception of severity.

Perineal trauma: First and second degree lacerations are normal occurrences after a vaginal delivery. Unless these tears are associated with excessive pain and/or infection, they should not be reported as adverse events. Third and fourth degree lacerations are unusual occurrences after a vaginal delivery and should be captured as an Adverse Event. The event should be graded by the "estimating severity grade" row of the toxicity table.

STIs/RTIs

The following terminology should be used only if STI diagnosis is based on clinical evaluation and confirmed, when appropriate/possible, by laboratory result(s). For example, symptomatic BV and symptomatic vulvovaginal candidiasis should not be reported as AEs based on participant symptoms alone.

Bacterial Vaginosis (BV): Only report symptomatic infections that are confirmed with saline wet mount testing and that fulfill Amsels criteria as AEs, using the term "symptomatic bacterial vaginosis." "Asymptomatic bacterial vaginosis" should not be recorded as an AE. If a clinician notes abnormal vaginal discharge and ultimately diagnoses the participant with asymptomatic bacterial vaginosis, this clinical event should be captured as "vaginal discharge- clinician observed".

Candidiasis: Only report symptomatic infections that are confirmed with KOH wet prep and/or culture as AEs, using the term "vulvovaginal candidiasis."

Chlamydia: Report all infections using the term "genitourinary chlamydia infection." No need to report symptomatic or asymptomatic.

Gonorrhea: Report all infections using the term "genitourinary gonorrhea infection." No need to report symptomatic or asymptomatic.

Suspected genital herpes outbreaks: Because herpes testing is not required or expected in MTN-042, each suspected genital herpes outbreak should be reported using the term marked on the Pelvic Exam CRF describing the lesion together with the anatomical location (e.g., vulvar ulceration, vaginal blister).

Genital herpes: The criterion for diagnosing genital herpes per the *Female Genital Grading Table for Use in Microbicide Studies* (FGGT) is below. Note that laboratory testing is required in order to use the term "genital herpes" for AE reporting. Such testing is not required per protocol and should only be done if it is the local standard of care. Any new lesion/ulcer observed during the study should be reported as an AE even if it thought to be due to prior herpes diagnosis/infection.

PARAMETER	Grade 0 NORMAL	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	Grade 4 POTENTIALLY LIFE-THREATENING

Genital herpes	No lesions	Characteristic ulcerative or vesicular lesions confirmed by culture, PCR, Tzanck prep or other diagnostic test of lesion or previous type-specific serology, covering < 25% of vulva, vagina, or cervix	Same criteria as mild but covering 25-50% of vulvar, vaginal, or cervical surface	Same criteria as mild but covering > 50% of vulvar, vaginal, or cervical surface	Symptoms of significant systemic involvement, e.g., encephalitis, hepatitis

Genital warts: Report all outbreaks of genital warts as AEs, regardless of whether infection with HPV was known to be pre-existing before enrollment. Report the AE using the term "condyloma" and include the anatomical location of the warts (e.g., cervical, vaginal, vulvar, perianal). Grade according to the "Condyloma" row of the FGGT.

Syphilis: Per the FGGT, a Grade 2 Syphilis AE is defined as a positive treponemal test together with a positive non-treponemal test and no previous treatment OR a four- fold rise in titer on the non-treponemal test after previous treatment regardless of symptoms or non-oral lesions positive by darkfield exam for treponemes. Report all syphilis AEs as "syphilis infection" (no anatomical location is required when reporting syphilis infections).

Trichomoniasis: Report only Grade 2 infections per FGGT, using the term "vaginal trichomoniasis." Trichomoniasis may be diagnosed by positive wet mount, culture, PCR, rapid Trichomoniasis or other licensed test (excluding pap smear), showing *T. vaginalis*, regardless of symptoms.

Vulvovaginitis and Cervicitis

In the absence of a laboratory-confirmed STI or RTI diagnosis, use the term "vulvovaginitis" when two or more of the genital/vaginal signs or symptoms listed below are present. Comment on the individual signs/symptoms in the "Comments" field of the AE Log CRF.

- pain
- itching
- erythema
- edema
- rash
- tenderness
- discharge

Similarly, use the term "cervicitis" when 2 or more of the genital/vaginal signs or symptoms listed below are present in the absence of a laboratory-confirmed STI/RTI. Comment on the individual signs/symptoms in the "Comments" field of the AE Log CRF.

- dyspareunia
- erythema
- edema
- tenderness
- discharge

If the above 2 or more symptom criteria is not met but STI/RTI suspected and treatment started, report the sign/symptom as the AE term.

Urinary Tract Infection: Report “urinary tract infection” for all instances of lower urinary tract infections diagnosed by symptoms and positive lab results (i.e. urine culture or dipstick). Do not report “bacterial urinary tract infection” or “cystitis”. The term “urinary tract infection” is sufficient. Do not report UTIs based on participant report of symptoms alone.

Sexually Transmitted Infection treated outside the clinic: At times a participant may report that she was treated for a sexually transmitted infection by an outside clinic and she is unclear about the precise infection. If further information cannot be obtained from the treating facility, report “sexually transmitted infection” and note in the comments that she was treated at an outside facility and no further information is available.

8.7 Reporting Abdominal Pain as an AE

For pregnant participants, the terms and guidance as outlined in table 8-1 above should be used to report pelvic pain.

Note that 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.

For participants who are no longer pregnant, when reporting abdominal pain as an AE, pain that is gastrointestinal in nature must be differentiated from pain that is genitourinary or reproductive in nature:

- If abdominal pain is assessed as gastrointestinal in nature and no other overarching or unifying diagnosis is available, the term “abdominal pain” should be used to describe the AE within the AE Log CRF. Do not report “upper abdominal pain” or “lower abdominal pain”. The term “abdominal pain” is sufficient.
- If the pain is assessed as genitourinary and a specific anatomic location is known, the term reported within the AE Log CRF should be described as such (i.e., “bladder pain”).
- If the pain is assessed as reproductive in nature and a specific anatomic location is known, the term reported within the AE Log CRF should be described as such (e.g., “adnexal pain”, “uterine pain”). Pain associated with menstruation is reproductive in nature and the term reported within the AE Log CRF should be described using the term “dysmenorrhea”.
- If the pain cannot be localized to a specific organ, it should be described within the AE CRF using terms that identify a reproductive or genitourinary anatomical location (e.g., “pelvic pain”, “urinary tract pain”).

8.8 Reporting Weight Loss as an AE

Unintentional weight loss prior to the pregnancy outcome should be graded and reported per the DAIDS toxicity table. The DAIDS AE Grading Table parameter for unintentional weight loss excludes postpartum weight loss. Therefore, maternal weight loss will not be graded after pregnancy outcome in this study.

8.9 Reporting Terminology Considerations for Additional Adverse Events

When the below AEs are identified, please use the following guidance on the reporting terminology:

Respiratory Tract Infection: Please use the terms “upper respiratory tract infection” or “lower respiratory tract infection” only. Do *not* use “upper respiratory-bacterial” or “upper respiratory-viral”. Note: If a participant is suspected or confirmed to have COVID-19, “COVID-19” should be reported as the AE term. If deemed not to be related to COVID-19, this should be indicated this in the comments along with the rationale (for example, the participant has a negative COVID-19 test result).

Viral Illness: Please use the terms “viral illness” rather than “flu-like illness” to refer to a generalized illness presumed to be due to a virus. Note that this does not apply to acute seroconversion illness, which should be reported as “seroconversion illness” – see section 8.13 below on “Reporting HIV

Infection Illness". Note: If a participant is suspected or confirmed to have COVID-19, "COVID-19" should be reported as the AE term.

COVID-19: If a participant is suspected or confirmed to have COVID-19, "COVID-19" should be reported as the AE term. Grade based on the "estimating severity grade" row of the toxicity table. It is not necessary to include details on whether suspected or confirmed in the comments.

Anemia: If treatment, including diet recommendations, are offered, use the term "anemia". If no instruction is provided to the participant, report "decreased hemoglobin". It is anticipated that most participants will be informed of low hemoglobin and encouraged to increase iron-rich foods. Therefore, "anemia" will be more commonly reported.

Diarrhea: Please use the terms "diarrhea" rather than "diarrhea infectious etiology," "infectious diarrhea" or "diarrhea related to bacterial infection." It is not necessary to specify the cause of the diarrhea in the AE term.

Gastroenteritis: Please use the term "gastroenteritis" for clinical conditions of nausea and diarrhea. No need to specify "viral" or "bacterial" gastroenteritis.

8.10 Reporting Pelvic Examination Findings as AEs

In general, and unless otherwise specified in this manual, report pelvic exam findings using terminology corresponding to the DAIDS FGGT and provided within the Abnormal Findings section of the Pelvic Exam CRF.

All AEs should be documented per the term marked on the Pelvic Exam form. Always include the specific anatomical location of pelvic exam findings (e.g., cervical, vaginal, vulvar) in the AE term.

8.11 Reporting Laboratory Abnormalities as AEs

If an abnormal laboratory test result is reported as an AE, separate from any clinical diagnosis associated with the result, the type of test performed and the direction of the abnormality should be reported (e.g., reduced CrCl). The severity grade of the result should not be reported as part of the AE term.

Laboratory values that fall outside of a site's normal range but are below severity Grade 1 are not considered AEs. These out of normal range, but below Grade 1 values are not documented as baseline medical history conditions or adverse events on the Baseline Medical History Log or AE Log unless requested by the IoR or designee.

When assigning severity grades, note that some sites may have normal reference ranges that overlap with the severity grade ranges. Thus, it is possible for a participant to have a result that falls within the site's normal range but is still gradable per the DAIDS Grading Table. Assign the severity grade based on the DAIDs Grading Table severity grade ranges, regardless of whether the lab result falls within the site's normal reference range.

In follow-up, isolated findings (i.e. not otherwise associated with diagnosis of a UTI) of abnormal protein and glucose on the dipstick should be reported on the AE Log CRF as indicated. Grade the severity of the urine glucose value according to the "Proteinuria, random collection" row of the Toxicity Table, and glucose according to the "glycosuria" row. Note that findings of LE/nitrites are not gradable per the DAIDs toxicity table, and like other non-gradable labs should not be reported as a baseline conditions or AEs.

The IoR or designee should carefully review all laboratory abnormalities relevant to the participant's health to identify any adverse events or health problems. Documentation of this review is required by initialing and dating each page of lab results. The severity of all lab abnormalities will be graded and recorded in the source documentation. Results of protocol-specified local laboratory results will also be submitted via the Laboratory Results CRF. Sites should document other results if any, in visit chart notes, or in other designated site-specific documents. Through the participant's study involvement, lab abnormalities that meet the criteria for expedited reporting to DAIDS will be reported separately on the AE Log CRF and reported to DAIDS via the DAERS Reporting System.

8.12 AEs Involving Hospitalizations/ Surgical Procedures

Procedures should not be captured as AEs; rather the underlying condition which leads to a procedure may be considered an adverse event. For example, an infant is hospitalized to undergo a lumbar procedure for presumed sepsis—sepsis would be considered an AE, not the lumbar puncture. Another example would be a mother that undergoes a cesarean hysterectomy for post-partum hemorrhage— post-partum hemorrhage would be considered an AE, not the hysterectomy. If the condition is considered immediately life-threatening or the condition and its resultant surgery result in a prolonged hospitalization, the adverse event should be considered a serious adverse event.

8.12.1 Reporting Guidance for Cesarean Sections

A “cesarean section” would not be considered an AE; however, the indication for the cesarean section may be reportable as either a maternal or fetal AE. For example, maternal conditions (i.e., hemorrhage, preeclampsia, etc.) or fetal conditions (i.e. fetal distress, meconium aspiration syndrome, or malpresentation) which result in a cesarean section should be captured as AEs.

If the cesarean was performed for failure to progress in labor (including conditions such as cervical dystocia, contracted maternal pelvis, large fetus, poor contraction pattern) the event should be captured as an adverse event but the preferred term should be "cephalo-pelvic disproportion." AEs reported for cephalo-pelvic disproportion should be reported as grade 2.

A scheduled repeat cesarean section would not be expected to have an AE associated; however most intrapartum cesarean sections would.

Maternal complications following cesarean section (hemorrhage, infection, scar disruption, post procedural pain, etc.) will be considered AEs regardless of the indication for the surgery. If the complication results in re-hospitalization or a prolonged hospital stay, it will be considered serious.

8.12.2 Reporting Guidance For Preterm Delivery

Often the etiology of a preterm birth is unknown. If this is the case, the AE term preterm contractions should be used and graded per the FGGT. If the etiology of the preterm delivery is known (for example abruption or chorioamnionitis) an AE for the etiology should be submitted. There is no need to report a separate AE for preterm birth itself as this will be captured in the pregnancy outcome and should be indicated in the comments section.

In the infant, the most severe complication (if any) of prematurity should be reported, if there are no complications but the infant is still admitted, report an AE for “prematurity”.

8.13 Reporting HIV Infection Illness

HIV acquisition (seroconversion) is not considered an AE for data collection or reporting purposes in MTN-042. “HIV infection” should not be reported as an AE or written anywhere on an AE Log CRF. Final determination of HIV status will instead be captured on the **HIV Confirmatory Results CRF**.

However, primary HIV infection is often symptomatic, and a constellation of symptoms may best be summarized as primary HIV infection illness. In this case, as in other cases when symptoms are best expressed as a unifying diagnosis, it is important to use that summary diagnosis. Thus, if a participant seroconverts and develops one or more signs or symptoms of acute HIV- infection, it is appropriate to report these sign(s)/symptom(s) as a single AE using ONLY the term “seroconversion illness” for the AE Term on the AE Log CRF. Use the comments section of the AE Log CRF to describe each HIV-related sign/symptom (e.g., fatigue, pharyngitis) and to note the alternative etiology as due to “acute HIV”. To avoid generating a clinical query, please ensure that the term “acute” is included when describing the required alternative etiology in the Comments section.

Complete the other items on the AE Log CRF per the general form instructions. The onset date should be completed using the date on which the participant first reported experiencing the first sign/symptom of acute HIV-infection. If there is more than one HIV-related sign/symptom, record the highest severity grade. A seroconversion illness AE is considered 'resolved' when all of the associated signs/symptoms have resolved or returned to baseline per participant report, and medications for the symptoms are no longer indicated. Mark any medications indicated and taken for the associated symptoms, if applicable.

If one or more signs/symptoms, reported on separate AE Log entries, are later attributed to acute HIV-infection, update the AE term for the earliest reported sign/symptom AE to the "seroconversion illness" diagnosis and list any other signs or symptoms in the comments section of this AE Log CRF. Inactivate the applicable AE log line within Medidata Rave.

8.14 Reporting Sexual Assault

Any physical and/or psychological sequelae that result from a sexual assault reported during the study and that meet AE reporting criteria should be reported on a AE log CRF(s). Each physical and/or psychological sequela should be reported as its own AE with the description of the physical and/or psychological sequela as the AE text (i.e., do not mention sexual assault) and with sexual assault (and additional details, if applicable), referenced in the Comments section of the AE log form. In this instance, do not complete a separate AE log form for 'sexual assault' as the AE term. In the event that a participant reports a sexual assault which did not result in physical and/or psychological sequelae, sites should report the event as a "survivor of sexual assault" as the AE text. Note that site staff should accept participant report of sexual assault rather than probing regarding this issue for the purposes of AE reporting. Sites should consult the PSRT if there are any questions about classification or documentation of a sexual assault.

Women who disclose any form of violence by an intimate partner (or other individual) or sexual assault by any perpetrator should be offered immediate support, care, and referrals according to site-specific SOPs and as advised by site social harms response mechanisms. The World Health Organization (WHO) publication, *Responding to intimate partner violence and sexual violence against women* (available at http://apps.who.int/rhl/guidelines/9789241548595/en/) is a useful resource that may help inform site-specific policies for responding to reports of sexual assault or other violence. Generally, response to reports of sexual assault should include first line support—listening and offering comfort, help, and information/referrals to connect her to services and social support—as well as offering the participant an opportunity to provide a complete history of events, and receive relevant physical evaluations, and treatment and/or referral for any injuries. Emergency contraception and STI prophylaxis/treatment should be offered. Depending on the time between the assault and presentation to the clinic (i.e. if within 72 hours), the use of PEP should also be considered. If PEP is used, refer to the MTN-042 protocol for instructions on product hold. Plans for continued follow-up and care should be outlined to check in on the participant's well-being and uptake of referrals, as appropriate.

Sexual Assault, or SA, is any type of sexual contact or behavior that occurs without the explicit consent of the recipient. Sexual assault can be perpetrated by someone who is a stranger to the survivor, and it can also occur within intimate partnerships, or friendships or familial relationships. Sexual assault includes a range of behavior from unwanted touching and indecent exposure to forced intercourse. Examples of "force" used to commit sexual assault include but are not limited to, threats or intimidation, physical violence, abuse of power – including power related to an age differential in the case of minors – or using drugs or alcohol to incapacitate a survivor.

8.15 Reporting alcohol or drug use during pregnancy

Any alcohol or drug use during pregnancy, no matter how much, should be reported as an Adverse Event. If a participant reports any alcohol use while pregnant, sites should report the event as "antepartum alcohol consumption" as the AE text. If a participant reports any recreational drug use while pregnant, sites should report the even as "antepartum recreational drug use".

8.16 Infant/Fetal AE Reporting

Infant/fetal AEs are defined as outlined in section 8.1.1 (untoward medical occurrence that does not necessarily have a causal relationship with the investigational product), with the exception that infants/fetuses are not administered study product, rather, drug exposure will be considered to start in utero on the fetus at the point of mother enrollment (randomization).

Reporting conventions for diagnosed conditions related to the fetus will depend on whether the AE is or is not considered a congenital anomaly:

- Fetal AEs that are not congenital anomalies should be reported on the maternal **AE Log CRF** at the time of diagnosis. Isolated findings such as abnormal fetal heart rate should not be reported as an AE, only the outcome if relevant—for example, fetal distress. Poor fetal growth (as defined in the DAIDS grading table) or any other fetal abnormalities diagnosed by ultrasound, doppler, or other means that are not considered congenital anomalies should also be reported as AEs within the maternal casebook. Some fetal AEs may resolve prior to pregnancy outcome, but if not resolved while the participant is still pregnant, AEs related to the fetus should be resolved at the time of delivery. Any infant-associated conditions that are present after birth should be opened as new AEs in the infant casebook using the Infant **AE Log CRF**.

  *Example: Intrauterine growth restriction is diagnosed on ultrasound. This should be reported in real time on the maternal **AE Log CRF.** At delivery, the AE should be marked "resolved." If, after delivery, the infant is found to be low birth weight and/or small for gestational age, a new AE should be reported using the infant **AE Log CRF** (if infant enrolled) or the **Non-Enrolled Infant AE Log CRF** (if infant not enrolled).*

- Congenital anomaly AEs (i.e. congenital, familial, and genetic disorders) identified while the fetus is in utero (e.g. on ultrasound) should be source documented in chart notes, but only reported as an AE after the infant is born and a full evaluation can be conducted. In most cases, reporting of congenital anomalies will be done using the Infant **AE Log CRF.** In the rare event that an infant is not born alive or consent for infant study participation is not on file at the time of birth, the infant-associated AE would be reported on the **Non-Enrolled Infant AE Log** under the maternal PTID. Should a non-enrolled infant be subsequently enrolled, any AEs reported on the **Non-Enrolled Infant AE Log CRF** should be transferred over to Infant **AE Log CRF** within the infant casebook for further tracking and management. All **Non-Enrolled Infant AE Log** lines should be deactivated.

  *Example: A fetus is diagnosed with an atrial septal defect on ultrasound. The site team should source document this in the maternal study file at the time the defect is identified, but no AE reporting is required at this time. Upon delivery, a full evaluation of the infant should be conducted and, if the atrial septal defect (or another cardiac defect) is confirmed, a new AE should be reported using the infant **AE Log CRF** (enrolled infants) or the **Non-Enrolled Infant AE Log** (stillbirths or non-enrolled infants).*

Infant AEs should be graded using the DAIDS AE grading Table, version 2.1, dated July 2017. Small for gestational age (SGA) AEs in newborns (defined as <28 days old) should be graded per the "poor fetal growth" row in the DAIDS FGGT. In addition, the following protocol-specific grading tables should be used (as outlined in protocol 8.3.1):

Axillary measured fever

- Grade 0 None
- Grade 1 37.4 to <38.0°C
- Grade 2 38.0 to <38.7°C
- Grade 3 38.7 to <39.4°C
- Grade 4 ≥39.4° C

Creatinine (neonates 0-28 days old)

- Grade 0: None
- Grade 1: 1.1 mg/dL to <1.6 mg/dL
- Grade 2: 1.6 mg/dL to <2.1 mg/dL
- Grade 3: 2.1 mg/dL to 3.0 mg/dL

- Grade 4: >3.0 mg/dL
-

Creatinine (infants >28 days old)

- Grade 0: None
- Grade 1: 0.5 mg/dL to <0.7 mg/dL
- Grade 2: 0.7 mg/dL to <0.9 mg/dL
- Grade 3: 0.9 mg/dL to 1.2 mg/dL
- Grade 4: >1.2 mg/dL

As noted in section 8.1.1 above and the MTN-042 protocol, fetal losses (Stillbirth, Preterm Birth, and Spontaneous Abortions/Miscarriages) will not be reported as AEs however they are captured as a primary outcome on the pregnancy outcome CRF. Maternal conditions that either result in or result from fetal losses are reported as AEs.

8.16.1 Common Infant Conditions AE Reporting Guidance

There are a number of conditions that are common within the first year of an infant's life which are summarized in this section along with guidance for preferred AE reporting term and grading. Close attention and appropriate clinical management and/or prompt referrals should be made whenever infant AEs are identified. More information on infant clinical care is provided in section 7.19.2.

- **Rash**: seborrheic dermatitis common in the first month; after three months of age commonly atopic dermatitis. Seborrheic dermatitis should be reported as seborrheic dermatitis. Atopic dermatitis should be reported as atopic dermatitis. Specify the type of rash as diaper rash, nappy rash, or candida nappy rash. Grade using the Estimating Severity Grade row of the DAIDS toxicity table.
- **Thrush (candida infection):** Thrush should be reported as candida infection. If the infant is a newborn (< 28 days), report as neonatal candida infection. Grade using the Estimating Severity Grade row of the DAIDS toxicity table. Report associated maternal AEs as appropriate (i.e. Nipple Thrush).
- **Small for gestational age (poor fetal growth):** Newborns (defined as infants <28 days old) should be assessed for poor growth based on weight-for-age percentiles per the DAIDS FGGT (see below). Appropriate growth charts as specified in SSP section 7.19.7 should be used to calculate weight-for-age percentiles (i.e., intergrowth 21st charts at birth for all infants, intergrowth postnatal charts for preterm babies after delivery, and WHO charts for term babies after delivery). Report AEs using the term "small for gestational age". AEs reported for SGA should remain as ongoing until either weight-for-age measurements resolve to non-gradable OR until 28 days old. If grading criteria are met for 'poor weight gain' in infants ≥28 days (see next bullet below), a new AE for 'poor weight gain' should be reported and followed to resolution or stabilization.

PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Poor fetal growth	At or above 10th percentile	Fetal growth < 10th percentile but ≥ 3rd percentile for gestational age by ultrasound or newborn exam	NA	Fetal growth < 3rd percentile for gestational age by ultrasound or newborn exam	NA

- **Undernutrition, stunting, and wasting (poor weight gain):** Severe acute malnutrition (SAM) is diagnosed by using the WHO weight-for-length z score (WLZ) and graded using the underweight row (<2 years of age) in the DAIDS tox table (see below). In infants <6 months, SAM defined by a very low weight-for-length or the presence of bilateral pitting edema. In infants ≥28 days, report as "poor weight gain" and grade using the underweight row of the DAIDS Toxicity table.

Note: In infants ≥28 days, WHO weight-for-length z-scores should be calculated each time anthropometric measurements are taken to grade and report AEs for poor weight gain per the DAIDS Toxicity Table. The following online calculator can be used to facilitate this, as needed:

https://www.merckmanuals.com/medical-calculators/WHOInfantWeightForLength.htm

While all AEs related to fetal or infant growth that meet DAIDS grading criteria must be reported and followed to resolution or stabilization, appropriate clinical management is based on the discretion of the study clinician. The clinician may determine that no immediate action is necessary and that infant growth be monitored per protocol at the next scheduled study visit. More information on clinical management of infant growth is provided in SSP section 7.19.7.

DAIDS Toxicity Table Row: Underweight

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences

- **Infant diarrhea:** Grade using the Diarrhea <1 year of age row of the toxicity table. Report as diarrhea or infectious diarrhea. If the infant is a newborn (< 28 days), report neonatal diarrhea or neonatal infectious diarrhea.

PARAMETER	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	Grade 4 POTENTIALLY LIFE THREATENING
Diarrhea <1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)

- **Infant vomiting:** Report if determined to be vomiting based on clinical judgement (i.e. not spit up). Grade using the vomiting row of the DAIDS Toxicity table:

PARAMETER	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	Grade 4 POTENTIALLY LIFE THREATENING
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life--threatening consequences (e.g., hypotensive shock)

- **Serious respiratory bacterial infection:** Report as pneumonia. if the infant is a newborn (< 28 days), report neonatal pneumonia. Grade pneumonia using the Dyspnea or Respiratory Distress row of the toxicity table:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

- **Lower Respiratory Tract Infection:** Characterized in infants by poor feeding, irritability and lethargy, grunting/cyanosis, fever, cough/wheeze, chest indrawing. Report as lower respiratory tract infection and grade per the Estimating Severity Grade row of the DAIDS toxicity table.

8.17 Reporting Congenital Anomalies

Congenital Anomalies may be considered SAE/EAEs per DAIDS definitions. **Note that all congenital anomalies (major/minor) should be reported on the Pregnancy Outcome CRF (if diagnosed through 6-week PPO) and the infant's AE Log CRF (diagnosed at any visit), regardless of whether they are reported as an SAE/EAE.**

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) for defining minor anomalies and Chapter 3.3 (EUROCAT Subgroups of Congenital Anomalies) for defining major anomalies:

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

Conditions outlined in the EUROCAT guidelines Chapter 3.3 (EUROCAT Subgroups of Congenital Anomalies) are reportable to DAIDS as SAE/EAEs, unless the DAIDS EAE manual specifies the condition should not be reported (e.g., polydactyly). It should be noted although organized slightly differently, the major anomalies listed in EUROCAT cover those listed in the Guidelines for Conducting Birth Defects Surveillance, National Birth Defects Prevention Network (NBDPN), as referenced in the DAIDS EAE manual. This listing should not restrict the reporting of anomalies that the site investigator deems important for the sponsor to know. Sites should always overreport versus not reporting and potentially missing an important primary outcome.

As per the DAIDS EAE manual, clinically insignificant physical findings at birth, including those regarded as normal variants, do not meet reporting criteria as an SAE/EAE. **Examples of conditions considered to be minor anomalies are summarized in EUROCAT guidelines Chapters 3.2 (Minor Anomalies for Exclusion).** However, if a clinically significant anomaly is reported, all other findings (including those of no individual significance) should be included in the same EAE report. For example, an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant with no other findings would not be reported as an SAE, but polydactyly or Mongolian spot occurring with a major cardiac defect would be reported and included in the SAE report. Sites should always err on the side of overreporting versus not reporting.

As stated above, all anomalies, whether considered major or minor, should be recorded on the **Pregnancy Outcome CRF (through 6-week PPO) as well as the AE Log CRF**.

8.18 Adverse Event Severity Grading

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in MTN-042 must be graded on a five-point scale:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Potentially life-threatening
- Grade 5 = Death

Severity is not the same as seriousness, which is based on the outcome or action associated with an event, as described in Section 8.1.2.

The severity of all AEs identified in MTN-042 will be graded using the:

- Protocol-specific grading tables as outlined in protocol section 8.3.1
- *DAIDS Table for Grading Adult and Pediatric Adverse Events* (hereafter referred to as the Toxicity Table), Version 2.1 dated July 2017.
- *Female Genital Grading Table for Use in Microbicide Studies* (FGGT), dated November 2007 (with the exception of asymptomatic candidiasis and asymptomatic BV, which will not be considered adverse events for MTN-042).

AEs listed in both the FGGT and the Toxicity Table should be graded according to the FGGT. AEs not listed in the FGGT should be graded according to the Toxicity Table. AEs not listed in the FGGT or the Toxicity Table should be graded according to the "estimating severity grade" row of the Toxicity Table

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Both the FGGT and the Toxicity Table can be accessed on the DAIDS RSC web site (http://rsc.tech-res.com/safetyandpharmacovigilance).

Further clarifications, guidelines, and tips for grading the severity of AEs in MTN-042 are as follows:

- Genital petechia/e and genital ecchymosis should be considered Grade 1 as neither requires treatment.
- If the severity of an AE falls into more than one grading category on the FGGT or the Toxicity Table, assign the higher of the two grades to the AE.
- If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, and the diagnosis is not specifically listed in the FGGT or Toxicity Table (e.g. preeclampsia), assign the AE the highest severity grade among each of the associated signs and symptoms. Record the diagnosis as the AE term and record each associated sign and symptom (e.g. headache, elevated blood pressure, proteinuria) in the AE CRF comments section.
- Seasonal allergies should be graded according to the "estimating severity grade" row of the Toxicity Table (not the "acute systemic allergic reaction" row).

- Urinary tract infection (UTI), which is expected to be diagnosed on the basis of symptoms and positive laboratory testing (i.e. dipstick and/or culture) should be graded according to the estimating severity row of the Toxicity Table. If culture and/or microscopy are done per site standard of care, Grade 1 and Grade 2 UTI can be graded per the UTI row of the FGGT.
- When grading adverse events per the "estimating severity grade' row (i.e. for AEs not listed specifically in the FGGT or DAIDS Toxicity table), 'intervention' should be defined as outlined in the "Glossary and Acronyms" section of the Toxicity Table 2.1: "medical, surgical or other procedures provided by a healthcare professional for the treatment of an adverse event." If a participant reports treatment, the clinician must obtain further information as to whether it was self-initiated (Grade 1) vs. provider-recommended (Grade 2). Importantly, clinicians should note that grading is dependent on participant-reported impact of symptoms on her life, and whether intervention (defined as above) is *indicated,* regardless of whether the treatment was actually provided or taken by the participant. It is at the discretion of clinician to determine whether intervention was indicated for the reported AE. In the event that a (provider-recommended) intervention was indicated but not taken, the treatment should be marked as "other" rather than 'medications' and additional details should be included in the line provided. The AE severity grade, per the toxicity table, would be assigned Grade 2.

8.19 Reporting Maternal or Infant Deaths

All deaths related to an AE are to be classified as grade 5 and reported as an SAE/EAE. In the event of a maternal or infant death, sites should capture as much information as possible related to the circumstances of the death. An autopsy report should be pursued, if possible. SAE/EAEs and AEs should be updated as appropriate if new information becomes available as a result of the autopsy. See SSP section 7.19.2 for a summary of common causes of infant mortality and signs that should prompt immediate attention.

Sites must outline in SOPs procedures detailing site actions related to children enrolled in any study in the event of the death of a parent or legal guardian. For MTN-042 specifically, this should address continued participation of the infant through Month 12 in the event of a maternal death after delivery.

8.20 Adverse Event Relationship to Study Product

One of the following relationship categories must be assigned to each reportable AE:

- Related: There is a reasonable possibility that the AE may be related to the study product.
- Not related: There is not a reasonable possibility that the AE is related to the study product.

For both 'related' and 'not related' assignments, a rationale (such as alternative etiology or explanation) is required to be provided within the Comments Section at the bottom of each AE CRF. Recording "no other cause identified" is not adequate. Although an AE's relationship status defers to clinician discretion, some clinical explanation is helpful to present a more complete safety profile of the study product. For example, what investigations were performed, did the problem resolve spontaneously or only with cessation of study product use, and what was the onset date of the AE in relation to study product exposure?

Familiarity with previously identified adverse drug reactions (adverse events with a possibility of a causal relationship) may aid in determining relationship status. This information can be found in the current Investigational Brochure for the Dapivirine Vaginal Ring and Emtricitabine/ Tenofovir Disoproxil Furmerate (Truvada) Package Insert.

The relationship status of an AE may be changed if new information becomes available at a later date, after the AE is first reported, that would change the assessment. If the relationship status is changed at a later date update the "Relationship to Study Product" item. Then, review the entire form for completeness and add additional rationale in the Comments.

Example: Participant-reported “headache” is reported as an AE and deemed ‘related’ in the “Relationship to Study Product” item with the rationale that the headache presented after the participant started using Truvada. The site evaluation was unremarkable. Days later, the participant was diagnosed with preeclampsia. At this point the site might conclude that the headache is not related to Truvada use but rather due to preeclampsia. The “Relationship to Study Product” item of the AE Log entry should be updated from “related” to “not related”. Additional notes should be added the Comments Section to clarify the rationale.

As noted in section 8.4.2 above, all maternal AEs determined to be associated with pregnancy must be indicated as such of the AE Log CRF. Association with pregnancy is independent of determination of relatedness to study product.

8.20.1 Dapivirine Ring: Relationship to Drug or Device

An additional field was added to the AE Log CRF to document if Dapivirine (DPV) vaginal ring relatedness is attributed to the device or drug. If a mother participant is randomized to the DPV vaginal ring, and an AE reported on the AE log in a mother casebook is related to study product, the “If “related” to the DPV vaginal ring, is the AE related to the drug (dapivirine) or device (ring itself or ring insertion)?” field must be completed to document if the clinician thinks the AE is related to the drug, device, or if they cannot distinguish between the drug and device components. This field should be left blank for infant AEs.

8.21 Adverse Event Outcomes and Follow-Up Information: During the Study

All AEs identified in MTN-042 must be followed clinically until they resolve (return to baseline) or stabilize (persist at a certain severity grade above baseline for one month).

- At each follow-up visit, an authorized study clinician should review all previously identified ongoing AEs (all AE CRF entries with an “ongoing” status in the ‘status/outcome’ field) and evaluate and document their current status. If an AE is improving in grade but not yet back to baseline, the AE should remain open and the status marked as recovering/resolving on the AE CRF. Details about the change should be documented in the comments section. For example, “as of XX date, improved to grade1, will continue to follow.”
- For all AEs, outcomes must be reported within the AE CRF, or chart notes or other site specific tracking log
- In many cases, the final outcome of a reportable AE will not be available when the AE CRF is first completed. In such cases, the AE CRF should be updated when the final outcome becomes available.

Clinical management and follow-up of AEs detailed in Section 9 of the MTN-042 protocol should proceed per those specifications. If an AE is not addressed in Section 9 of the protocol, follow-up evaluations should be performed at an appropriate schedule as determined by the clinician until resolution or stabilization (the same grade for one month) has been documented. In general, evaluations of an AE may be performed at any time if required to properly monitor and/or manage participant safety, at the discretion of the IoR or designee. It is acceptable for AE follow-up/evaluation to be conducted over the phone, as clinically appropriate.

If an AE increases in severity per the DAIDS toxicity table after it has been reported initially within the AE Log, it must be reported as a new AE within a new Adverse Event Log (AE) entry at the increased severity per the DAIDS toxicity table. In this case, the outcome of the first AE will be documented as “Severity/frequency increased” on the initial AE CRF. The outcome date of the first AE and the onset date of the new (worsened) AE will both be the date upon which the severity per the DAIDS toxicity table increased (see instructions for these items within the CRF Completion Guidelines for additional guidance).

Resolution dates for AEs of any AE requiring treatment should be based on the date when all associated symptoms resolve or when treatment is completed (whichever occurs later). For asymptomatic STIs, the resolution date is the date the participant completes treatment.

8.22 Adverse Event Outcomes and Follow-Up Information: After Study Termination

A subset of AEs must be followed after a participant's termination visit.

- SAEs/EAEs that are ongoing at the termination visit:
- AEs that are found to have increased in severity at the termination visit
- Any new grade 3 AEs uncovered at the last visit

For any AEs that fall into the categories above, the IoR/designee must establish a clinically appropriate follow-up plan. At a minimum, the AE must be re-assessed by study staff 30 days after the participant's study exit visit; additional evaluations also may take place at the discretion of the IoR/designee. If the AE is not resolved or stabilized at the time of re-assessment, additional assessments should occur at the following frequency:

- If the study is ongoing, continue to reassess at least once per month while the study is ongoing until resolution/stabilization.
- If the AE has not resolved by study end (i.e., once all participants are exited), these AEs should be re-assessed at least once within 30-60 days after the study end date. The site is to send an informational query regarding the case to the PSRT at the time of reassessment. The MTN-042 PSRT also may advise on whether any additional follow-up is indicated on a case by case basis.

For AEs that are continuing at the termination visit but do not meet the criteria above (i.e., not an SAE/EAE, not an AE that has increased in severity at the termination visit, and not a newly diagnosed grade 3 AE) it is left to the discretion of the IoR or designee as to whether the AE needs to be followed. For example, should a participant have an elevated EPDS score at her 6-week follow-up visit and be referred for further evaluation, the IoR/designee may determine that follow-up is warranted. Should the IoR or designee determine the AE needs follow-up, the plan and frequency for clinical management will be as determined by the IoR/designee. The PSRT can be consulted as needed.

Documentation: For AEs that are re-assessed after a participant's termination visit, information on the status of the AE at the time of re-assessment will be recorded in chart notes, and may be communicated to the PSRT, if applicable; however, no updates should be made to any AE Log CRF. All AEs that are ongoing at the time of final clinic visit should have a status/outcome marked as "continuing at the end of study participation." Regardless of whether a participant has an ongoing AE requiring reassessment per protocol or clinical discretion, or if lab results from samples drawn during her final visit are still pending, the termination date should be documented as the date of her final visit.

8.23 Reporting Recurrent Adverse Events

If an AE previously reported within an AE log CRF resolves and then recurs at a later date, the second occurrence may be reported as a new AE on a new AE Log CRF as applicable, or previous occurrences of this AE may be reopened and documented as ongoing, depending on participant well-being and site preference.

Regular occurrences of the same adverse event that are expected in follow-up are not typically considered separate adverse events. For example, a participant reports a single episode of acid reflux that the clinician assesses as Grade 1 not related to study product. The first event is captured as an AE with an onset and outcome date. At the next visit, the participant notes that Grade 1 acid reflux is now a recurring issue that she experiences 1-2 times a week. Rather than open separate AEs for each occurrence of acid reflux, the site can update the first AE for acid reflux and note in the comments section that this is a recurring event. The status should be changed to ongoing.

Some participants may have chronic, episodic, pre-existing conditions. In these situations, if the participant experiences an episode of the condition during follow-up that has not increased in severity or frequency from the baseline condition, it would not be considered an AE. For example, if a woman reports that she has ear pain about three times a month before the study, and this continues at the same frequency and severity during the study, ear pain should not be reported as an AE.

8.24 Social Harms (Social Impacts)

In addition to medical AEs, participants in MTN-042 may experience social harms — non-medical adverse consequences — as a result of their participation in the study, including as a result of their use of the tablets or ring. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends. They also could experience stigma or discrimination from family members and members of their community. In the event that any social harms occur, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section.

MTN-042 participants will be asked at their 1st 4-week Visit and the 6-week PPO visit if "At any time during your study participation, have you experienced a negative change, event, or experience in your life related to your study participation?" on the **Social Impacts CRF**. In addition to responding to this standardized asked at the end of study participation, participants also may spontaneously report study-related issues and problems to study staff at any study visit. If a social harm is reported at any time, an entry on the **Social Impact log CRF** should be completed. Ongoing social harms should be followed up on until they have resolved, it has been determined that they will not be resolved, or the participant's study participation has ended. For newly reported social harms identified at the 6-week PPO visit, it is recommended that follow-up for support and management occur within 30 days of study exit, and as needed during the infant visits at Months 6 and/or 12. Note that any follow-up on social harms that occurs after study exit is not recorded on CRFs, rather, documentation is made only in the chart notes only.

Site teams should discuss as a group, and with community representatives, what issues and problems are most likely to be encountered by participants at their site and should agree upon how these issues and problems should be handled logistically. Roles and responsibilities should be defined for all staff members, such that each staff member is aware of what actions he/she can appropriately take, and what actions should be referred to other members of the team. During study implementation, staff teams at each site should continue to discuss actual participant experiences, successful and unsuccessful response strategies, and other lessons learned among themselves and with community representatives. Based on these discussions and lessons learned, procedures for responding to issues and problems should be reassessed and updated as needed throughout the study.

The following are suggested strategies for responding to social harms that may be adapted and tailored to best meet participant needs at each site:

- When first responding to an issue or problem, actively listen to the participant's description of the problem and ask questions to elicit as much detail as possible about the problem, including the participant's perception of the severity of the problem. Record all pertinent details in signed and dated chart notes.
- Ask the participant for her thoughts on what can/should be done to address the problem, including what she would like study staff to do in response to the problem (if anything).
- Discuss with the participant any additional or alternative strategies that you might suggest to address the problem and collaborate with her to develop a plan to try to address the problem. Document the plan in signed and dated chart notes.
- Take all possible action to try to address the problem, per the plan agreed upon with the participant. Document all action taken, and outcomes thereof, in signed and dated chart notes.
- As with medical AEs, follow all problems to resolution or stabilization, up through study termination.
- Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.
- If the reported social harm is associated with an AE (per the definition in Section 8.1.1) report the AE within an AE Log CRF. If the social harm is associated with an AE that meets criteria for expedited reporting to the DAIDS RSC, report it as an AE as described in Section 8.2. Also report the issue or problem to all IRBs/ECs responsible for oversight of MTN-042, if required per IRB/EC guidelines.
- Consult the MTN-042 PSRT for further input and guidance as needed.

8.25 Reports of Intimate Partner Violence (IPV)

According to the World Health Organization, ***Intimate Partner Violence***, or IPV, refers to any behavior within an intimate relationship that causes physical, psychological or sexual harm to those in that relationship. It includes acts of physical aggression (slapping, hitting, kicking, or beating, for example), psychological abuse (intimidation, humiliation, and threats, for example), forced sexual intercourse or any other controlling behavior (including isolating a person from family or friends, monitoring their movements or restricting access to information or assistance, for example). Intimate partner violence also includes violence committed by former partners and individuals in dating relationships.

IPV may also be reported directly to site staff and if it is related to study participation, it will be reported on the **Social Harms Log** as indicated above. IPV not related to study participation should be recorded in source documentation. Irrespective of whether IPV is related to study participation, participants should be provided the appropriate support, counseling, and referrals per site SOPs and social harm response plans to help manage any reported IPV, and steps should be taken as needed to improve participant safety. See also SSP section 8.14 above on reporting sexual assault and also the WHO guidance document, *Responding to intimate partner violence and sexual violence against women,* which can be used as a resource for developing site-specific policies for responding to reports of IPV.

If the reported IPV is associated with an AE (per the definition in Section 8.1.1) report the AE within an **AE Log CRF**. If the IPV is associated with an AE that meets criteria for expedited reporting to the DAIDS RSC, report it as an EAE as described in Section 8.2.

8.26 MTN-042 Safety Monitoring, Review, and Oversight

Refer to Section 8 and 10.7 of the MTN-042 protocol for a complete description of the participant safety monitoring procedures in place for MTN-042. Also refer to Section 13 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN-042 safety monitoring procedures.

Participant safety is of paramount importance in MTN-042. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study staff, under the direction of the IoR. Any study staff member who is regularly involved in the source documentation of safety data for this trial (including documentation of participant symptoms, physical or obstetric exam findings, pelvic exam findings etc.) should be listed as a sub-investigator on the FDA Form 1572. If allowable per country standards and guidelines, nurses may perform these tasks, but study doctors must be able to demonstrate that appropriate oversight was conducted. Decisions regarding severity determination for an AE, relationship to study product, and study product management must be done by a study doctor. Documentation of this clinical oversight for AEs must be present in the participant file, particularly if nursing staff is responsible for completing the AE Log CRF.

The IoR and designated study staff are also responsible for completing CRFs within the clinical database and EAE reports to the DAIDS RSC, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- Clinical staff at the MTN SDMC will review clinic and laboratory data received at the SDMC and apply clinical data quality control notes (queries) to data requiring confirmation, clarification, or further follow-up by site staff. These queries will be placed in the clinical database for site staff to review and resolve on an ongoing basis throughout the period of study implementation. In addition, Protocol Safety Physicians may contact site staff directly, if needed, for additional clarification of safety data.

- The DAIDS RSC, DAIDS RAB Safety Specialist, and DAIDS PSB Medical Officers will review all EAE Forms received for MTN-042 and follow up on these reports with site staff, the MTN-042 Protocol Team, and drug regulatory authorities when indicated.

- The MTN-042 PSRT will routinely review safety data reports prepared for MTN-042 by the MTN SDMC. As described further in Section Appendix 8-1, the PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns.

- An Interim Review Panel (IRP) of multidisciplinary experts will review safety data collected after the last pregnancy outcome in each cohort to look for higher frequencies for the primary outcomes compared to baseline estimates. In addition, a safety review of secondary outcomes related to pregnancy will be conducted. If high rates of poor pregnancy outcome(s) were noted at interim review, serious consideration would be given as to the prudence of enrolling women in subsequent cohorts. Interim review results will be relayed to site IRBs/IECs and to study participants as appropriate. The IRP is further described in the MTN-042 IRP charter.

The PSRT and an Interim Review Panel (IRP) will be charged with reviewing participant safety data as no DSMB is planned for this study.

The MTN Study Monitoring Committee (SMC) also will periodically review MTN-042 study progress, including rates of participant accrual, retention, completion of primary and secondary endpoint assessments, and study or laboratory issues. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

If at any time, a decision is made to discontinue participants, DAIDS after consultation with the protocol team, will inform the US Food and Drug Administration (FDA). The Site PIs will notify the responsible IRBs/ECs expeditiously. While site staff are not typically involved in these reviews, site staff should be aware that the SMC or IRP may make recommendations to DAIDS and/or the MTN leadership that could affect the study and sites in significant ways. These decisions are based on a detailed review of the available study data and careful consideration of ongoing participant safety and study viability.

8.27 Safety Distributions from DAIDS

Study sites will receive product- and safety-related information throughout the period of study implementation. This information will be distributed by DAIDS, through its RSC and/or the MTN LOC, and may include:

- Updated Investigators Brochures and Package Inserts
- IND Safety Reports
- Other safety memoranda and updates

Each distribution will include a cover memo providing instructions on how the document is to be handled. In all cases, a copy of the distribution must be filed in on-site essential document files. Also in all cases, study staff responsible for clinical oversight of study participants should be made aware of any newly available safety information. In many cases, the distribution will need to be submitted to site IRBs/ECs. Safety distributions do not require IRB/EC approval; however, acknowledgement of receipt is desirable. Submission letters/memos for IRB/EC submissions should specify the name and date of all documents submitted.

Appendix 8-1 MTN-042 Protocol Safety Review Team Plan

Roles and Responsibilities of the PSRT

Per the MTN-042 protocol, the roles and responsibilities of the MTN-042 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports. Once the SDMC begins receiving follow-up safety data, the PSRT will convene via regularly scheduled monthly

conference calls. The frequency of calls may be adjusted throughout the period of study implementation as agreed upon by the PSRT. Should any unexpected safety concerns be identified by the PSRT, these will be referred to the Interim Review Panel (IRP) for further review, as appropriate.

2. Respond to queries regarding product use management. The protocol specifies a number of situations in which study product use should be temporarily held, permanently discontinued and/or resumed; designated site staff will implement these holds, discontinuations, and/or resumptions in the absence of consultation with the PSRT. In other situations, however, product use management must be undertaken in consultation with the PSRT.
3. Respond to queries regarding study eligibility and adverse event (AE) assessment, reporting, and management.
4. Respond to notifications of participant withdrawal from the study.

PSRT Composition

The following individuals comprise the MTN-042 PSRT:

- DELIVER Protocol Chairs
- MTN Safety and Protocol Physicians
- DAIDS Medical Officer (MO)
- NICHD MO
- IPM Representative
- Gilead Representative

Ideally all PSRT members will take part in routine PSRT conference calls. At a minimum, a Protocol Chair, the DAIDS Medical Officer or NICHD MO (or their designee), and a MTN Safety Physician must take part in all calls. If these three members are not present, the call may be deferred until the next scheduled call time unless a PSRT member requests a more immediate call. MTN LOC Clinical Research Managers, SDMC Clinical Data Managers, and SDMC Statistical Research Associates may attend PSRT calls as observers and/or discussants.

The SDMC Clinical Safety Associate (CSA) serves as the primary liaison between the PSRT and the SDMC. The CSA will participate in the PSRT calls, and, based on PSRT discussion and request, will place clinical queries in the study database and communicate with sites as needed. The CSA will also bring to the calls for discussion any data trends or issues observed in the context of routine study clinical data reviews.

PSRT Communications

A group email address (mtn042psrt@mtnstopshiv.org) will be used to facilitate communication with the PSRT. All PSRT communications will be sent to this email address.

Site consultation with the PSRT will be facilitated using the MTN-042 PSRT Query Form, which is available on the MTN-042 web page (https://www.mtnstopshiv.org/research/studies/mtn-042). Site staff will email completed query forms to the Protocol Safety Physicians (mtn042safetymd@mtnstopshiv.org) who will work with the PSRT to prepare a consensus response to the query, and then email the final response to the site. This process is expected to occur within three business days. When necessary, site requests for responses within one business day can usually be accommodated provided the need for an expedient response is indicated in the text of the email. All members of the PSRT are encouraged to review the information provided by the site in the query form and to contribute to the response; however, final determination rests with the Protocol Chair(s).