

Section 11. Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-003. Please also refer to Section 8 of the MTN-003 protocol and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events
- Female Genital Grading Table for Use in Microbicide Studies
- Manual for Expedited Reporting of Adverse Events to DAIDS
- DAERS Reference Guide for Site Reporters and Study Physicians
- Package Insert for tenofovir disoproxil fumarate (Viread)
- Package Insert for emtricitabine/tenofovir disoproxil fumarate (Truvada)
- Investigators Brochure for tenofovir gel

11.1 Definitions and General Reporting Guidance

11.1.1 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-003, the ICH-E6 definition is applied to all participants in all five study groups, beginning at the time of random assignment. Study staff must document in source documents all AEs reported by or observed in MTN-003 participants, beginning at the time of random assignment, regardless of severity and presumed relationship to study product. Source documentation for all AEs should minimally include the following:

- AE term/diagnosis
- Severity grade
- Onset date
- Outcome
- Outcome date
- Treatment (if any)

Study staff also must follow all AEs to resolution or stabilization. As a general operational guideline, “resolution” is defined as returning to the condition or severity grade that was present at baseline (i.e., at the time of randomization) and “stabilize” is defined as persistence at a certain severity grade (above baseline) for three consecutive monthly evaluations.

Medical conditions, problems, signs, symptoms, and findings identified prior to random assignment are considered pre-existing conditions. Such conditions should be documented per the screening and enrollment visit guidance provided in Sections 4, 7, and 10 of this manual, and reported on the Pre-Existing Conditions case report form. If a pre-existing condition worsens (increases in severity or frequency) after randomization, the worsened condition is considered an AE. If a pre-existing condition resolves after randomization, but then recurs at a later date, the recurrence is considered an AE.

11.1.2 Reportable Adverse Events

Per Section 8.2 of the MTN-003 protocol, study staff will report on case report forms the following subset of AEs reported by or observed in enrolled participants:

- All genital, genitourinary, and reproductive system AEs except asymptomatic bacterial vaginosis
- All fractures
- All AEs of severity grade 2 or higher in the following categories: dizziness, headache, nausea, vomiting, diarrhea, abdominal pain, rash
- All AEs of severity grade 3 or higher
- All serious AEs, as defined by ICH-E6 (see also Section 11.1.3)
- All AEs that result in permanent discontinuation of study product use
- All laboratory test abnormalities not otherwise associated with a reported clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited AE reporting requirements (see also Section 11.1.4)

See Figures 11-1 and 11-2 for clarifying information related to reporting genital, genitourinary, and reproductive system AEs and reporting AEs involving abdominal pain.

Although not explicitly stated in the MTN-003 protocol, asymptomatic candidiasis is not reportable as an AE in MTN-003. This is because the *DAIDS Female Genital Grading Table for Use in Microbicide Studies* (FGGT) that is used to grade the severity of genital findings characterizes the identification of candida in the absence of symptoms as a normal finding. See Section 11.3 below for more information on severity grading.

Laboratory values that fall outside of a site's normal range, but do not meet criteria for severity grading as grade 1 or higher per Section 11.3 below, should not be considered "abnormal" for purposes of AE reporting, unless the Investigator of Record (IoR) or designee determines otherwise based on his/her clinical judgment. Similarly, vaginal pH levels greater than 4.5 should not be reported as AEs. Similarly, a laboratory result that is not listed in the DAIDS toxicity table will not be reported as an AE. For example, a positive urine LE or positive nitrites result on dipstick urinalysis should not be reported separately as its own AE on its own AE Log form. Rather, the positive dipstick results will be captured on the Safety Laboratory Results CRF completed for the visit.

The Adverse Experience Log case report form is used to report the above-listed reportable AEs to the MTN Statistical and Data Management Center (SDMC). All sites are strongly encouraged to use AE tracking tools to ensure that all AEs are source documented and that all reportable AEs are reported to the MTN SDMC on the Adverse Experience Log form; sample tracking tools are available in the Study Implementation Materials section of the MTN-003 web page.

Figure 11-1
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, sexually transmitted infections (STIs), reproductive tract infections (RTIs), and urinary tract infections (UTIs) fall in this category.

For pregnant participants, AEs that are related to the pregnancy, worsened by the pregnancy, or require changes in clinical management of the pregnancy are considered reproductive system AEs and will be reported as such. For example:

- Nausea and vomiting related to pregnancy (hyperemesis) are considered reproductive system AEs, but nausea and vomiting due to gastroenteritis during pregnancy are not.
- New occurrences of hypertension or diabetes due to pregnancy are considered reproductive system AEs.
- Pre-existing hypertension worsened by pregnancy is considered a reproductive system AE, as is pre-existing diabetes previously controlled by diet that requires insulin during pregnancy.

Under protocol Version 1.0, all fetal losses — including spontaneous abortions, still births, and intrauterine demise — are considered reproductive system AEs.

Under protocol Letter of Amendment #01, fetal losses are not reportable as AEs. However, untoward maternal conditions that either result in or result from fetal losses should be reported as reproductive system AEs.

Elective abortions are not AEs.

Figure 11-2
Reporting Abdominal Pain as an AE

When reporting abdominal pain as an AE in MTN-003, 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” or “lower abdominal pain” should be used to describe the AE. As noted above, abdominal pain of severity grade 2 and higher is reportable in MTN-003.

If abdominal pain is assessed as genitourinary or reproductive in nature, the pain should ideally be localized to a genitourinary or reproductive organ and described as such (e.g., adnexal pain, bladder pain). If the pain cannot be localized to a specific organ, it should be described using terms that identify a reproductive or genitourinary anatomical location (e.g., pelvic pain, urinary tract pain). Pain associated with menstruation is reproductive in nature and should be described using the term dysmenorrhea. As noted above, all genitourinary and reproductive pain is reportable in MTN-003, regardless of severity grade.

As noted above, source documentation for all AEs should minimally include the following: AE term/diagnosis, severity grade, onset date, outcome, outcome date, and treatment (if any). For reportable AEs, the following also must be source documented:

- Date reported to site
- Relationship to study product
- Action taken with study product as a result of the AE
- Whether the AE is serious per ICH guidance (see Section 11.1.3)
- Whether the AE meets expedited AE reporting requirements (see Section 11.1.4)
- Whether the AE is a worsening of a pre-existing condition (see Section 11.1.1)

Each site's SOP for source documentation should define the extent to which the Adverse Experience Log form will be used as the source document for these data elements.

Site-specific delegation of duties documentation should designate study staff authorized by the IoR to complete Adverse Experience Log forms. 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.

11.1.3 Serious Adverse Events (SAEs)

ICH-E6 defines a serious adverse event (SAE) as any untoward medical occurrence that at any dose:

- 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 Toxicity 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)*
 - *Admission for diagnosis or therapy of a condition that existed before randomization AND has not increased in severity or frequency since baseline.*
- Results in persistent or significant disability/incapacity, or
 - Is a congenital anomaly/birth defect.

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. In addition, the guidance states that "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 in the definition above" should usually be considered serious.

SAEs are a subset of all AEs. For MTN-003, all SAEs are reportable AEs. For each AE identified in MTN-003, an authorized study clinician must determine whether the AE meets the ICH definition of “serious”. The Adverse Experience Log case report form includes an item (item 8) 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 11.3 for more information on severity grading). Further note that the *DAIDS Table for Grading Adult and Pediatric Adverse Events* and the *Female Genital Grading Table for Use in Microbicide Studies* identify AEs of severity grade 4 as potentially life-threatening. As such, it is not necessary or expected that all grade 4 AEs will be assessed as serious. Rather, each AE should be assessed for seriousness according to whether it is immediately life-threatening (i.e., places the participant at immediate risk of death) or otherwise meets the definition of serious as listed above. In particular, it is not expected that asymptomatic grade 4 laboratory abnormalities will be assessed as “serious”.

11.1.4 Expedited Adverse Events (EAEs)

Under Protocol Version 1.0

Expedited adverse events (EAEs) are AEs that meet criteria specified in the study protocol as requiring additional reporting for rapid review and assessment by DAIDS. In some cases, DAIDS may be required to report an EAE to the US Food and Drug Administration (FDA). All EAEs must be reported within three business days of site awareness of the EAE.

Although seriousness is a consideration in determining whether an AE meets the definition of EAE, the terms SAE and EAE are not synonymous. The two terms refer to two different, but overlapping, subsets of AEs. For MTN-003, the subset of AEs that are considered EAEs includes some AEs that are serious and some that are not serious.

The *Manual for Expedited Reporting of Adverse Events to DAIDS* defines levels of EAE reporting that may be used in DAIDS-sponsored studies. For MTN-003, the “standard” reporting level will be followed. Figure 11-3 details EAE reporting requirements per the standard level of reporting. For each MTN-003 participant, the EAE reporting period begins with study randomization, and ends with completion of the participant’s termination visit.

Under Protocol Version 1.0, Letter of Amendment (LoA) #02 [Implement only after all required approvals are obtained]

For MTN-003, under LoA#2, Expedited adverse events (EAE) are AEs that meet the definition of “serious”, (SAEs), regardless of relationship to study product, 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. In some cases, DAIDS may be required to report an EAE to the US Food and Drug Administration (FDA).

All EAEs must be reported within three reporting days of site awareness of the EAE. The definition of a “reporting day” are those that count towards the 3-day timeline provided for reporting of EAEs to DAIDS. The criteria are as follows:

- Monday through Friday count as reporting days.
- Saturday and Sunday are not considered reporting days.
- Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday counts as a reporting day.
- A reporting day starts at 12:00 AM (midnight) and ends at 11:59 PM local time (in the site's time zone).
- The day site personnel become aware that an AE has met the definition of an EAE shall count as day 1 if that day occurs on a reporting day (i.e., Monday through Friday). This is true, regardless of the time of the day site personnel become aware of the EAE. If the day site personnel become aware of the EAE is a non-reporting day (i.e., Saturday or Sunday), then the next reporting day shall count as day 1.

The Manual for Expedited Reporting of Adverse Events to DAIDS defines levels of EAE reporting that may be used in DAIDS-sponsored studies. For MTN-003, the “standard” reporting level will be followed. Figure 11-3a details EAE reporting requirements under Letter of Amendment #02. For each MTN-003 participant, the EAE reporting period begins with study randomization, and ends with the participant's termination visit. All EAEs should be reported to the DAIDS Regulatory Compliance Center (RCC) using the internet-based DAIDS Adverse Experience Reporting System (DAERS), per instructions provided in the DAERS Reference Guide for Site Reporters and Study Physicians. The process of EAE reporting via DAERS involves a designated “Study Reporter” creating an electronic EAE report and a designated “Study Physician” reviewing the EAE report, signing the EAE report with an electronic signature, and submitting the EAE report to the DAIDS RCC. If an EAE report is not completed and submitted within three business days of site awareness of the EAE, an explanation must be entered in DAERS before the report can be submitted.

DAERS also may be used to modify or update an EAE report or to withdraw an EAE report that was submitted in error.

DAERS incorporates a report printing function that should be used to print all EAE reports—including modifications and updates—for filing in participant study notebooks. Automated email messages confirming submission of EAE reports also should be printed and filed with the print-out of the associated EAE report.

Figure 11-3

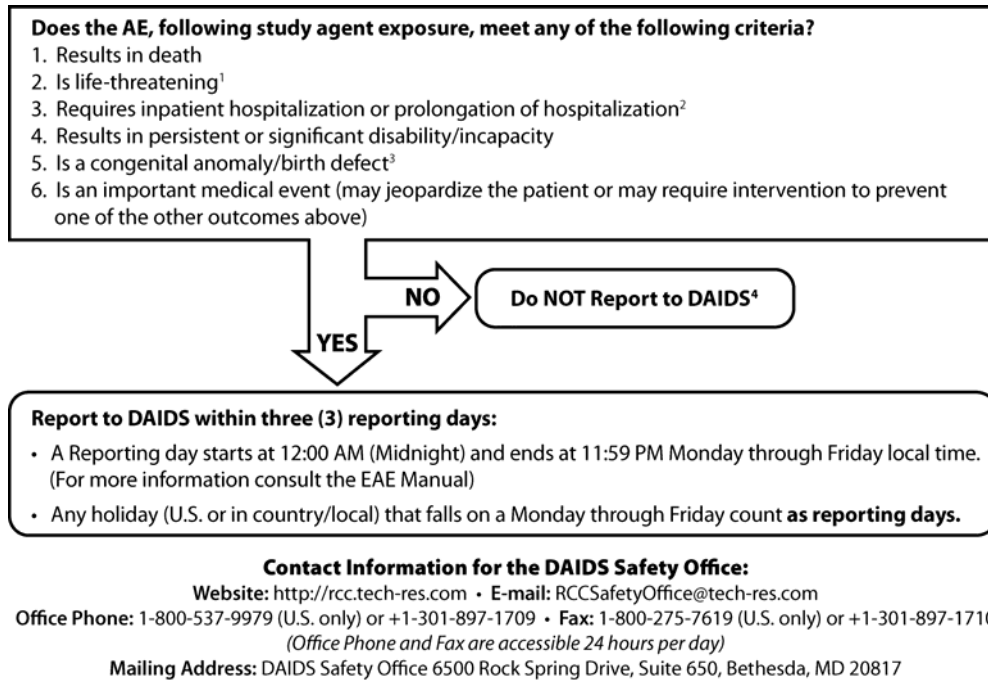
Expedited Adverse Event Reporting Requirements for MTN-003, under Protocol Version 1.0

Type of Adverse Event	Standard EAE Reporting
Results in death	Report as EAE regardless of relationship to study product
Is a congenital anomaly or birth defect or fetal loss*	Report as EAE regardless of relationship to study product
Results in persistent or significant disabilities or incapacities	Report as EAE regardless of relationship to study product
Requires or prolongs hospitalization or requires intervention to prevent significant/permanent disability or death	Report as EAE if relationship to study product is: <ul style="list-style-type: none"> • Definitely related • Probably related • Possibly related • Probably not related
Is life-threatening (includes all grade 4 AEs)**	Report as EAE if relationship to study product is: <ul style="list-style-type: none"> • Definitely related • Probably related • Possibly related • Probably not related
Other grade 1, grade 2, and grade 3 AEs	Do not report as EAE
<p>Also report as EAEs:</p> <ul style="list-style-type: none"> • AEs that may be related to study product (i.e., definitely, probably, possibly, or probably not related) that the IoR believes are of sufficient concern to be reported on an expedited basis to DAIDS. This includes AEs that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent a serious AE. • Serious AEs that are not related to study product but could be associated with study participation or procedures. • Unexpected serious AEs that may be related to study product (i.e., definitely, probably, possibly, or probably not related) that occur after the participant’s study exit visit. 	

*Under protocol Version 1.0, fetal losses must be reported as EAEs, regardless of relationship to study product. Under protocol Letter of Amendment #01, fetal losses are not reportable as AEs or EAEs.

**The *DAIDS Table for Grading Adult and Pediatric Adverse Events* and the *Female Genital Grading Table for Use in Microbicide Studies* identify AEs of severity grade 4 as potentially life-threatening. As such, it is recognized that all grade 4 AEs will not be immediately life-threatening. Nonetheless, all grade 4 AEs that are considered definitely related, probably related, possibly related, or probably not related must be reported as EAEs.

Figure 11-3a
 Expedited Adverse Event Reporting Requirements for MTN-003 (Under Letter of Amendment #02)
 [Implement only after all required approvals are obtained]



¹¹ “Life-threatening” refers to an event in which the patient was at risk of death at the time of the event. It does NOT refer to an event that hypothetically might have caused death if it were more severe.

² Per the ICH SAE definition, hospitalization is NOT an adverse event (AE), but is an outcome of the event. **DO NOT REPORT:** Any admission unrelated to an AE (e.g., for standard labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep); protocol-specified admission (e.g., for a procedure required by protocol); admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) **and** has not increased in severity or frequency as judged by the clinical investigator. (**NOTE:** A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and **would be** reportable.)

³ Clinically insignificant physical findings at birth, including those regarded as normal variants, do NOT meet reporting criteria. If a clinically significant anomaly is reported, all findings (including those of no individual significance) should be included in the same report. For example, do NOT report an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant. But if either finding occurred with a major cardiac defect, report all findings in the SAE Report.

⁴ Please ensure that any other protocol-specific reporting requirements are met.

All EAEs should be reported to the DAIDS Regulatory Compliance Center (RCC) using the internet-based DAIDS Adverse Experience Reporting System (DAERS). Follow the instructions provided in the *DAERS Reference Guide for Site Reporters and Study Physicians*. The process of EAE reporting via DAERS involves a designated “Study Reporter” creating an electronic EAE report and a designated “Study Physician” reviewing the EAE report, signing the EAE report with an electronic signature, and submitting the EAE report to the DAIDS RCC. The IoR or designee is responsible for designating on the designation log at least one other physician, who is listed on the FDA form 1572, at the site who can perform the assessment and signature. This will ensure uninterrupted coverage of AE/EAE monitoring and reporting in the event that the IoR is unavailable. If an EAE report is not completed and submitted within three reporting days of site awareness of the EAE, an explanation for the delay must be entered in DAERS before the report can be submitted.

DAERS also may be used to modify or update an EAE report or to withdraw an EAE report that was submitted in error.

DAERS incorporates a report printing function that should be used to print all EAE reports—including modifications and updates—for filing in participant study notebooks. Automated email messages confirming submission of EAE reports also should be printed and filed with the print-out of the associated EAE report.

In the event that 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 RCC via email. The EAE Form and form completion instructions are available on the DAIDS RCC web site (<http://rcc.tech-res-intl.com>). Contact details for submission of EAE Forms to the RCC are provided in the *Manual for Expedited Reporting of Adverse Events to DAIDS*.

All EAEs, including congenital anomalies and birth defects identified among infants born to study participants, must also be reported on Adverse Experience Log case report forms. When completing Adverse Experience Log case report forms 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) must be recorded consistently across all documents. All EAE reports received at the DAIDS RCC will be compared with Adverse Experience Log forms received at the MTN SDMC to ensure that all reports that should have been received by both the DAIDS RCC and the SDMC have been received and that the details recorded on each form are consistent. If any EAE reports are modified after initial reporting, the AE Log form must also be modified to correspond with the EAE report.

11.2 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in MTN-003. Whenever possible, a diagnosis should be assigned. When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, each individual sign and symptom must be identified and documented as an individual AE. When relevant, i.e., for AEs that may occur in more than one anatomical location, record the anatomical location in the AE term or description. Whenever possible, use specific terms to indicate the anatomical location of the AE (e.g., “vaginal” instead of “genital”).

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., elevated ALT). The severity grade of the result should not be reported as part of the AE term.

Further tips and guidelines for assigning AE terms are as follows: use specific medical terms whenever possible (e.g., “ulcers” instead of “sores”), use correct spelling for all terms, and do not use abbreviations. When reporting an AE that is associated with an underlying condition, include the underlying condition in the AE term or description. For example, if a participant is experiencing pain related to an underlying cancer diagnosis, include the cancer diagnosis in the AE term or description.

Additional guidance for reporting certain types of AEs in MTN-003 is provided in the figures below.

Figure 11-4
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 *Female Genital Grading Table for Use in Microbicide Studies* (FGGT) and the MTN-003 Follow-Up Pelvic Exam case report form.

For AEs in which the finding term marked on the Follow-Up Pelvic Exam form is more specific than the corresponding term on the FGGT, use the more specific term to report the AE. Consider for example a pelvic exam finding identified as a vulvar laceration. The term corresponding to this finding on the FGGT is “vulvar lesion” but the term marked on the Pelvic Exam form will be “laceration.” Because the term “laceration” is more specific than the term “lesion,” the term “vulvar laceration” should be used for AE reporting.

Always include the specific anatomical location of pelvic exam findings (e.g., cervical, vaginal, vulvar) in the AE term.

Use the term vulvovaginitis to report combinations of vulvar and vaginal pain, itching, erythema, edema, rash, tenderness, (any two or more) unless laboratory testing confirms the presence of a sexually transmitted or reproductive tract infection (STI/RTI) that is considered the underlying cause of all signs and symptoms. In this case, report the name of the STI/RTI as the AE term on the AE Log form, and record all related signs and symptoms in the comments section of the AE Log.

Use the term cervicitis to report combinations of dyspareunia, erythema, edema, tenderness, and/or discharge (any two or more) unless laboratory testing confirms the presence of an STI/RTI that is considered the underlying cause of all signs and symptoms. In that case, report the name of the STI/RTI as the AE term on the AE Log form.

Figure 11-5
Reporting Sexually Transmitted and Other Reproductive Tract Infections as AEs

Bacterial vaginosis: Only report symptomatic infections as AEs, using the term “symptomatic bacterial vaginosis.”

Candidiasis: Only report symptomatic infections as AEs, using the term “vulvovaginal candidiasis”

Chlamydia: Report all infections using the term “genitourinary chlamydia infection.”

Gonorrhea: Report all infections using the term “genitourinary gonorrhea infection.”

Genital herpes: Report all genital herpes outbreaks as AEs, regardless of whether infection with genital HSV-1 or HSV-2 was known to be pre-existing before enrollment/randomization. Note however that the *Female Genital Grading Table for Use in Microbicide Studies* (FGGT) requires laboratory testing (of lesion or by serology) in order to use the term “genital herpes” for AE reporting. Because such testing is not required or expected in MTN-003, genital herpes outbreaks should be reported using the term marked on the Follow-Up Pelvic Exam case report form to describe the lesion (e.g., vesicle, ulceration), together with the anatomical location of the finding (e.g., vulvar, vaginal).

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

Syphilis: Report all infections, using the term “syphilis infection” (no anatomical location is required when reporting syphilis infections).

Trichomoniasis: Report all infections, using the term “vaginal trichomoniasis.”

Figure 11-6
Reporting Pregnancy Losses as AEs

Under protocol Version 1.0, all pregnancy losses must be reported as AEs. Under protocol Letter of Amendment #01, pregnancy losses are **not** reportable as AEs. When reporting pregnancy losses as AEs, use the term marked on the Pregnancy Outcome case report form. These terms include:

- Spontaneous abortion (less than 20 weeks)
- Still birth or intrauterine fetal demise (20 weeks or more)
- Ectopic pregnancy

Do not report elective abortions as AEs.

Maternal complications associated with pregnancy loss should be captured as adverse events.

Figure 11-7
Reporting Bone Fractures as AEs

Report all bone fractures as AEs.

In the AE term, first specify the fracture as either “traumatic” or “pathological.” Ideally, traumatic or pathological should be the first word in the AE term. Compression fractures and other fragility fractures should be considered pathological.

In the AE term, further specify the type of fracture (e.g., stress, open, compression, fragility) and the anatomical location of the fracture.

In the comments section of the AE Log case report form, note whether the fracture diagnosis was confirmed by x-ray.

Figure 11-8
Reporting Hospitalization as AEs

Procedures should not be captured as adverse events; rather the underlying condition which leads to a procedure may be considered an adverse event. For example, while “appendectomy” would not be considered an adverse event, “appendicitis” would. Likewise, a “cesarean section” would not be considered an adverse event; however, the indication for the cesarean section may, depending on whether it reflects a maternal or fetal condition.

For example:

- Fetal conditions (i.e. breech, fetal distress, meconium staining, non reassuring fetal heart tones) which result in a cesarean section should not be captured as adverse events. Even though a cesarean section for a fetal condition may prolong the mother’s hospitalization, because the underlying problem is not maternal, it should not be captured as an adverse event.
- Maternal conditions (i.e. hemorrhage, preeclampsia, etc.) which result in a cesarean section should be captured as adverse events. 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.
- If the cesarean was performed for failure to progress in labor (no matter what the underlying cause- 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." This AE will be serious if the cesarean results in a prolonged hospitalization.
- A scheduled cesarean section performed because of a history of cesarean section, should not result in an adverse event as the indication for the cesarean section (uterine scar due to a previous cesarean section) would be a preexisting condition.

This guidance holds for both scheduled and unscheduled cesarean sections. Whether a cesarean section results in a reported adverse event or not completely depends on the indication.

Maternal complications following cesarean section (hemorrhage, infection, scar disruption, etc.) will be considered adverse events regardless of the indication for the surgery. If the complication results in a prolonged hospital stay, it will be considered serious.

11.3 Adverse Event Severity

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in MTN-003 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 11.1.3.

The severity of all AEs identified in MTN-003 will be graded using the:

- *DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table)*, dated December 2004 and
- *Female Genital Grading Table for Use in Microbicide Studies (FGGT)*, dated November 2007.

Under protocol Letter of Amendment #01, genital bleeding during pregnancy prior to the onset of labor (regardless of trimester) will be graded as follows:

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Spotting or bleeding less than menses	Bleeding like menses or heavier, no intervention indicated	Profuse bleeding with dizziness or orthostatic hypotension, transfusion indicated	Potentially life-threatening bleeding and/or shock

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.

Both the FGGT and the Toxicity Table can be accessed on the DAIDS RCC web site (<http://rcc.tech-res.com/safetyandpharmacovigilance/>). Copies also are provided at the end of this section.

Further clarifications, guidelines, and tips for grading the severity of AEs in MTN-003 are as follows:

- 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, assign the AE the highest severity grade among each of the associated signs and symptoms. If the AE is reportable, record the diagnosis as the AE term and record each associated sign and symptom in the AE Log 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).
- Participant weight will be monitored throughout follow-up and unintentional weight loss should be graded according to the “unintentional weight loss” row of the Toxicity Table. The grading guidance in this row of the Toxicity Table references loss of body weight as a percentage of the participant’s baseline weight. The participant’s weight at her Screening Part 2 visit should be considered her baseline weight. An example of calculating a percentage decrease in weight is as follows: if a participant weighs 50.0 kg at Screening Part 2, and then is found to weigh 45.0 kg at Month 3, the percent difference is $[(50-45) \div 50] = [5 \div 50] = .10 = 10\%$

Note: Unintentional weight loss is considered a clinical AE, and not a laboratory abnormality, even though participant weight measurements are recorded on lab-related case report forms.

- Proteinuria should be graded per the “proteinuria” row of the Toxicity Table. Glycosuria also should be graded per the “proteinuria” row of the Toxicity Table.
- Urinary tract infection (UTI), which is expected to be diagnosed on the basis of symptoms and positive findings for nitrites and leukocyte esterase on dipstick urinalysis, should be graded according to the “infection (other than HIV infection)” row of the Toxicity Table. The row for grading UTI on the FGGT requires urine culture results and, because cultures are not required in MTN-003, the FGGT should not be used to grade UTI. A suspected UTI in the absence of both a positive urine LE and nitrites on dipstick urinalysis may be treated (with antibiotics) as a UTI; however, the AE should not be reported using the term “Urinary Tract Infection”. Instead, each related symptom should be reported as its own AE on a separate AE Log form. A positive urine LE or positive nitrites result on dipstick urinalysis should not be reported as its own stand-alone AE as it is a laboratory result that is not gradeable per the DAIDS Toxicity Table..
- Abnormal Pap smear findings should be graded according to the “Pap” row of the FGGT only if further evaluation of the Pap smear finding is not performed; otherwise, and preferably, findings should be reported and graded based on the results of the biopsy, using the “intraepithelial neoplasia by biopsy” row of the FGGT.
- Bone fractures should be graded as follows:
 - Traumatic fractures should be graded according to the “estimating severity grade” row of the Toxicity Table.
 - Vertebral compression fractures and other fragility fractures should be graded according to the “bone mineral loss” row of the Toxicity Table and should fall into severity grade 3 or 4, which correspond to pathological fracture (including loss of vertebral height).

- Under protocol Version 1.0, for spontaneous abortions that occur during the first trimester of pregnancy, severity grading will depend on whether any genital bleeding was associated with the pregnancy loss. If any genital bleeding was associated with the pregnancy loss, the spontaneous abortion should be graded as either a Grade 3 or Grade 4 event according to the “first trimester bleeding” row of the FGGT. If no genital bleeding was associated with the pregnancy loss, the spontaneous abortion should be graded according to the “estimating severity grade” row of the Toxicity Table, based on any impacts the spontaneous abortion may have had on the functional status of the participant.
- Under protocol Version 1.0, for spontaneous abortions and other pregnancy losses that occur during the second or third trimester of pregnancy, severity grading will depend on whether any genital bleeding was associated with the pregnancy loss. If any genital bleeding was associated with the pregnancy loss, the spontaneous abortion should be graded according to the “second/third trimester bleeding” row of the FGGT. If no genital bleeding was associated with the pregnancy loss, the spontaneous abortion should be graded according to the “estimating severity grade” row of the Toxicity Table, based on any impacts the spontaneous abortion may have had on the functional status of the participant.

- When assigning severity grades to laboratory test results that require calculations based on the site normal reference range, the calculated severity grade range may have more significant digits than the reported test result. This can lead to uncertainty in determining what severity grade to assign to the test result. Do not round calculated grade ranges when determining the severity grade. Once the severity grade ranges are calculated, the lab value as recorded on the case report form should then be compared to the calculated grade ranges. If the lab value recorded on the case report form has fewer digits than the calculated grade range, then the missing digit(s) should be treated as zero(es), *regardless* of how the original lab result is reported by the site laboratory. Below is an example.

For creatinine, the grade 1 range per the Toxicity Table is 1.1-1.3 times the site's upper limit of normal (ULN) and the grade 2 range is 1.4-1.8 times the ULN. If the site's ULN is 1.5 mg/dL, the calculated grade 1 range is 1.65 – 1.95 mg/dL and the calculated grade 2 range is 2.1 – 2.7 mg/dL. Do not round the calculated grade ranges, as these are interim steps. Since the Safety Laboratory Results form captures serum creatinine results to the tenths digit, a test result of 1.64 mg/dL at this site is rounded to one decimal place and recorded on the form as 1.6 mg/dL. Since the value of 1.6 mg/dL has less significant digits than the calculated grade ranges, the missing digit can be treated as a zero for purposes of assigning a severity grade. In this case, 1.6 mg/dL is treated as 1.60 mg/dL, which is less than 1.65 mg/dL and thus should not be assigned a severity grade. Even though the original lab result was reported by the site laboratory as 1.64 mg/dL, for purposes of assigning severity grades, site staff should a) use the value recorded on the CRF, and b) fill in zeroes for the missing digits, as needed, so that the lab value has the same number of significant digits as the calculated grade ranges. This is the only way that SCHARP can check that the appropriate severity grade has been assigned to a given lab value, as SCHARP does not have access to the site's original laboratory result reports. Continuing with this same example, a test result of 1.95 mg/dL is rounded to one decimal place and recorded on the Safety Laboratory Results form as 2.0 mg/dL. Again, the value on the case report form should be used to assign a severity grade. In this case, 2.0 mg/dL is treated as 2.00 mg/dL, which is greater than the grade 1 range and less than the grade 2 range. It should be assigned severity grade 2, because a result that falls between two grade ranges should always be assigned the higher of the two grades.

Creatinine	Test result	Grade 1 range	Grade 2 range
		1.1-1.3xULN	1.4-1.8xULN
Site ULN- 1.5 mg/dL		1.65-1.95 mg/dL	2.1-2.7 mg/dL
Test result 1 without rounding	1.64		
Test result 1 with rounding	1.6 (1.60)	No grade assigned	
Test result 2 without rounding	1.95		
Test result 2 with rounding	2.0 (2.00)		Grade 2 AE

- 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 Toxicity Table. Assign the severity grade based on the Toxicity Table severity grade ranges, regardless of whether or not the lab result falls within the site's normal reference range.

- Phosphate test results should be graded according to the “Phosphate, serum, low” rows of the Toxicity Table. The grade 1 range for phosphate is 2.50 mg/dL to < LLN. If a site’s lower limit of normal (LLN) is less than or equal to 2.50 mg/dL, then the grade 1 range for that site is simply the value 2.50 mg/dL.
- Hemoglobin test results should be graded according to the “hemoglobin” rows of the Toxicity Table:
 - For HIV negative persons ages 57 days and older, the grading guidance references both absolute hemoglobin values and decreases in hemoglobin values over time. Decreases should be calculated from the participant’s baseline hemoglobin value only, not between sequential hemoglobin tests. Both the absolute values and decreases from baseline must be considered when grading results. If the severity of the absolute value differs from the severity of the decrease, the higher of the two grades should be assigned to the AE.
 - For participants who become HIV-infected during follow-up, the hemoglobin row for HIV positive persons ages 57 days and older should be applied beginning on the collection date of the blood sample that confirms the participant’s HIV infection. For most participants who become infected with HIV, this will be the collection date of “sample 2” in the follow-up HIV testing algorithm. For those participants whose HIV infection is not confirmed until testing of “sample 3,” the hemoglobin row for HIV positive persons ages 57 days and older should be applied beginning on the collection date of “sample 3.”
 - For HIV-uninfected participants, lymphocyte test results should be graded according to the “absolute lymphocyte counts” row for HIV negative persons greater than 13 years of age in the Toxicity Table. For participants who become HIV-infected, the severity of lymphocyte test results should not be graded.
 - For participants who become HIV-infected, the severity of CD4+ cell counts and HIV viral load test results should not be graded.

11.4 Adverse Event Relationship to Study Product Under Protocol Version 1.0

For each reportable AE identified in MTN-003, an authorized study clinician must assess the relationship of the AE to study product, based on the temporal relationship of the AE to administration of product, product pharmacology, information provided in the product Package Inserts and Investigators Brochure, and clinical judgment.

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

- Definitely related: The AE and administration of study product are related in time, and a direct association can be demonstrated.
- Probably related: The AE and administration of study product are reasonably related in time, and the AE is more likely explained by study product than other causes.
- Possibly related: The AE and administration of study product are reasonably related in time, and the AE can be explained equally well by causes other than study product.

- Probably not related: A potential relationship between the AE and study product could exist (i.e., the possibility cannot be excluded), but the AE is most likely explained by causes other than study product.
- Not related: The AE is clearly explained by another cause not related to study product.

When assessing relationship, the study products that should be considered are the four oral tablets, the two vaginal gels, and the applicator in which the gels are packaged. For participants assigned to gel, any AEs thought to be related to an applicator should be documented as such by choosing one of the “related” categories and using descriptive text, comments, or other notations to indicate that the presumed relationship is with the applicator.

In addition to the relationship categories listed above, DAIDS allows a relationship of “pending” to be temporarily assigned to EAEs that result in death, if additional time and information are needed to determine the relationship of the AE to study product. However, a final relationship assessment must be submitted to the DAIDS RCC within three business days after first reporting the death. If a final assessment is not made within three business days, the AE will be considered possibly related to study product.

11.4.1 Adverse Event Relationship to Study Product Under Letter of Amendment #02

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.

NOTE: When compared to the previous DAIDS relationship categories (definitely related, probably related, possibly related, probably not related, not related); ‘related’ will encompass the first four categories and ‘not related’ will include only what was previously recorded as ‘not related’. When reporting “not related” AEs, one of the following should be provided: an alternative etiology, diagnosis, or explanation for the AE.

When an SAE is assessed as “not related” to the study products, an alternative etiology, diagnosis or explanation should be provided. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required.

When assessing relationship, the study products that should be considered are the four oral tablets (tenofovir, Truvada, tenofovir placebo, and Truvada placebo), the two vaginal gels (tenofovir gel, and placebo gel), and the applicator in which the gels are packaged. For participants assigned to gel, any AEs thought to be related to an applicator should be documented as such by choosing “related” and using descriptive text, comments, or other notations to indicate that the presumed relationship is with the applicator.

11.5 Adverse Event Outcomes and Follow-Up Information

All AEs identified in MTN-003 — regardless of whether they are reportable per Section 11.1.2 — must be followed clinically until they resolve (return to baseline) or stabilize (persist at a certain severity grade (above baseline) for three consecutive monthly evaluations).

At each follow-up visit, an authorized study clinician should review all previously identified ongoing AEs and evaluate and document their current status. For reportable AEs, outcomes must also be reported on Adverse Experience Log case report forms. In many cases, the final outcome of a reportable AE will not be available when the Adverse Experience Log form is first completed and faxed to DataFax. In such cases, the form should be updated when the final outcome becomes available and re-faxed to DataFax at that time.

As noted above, “resolution” of an AE is generally defined as returning to the condition or severity grade that was present at baseline (i.e., at the time of randomization) and “stabilize” is defined as persistence at a certain severity grade (above baseline) for three consecutive monthly evaluations. For laboratory test results that are reported as AEs, clinical management and follow-up of the AE should proceed per the specifications of Section 9 of the MTN-003 protocol. If, however, a laboratory AE is not addressed in Section 9 of the protocol, at a minimum, follow-up testing should be performed at scheduled monthly study visits until resolution or stabilization has been documented. An example of this approach is provided in Figure 11-8. More frequent testing may be performed at any time if required to properly monitor and/or manage participant safety, at the discretion of the IoR or designee.

For AEs that are ongoing at the termination visit, the status/outcome of the AE should be updated to “continuing at end of study participation” and the AE Log form should be re-faxed to DataFax. For any SAEs/EAEs that are ongoing at the termination visit, the IoR or designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the AE must be re-assessed by study staff 30 days after the termination visit; additional evaluations also may take place at the discretion of the IoR or designee. The same approach must be taken for any AEs that are found to have increased in severity at the termination visit. The MTN-003 Protocol Safety Review Team (PSRT) also may advise on whether any additional follow-up is indicated on a case by case basis.

For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within 30-60 days after the study end date. The MTN-003 Protocol Safety Review Team (PSRT) also may advise on whether any additional follow-up is indicated on a case by case basis. For AEs that are re-assessed after the termination visit, information on the status of the AE at the time of re-assessment will be recorded in source documents, and may be communicated to the PSRT, if applicable; however, no updates should be made to any case report forms based on the re-assessments.

If a reportable AE increases in severity or frequency (worsens) after it has been reported on an Adverse Experience Log case report form, it must be reported as a new AE, at the increased severity or frequency, on a new Adverse Experience Log case report form. In this case, the outcome of the first AE will be documented as “severity/frequency increased.” 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 or frequency increased. Under Protocol Version 1.0, if an EAE increases in severity to a higher grade than previously reported, it must be reported to the DAIDS RCC as a new EAE report until sites obtain approval to implement Letter of Amendment #02.

Changes Under Letter of Amendment #2: If an EAE/SAE increases in severity to a higher grade than previously reported, the existing EAE form must be updated using DAERS. Please note that a new EAE form does not need to be submitted for any change in the assessment of the severity grade or the relationship between the AE and the study product. However, the increase in severity must be reported as a new AE to the SDMC (as described in the previous paragraph).

Figure 11-9
Example of Follow-up of a Laboratory Test Result AE

Consider an HIV-uninfected participant with a baseline hemoglobin level of 11.4 g/dL, which is not gradable per the DAIDS Toxicity Table. At her Month 6 visit, this participant's hemoglobin level has decreased to 10.8 g/dL, which is a grade 1 abnormal result per the Toxicity Table. Grade 1 decreased hemoglobin should be source documented and reported as an AE when the hemoglobin test result is received. Although the MTN-003 protocol does not require hematology testing again until the Month 12 visit, the IoR or designee must ensure that additional testing is performed to follow-up this AE to resolution or stabilization. As such, hemoglobin testing should be repeated at the participant's Month 7 visit (or sooner, if clinically indicated per the clinical judgment of the IoR or designee).

- If the participant's hemoglobin level has returned to baseline (i.e., not gradable per the Toxicity Table) at Month 7, the AE is considered resolved at that time, and no further testing is required.
- If the participant's hemoglobin level has not returned to baseline at Month 7, the AE is considered continuing, and additional testing will be required. Repeat the test again at the Month 8 visit (or sooner if clinically indicated).
- If the participant's hemoglobin level has returned to baseline at Month 8, the AE is considered resolved at that time, and no further testing is required.
- If the participant's hemoglobin level has not returned to baseline at Month 8, additional testing will be required. Repeat the test again at the Month 9 visit.
- If the participant's hemoglobin level has returned to baseline at Month 9, the AE is considered resolved at that time, and no further testing is required.
- If the participant's hemoglobin level has not returned to baseline at Month 9, the AE is considered ongoing but stabilized at the grade 1 level, and no further testing is required until the next testing time point specified in the study protocol, which is at Month 12.

Note that this example assumes that the participant's decreased hemoglobin level either resolved or persisted at the grade 1 level between Months 6 and 9. If her hemoglobin level had worsened over this time (i.e., had increased in severity), additional safety monitoring and AE reporting would be required.

Study staff are not required to report the outcome of EAEs to the DAIDS RCC, unless outcome information is specifically requested. However, EAE follow-up information should be reported to the DAIDS RCC, 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”)
- Results of re-challenge with the study product, if performed

Under Letter of Amendment #02: Any change in the assessment of the severity grade of the AE will also require an update to the existing EAE report.

The last circumstance listed above relates to re-challenge with study product. In MTN-003, 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 cases such as this, site staff should provide follow-up information to the RCC 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.

11.6 Reporting Recurrent Adverse Events

If a reportable AE that was previously reported on an Adverse Experience Log case report form resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new Adverse Experience Log case report form.

An important clarification of this guidance for MTN-003 relates to genital herpes and genital warts. Genital herpes and genital warts are associated with chronic viral infections — HSV-2 and HPV — and periodic symptomatic outbreaks — genital ulcers and genital warts.

- If infection with HSV-2 or HPV is known to have occurred before randomization, the infection is considered a pre-existing condition: report the infection as ongoing on the Pre-existing Conditions form.
- For HPV, genital warts present before randomization are considered a pre-existing condition: report the infection as ongoing on the Pre-existing Conditions form.
- Any outbreaks that occur after randomization are considered AEs, regardless of whether the viral infection was known to be pre-existing before randomization: report the outbreak on an Adverse Experience Log form as described in Figure 11-5.

If an EAE that was previously reported to the DAIDS RCC resolves and then later recurs at a level requiring expedited reporting, the second occurrence must be reported as a new EAE report.

11.7 Social Harms

In addition to medical AEs, participants in MTN-003 may experience social harms — non-medical adverse consequences — as a result of their participation in the study. 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.

The MTN-003 Oral and Vaginal Product Adherence and Behavior Assessment forms actively ascertain, on a quarterly basis, whether participants have had “any problems with the following people [list] as a result of being in the study.” In addition to responding to this standardized question each quarter, participants also may spontaneously report study-related issues and problems to study staff at any study visit. Participants will also be asked similar questions during administration of the Study Exit Behavior Assessment form.

Prior to study initiation, study staff teams at each site 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 if reported. 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.
- 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 11.1) report the AE on an Adverse Experience Log form. If the social harm is associated with an AE that meets criteria for expedited reporting to the DAIDS RCC, report it as an EAE as described in Section 11.1.3. Also report the issue or problem to all IRBs/ECs responsible for oversight of MTN-003, if required per IRB/EC guidelines.
- Consult the MTN-003 PSRT for further input and guidance as needed.

As is the case for medical AEs, data collected on social harms will be monitored by the MTN-003 PSRT and the NIAID Vaccine and Prevention Data and Safety Monitoring Board (DSMB), as described below.

11.8 MTN-003 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-003 protocol and Section 14 of the MTN Manual of Operations for a complete description of the participant safety monitoring procedures in place for MTN-003. Also refer to Section 17 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN-003 safety monitoring procedures.

Participant safety is of paramount importance in MTN-003. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study staff, under the direction of the IoR. The IoR and designated study staff also are responsible for submitting case report forms to the MTN SDMC and EAE reports to the DAIDS RCC, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- Clinical Affairs 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 issued to site staff for resolution 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. In these cases, the Protocol Safety Physicians will document the contact (including the date of the contact, the persons involved, the reason for the contact, and the outcome of the contact).
- The DAIDS RCC, DAIDS RAB Safety Specialist, and DAIDS PSB Medical Officers will review all EAE Forms received for MTN-003 and follow up on these reports with site staff, the MTN-003 Protocol Team, and drug regulatory authorities when indicated.
- The MTN-003 PSRT will routinely review safety data reports prepared for MTN-003 by the MTN SDMC. As described further in Section Appendix 11-1, the PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns. To preserve blinding, data reviewed by the PSRT will be pooled across study groups.

- The NIAID Vaccine and Prevention DSMB will routinely review safety data reports prepared by the MTN SDMC. It is expected that the DSMB will review the MTN-003 data approximately every six months. Data reports prepared for the DSMB will present safety data in a coded manner by study group with codes provided separately to allow DSMB members to unblind themselves when reviewing the data. A brief summary report from each DSMB review will be distributed to the MTN-003 Protocol Team shortly after the review takes place. IoRs must forward copies of these reports to all IRBs/ECs responsible for oversight of research at their site.

Prior to reviews by the DSMB, and independently, the MTN Study Monitoring Committee (SMC) also will periodically review MTN-003 study data with a focus on performance indicators such as participant accrual and retention, protocol adherence, intervention adherence, and data quality. While site staff are not typically involved in these reviews, site staff should be aware that both the SMC and the DSMB 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.

11.9 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 RCC and/or the MTN Coordinating and Operations Center, and may include:

- Updated Package Inserts
- Updated Investigators Brochures
- IND Safety Reports
- DSMB review summaries
- 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.

Section Appendix 11-1
MTN-003 Protocol Safety Review Team Plan

Roles and Responsibilities of the PSRT

Per the MTN-003 protocol, the roles and responsibilities of the MTN-003 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 safety concerns be identified by the PSRT, these will be referred to the Protocol Team, MTN Study Monitoring Committee (SMC) and/or DAIDS Vaccine and Prevention Data and Safety Monitoring Board (DSMB), 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.
5. Respond to requests for participant unblinding. There are no circumstances under which it is expected that unblinding will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants. However, if an investigator feels that specific product knowledge is necessary to protect participant safety, the investigator may notify the PSRT to consider and rule upon the request.

PSRT Composition

The following individuals comprise the MTN-003 PSRT:

- Katie Bunge, Protocol Safety Physician
- Z Mike Chirenje, Protocol Chair
- Ross Cranston, Protocol Safety Physician
- Jeanne Marrazzo, Protocol Chair
- Benoît Mâsse, Protocol Statistician
- Patrick Ndase, Regional Physician
- Jeanna Piper, DAIDS Medical Officer
- Sharon Riddler, Protocol Physician
- Barbra Richardson, Protocol Statistician
- Molly Swenson, MTN SDMC Clinical Affairs Safety Associate

Ideally all PSRT members will take part in routine PSRT conference calls. At a minimum, a Protocol Chair, the DAIDS Medical Officer (or designee, if the DAIDS Medical Officer is not available), and a Protocol 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 CORE Clinical Research Managers, SDMC Project Managers, and SDMC Statistical Research Associates may attend PSRT calls as observers and/or discussants.

Routine Safety Data Summary Reports: Content, Format and Frequency

The SDMC will generate standard safety data reports to the PSRT one week prior to each PSRT conference call. Tabulations will be generated for all study participants combined (i.e., across all study groups) and will include:

- Listings of new AEs by body system (using MedDRA terms), severity, and relationship to study product
- A cumulative listing of all SAEs/EAEs reported to date
- A cumulative listing of all AEs reported to date as probably or definitely related to study product by body system and severity
- Under Letter of Amendment #02, a cumulative listing of all AEs reported to date as related to study product by body system and severity
- A cumulative listing of all grade 2, grade 3, grade 4, and grade 5 AEs reported to date by body system and relationship to study product
- Tabulations of pregnancies and pregnancy outcomes
- A cumulative listing of reported social harms
- Tabulations of product holds/discontinuations and resumptions

During PSRT conference calls, the DAIDS Medical Officer will summarize any additional EAE reports received at the DAIDS RCC after the cut-off date for the SDMC data summary.

PSRT Communications

A group email address (mtn003psrt@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-003 PSRT Query Form, which is available in the Study Implementation Materials section of the MTN-003 web page. Site staff will email completed query forms to the Protocol Safety Physicians (mtn003safetymd@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. 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).

An emergency safety telephone number (+001-412-641-8947) is also available to site staff. This telephone number is a US number (toll call from outside the US) and is manned by the Protocol Safety Physicians 24 hours a day, seven days a week. It is intended for use in emergency situations only, in which immediate consultation with a Protocol Safety Physician is needed. Questions that can wait for email communication should be handled using the PSRT query process described above.

To document calls made to the emergency safety telephone number, near the time of the call (either before or after) site staff will complete the site section of the MTN-003 Emergency Phone Contact form (available in the Study Implementation Materials section of the MTN-003 web page) and email the form to the Protocol Safety Physicians. Within 24 hours after

the call, the responding Protocol Safety Physician will complete the remainder of the form and email the completed version to site staff, copied to the study management team.