

Section 9. Adverse Event Reporting and Safety Monitoring

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This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-017.

9.1 Definitions

9.1.1 Adverse Event (AE)

An AE is defined 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.’

This definition is applied to each participant, regardless of assigned study sequence, beginning from the time the participant is enrolled/randomized through study termination (7 days post Period 3 End Visit).

Note: For participants in the rectal biopsy/fluid subset with a delayed product initiation, AEs that meet reporting criteria (per protocol section 8.4.2) and occur during the 3 days between enrollment/randomization and expected product start will still be reported on an AE Log CRF, and marked “not related” to study product.

9.1.2 Reporting AEs

Per protocol section 8.4.2, study staff must document on an **Adverse Experience (AE) Log case report form (CRF)** all AEs reported by or observed in each participant, regardless of severity and presumed relationship to study product. The AE reporting period begins once a participant is randomized, and ends at the termination date (expected 7 days after the Final Clinic Visit 10/End Period 3 Visit). All AEs with an onset date during the AE reporting period must be documented on an AE Log CRF.

The AE Log CRF will be used to document, and may serve as source documentation, for the following AE information:

- Date reported to site
- AE term/diagnosis
- Onset date
- Severity grade
- Relationship to study product (related or not related)
- Study product administration as related to the AE
- Outcome status and date (or ongoing at time of termination)
- AE treatment
- Whether the AE is serious per ICH guidance (see Section 11.1.2)
- Whether the AE meets expedited AE reporting requirements (see Section 11.1.2)
- Whether the AE is a worsening of a pre-existing condition
- Additional comments/details related to the AE

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

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.
- 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, an authorized study clinician must determine whether the AE meets the ICH definition of “serious”.

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 9.4 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 and CONRAD (see section 9.2). In some cases, DAIDS may be required to report an EAE to the US Food and Drug Administration (FDA).

9.2.1 Reporting SAEs/EAEs

SAEs/EAEs should be reported per the [Manual for Expedited Reporting of Adverse Events to DAIDS, version 2.0; January 2010](#).

The “SAE (Serious Adverse Event) Reporting Category” will be used to report EAEs.

Adverse events that require expedited reporting should be submitted through the DAIDS Adverse Experience Reporting System (DAERS). DAERS is an internet-based system for a clinical research site to report Expedited Adverse Events (EAEs) in an expedited time frame to DAIDS/RSC. If DAERS cannot be accessed for any reason at the time an AE must be reported (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. This form and form completion instructions are available on the DAIDS Safety Office website at <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* (<http://rsc.tech-res.com/safetyandpharmacovigilance/manualforexpeditedreporting.aspx>).

When completing Adverse Experience Log (AE-1) CRFs and EAE reports, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness, and consistency.

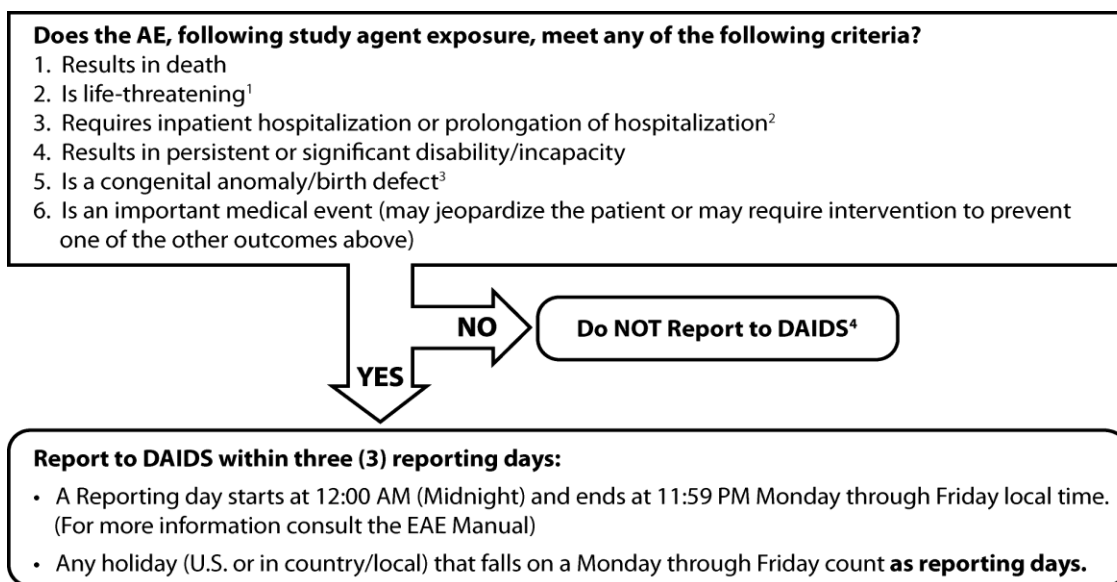
- All AE descriptions and details (e.g., onset date, severity grade, relationship to study product) must be recorded consistently across all documents.
- All EAE reports received at the DAIDS RSC will be compared with Adverse Experience Log CRFs received at the MTN Statistical and Data Management Center (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).

All EAEs must be reported within three reporting days of site awareness of the EAE. Figure 11-3 details EAE reporting requirements. The definition of a “reporting day” is that which counts toward 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.

If an EAE report is not completed and submitted within three reporting days of site awareness of the EAE, an explanation must be entered in DAERS before the report can be submitted.



Contact Information for the DAIDS Safety Office:

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¹ “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.

9.2.2 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 documenting the AE, 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 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 previously).

The last circumstance listed above relates to re-challenge with study product. In MTN-017, 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 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.

9.3 Adverse Event Terminology

When reporting an AE, study staff must assign a term or description for the event. The guidance below should be followed when assigning AE terms or descriptions (item 1 on the AE Log CRF):

- Whenever possible, use a diagnosis as the AE term to describe a cluster of signs and/or symptoms.
- For example, symptoms such as anal discomfort, inflammation, and bleeding during bowel movements should be reported under the diagnosis “hemorrhoids”, if applicable.
- Document associated signs and/or symptoms related to a diagnosis in the comments section of the AE Log 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.
- For example, symptoms such as anal itching and pain should each be reported as a separate AE (e.g., “anal pruritis” and “anal pain”).
- Include anatomical location when applicable, and use a specific location term (e.g., “rectal ulcer”, “anal fissure”)
- Use medical terms and correct spelling of such terms
- Do not use abbreviations
- Do not include information on severity grade, relatedness to study product or timing of study product use in the AE term/description. This information is captured in items

2, 3 and 4 of the AE Log CRF, and including text such as “following gel insertion” affects the way the AE is coded at SCHARP and how it will appear in safety reports. Limit the AE text to the medical description and anatomical location, when needed.

- Do specify in the AE term/description if the AE is related to a procedure (iatrogenic); for example, “rectal bleeding due to rectal biopsy” or “anal fissure due to applicator trauma”. This information must be documented in item 1 on the AE Log CRF (and not in the comments section) in order for the AE to be properly coded and appear correctly in the safety reports.
- If an STI result warrants AE reporting, document the STI diagnosis, and not the test result, in the AE term/description. For example, report an AE of chlamydia as “rectal chlamydia”, and not “positive NAAT/chlamydia result”.
- The presence of study gel leakage by itself is not an AE and should not be reported on an AE Log CRF. However, any untoward effect the gel or gel leakage has on a participant – for example, “perianal irritation” or “anorectal discomfort” - should be reported as an AE on an AE Log CRF. “Genital ulcer disease” is not a codable event. Rather, an STI diagnosis should be reported in the AE term/description. If there is no STI diagnosis, the AE should be reported as “ulcers” with the anatomical location (e.g., “anal” or “rectal”) specified.
- The Rectal Grading Table requires biopsy confirmation in order to report an AE under the diagnosis of “proctitis”. If a biopsy is not done or is pending, report each associated symptom (e.g., abdominal pain, hematochezia) as a separate AE on its own AE Log CRF.

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

- If the severity of an AE falls into more than one grading category on the Rectal Grading Table 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 *Rectal Grading Table* or Toxicity Table, 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 in the AE Log 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).

Source documentation requirements for all AEs are listed in Section 9.1.2. Sites should check local IRB and drug regulatory bodies' requirements regarding the reporting of adverse events 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 CRF. 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.

9.4 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., “elevated ALT”). The severity grade of the result should not be reported as part of the AE term/description.

Laboratory values that fall outside of a site's normal range but are below severity grade 1 are not considered AEs. These ranges which are outside of the normal range but below Grade 1 values are not documented as pre-existing conditions unless requested by the Investigator of Record (IoR) or designee. These ranges which are outside of the normal range but below Grade 1 values

are not documented as adverse events. These laboratory results can be identified as “NCS” (Not Clinically Significant) in the source documentation, if determined by a study clinician.

When assigning severity grades, note that some sites may have normal reference ranges that overlap with the DAIDS Toxicity Table 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.

9.5 AEs Involving Hospitalizations/Surgical Procedures

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.

Also, planned procedures or surgeries are not AEs. Rather, the underlying diagnosis or condition that warrants the procedure or surgery may be a reportable AE. For example, a “tonsillectomy” is not an AE and should not be reported as an AE. Rather, the underlying condition of “tonsillitis” is the reportable AE.

Any adverse experiences resulting from a planned procedure or surgery are AEs and should be reported on an AE Log form. The AE term/description should specify the procedure as the cause of the AE. For example, a throat infection that resulted from the tonsillectomy should be reported as an AE of “throat infection due to tonsillectomy”.

9.6 Adverse Event Severity Grading

The severity of all AEs identified in MTN-017 will be graded per the following:

- [Division of AIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 \(Clarification dated August 2009\)](#)
- [Rectal Grading Table for Use in Microbicide Studies, Addendum 3 in the Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 \(Clarification dated May 2012\)](#)

All available tables are on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx/>.

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in MTN-017 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.

AEs listed in both the *Rectal Grading Table* and the Toxicity Table should be graded according to the *Rectal Grading Table*. AEs not listed in the *Rectal Grading Table* should be graded according to the Toxicity Table. AEs not listed in the *Rectal Grading Table* or the Toxicity Table should be graded according to the “estimating severity grade” row of the Toxicity Table:

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

Reminder: Medical conditions, problems, signs, symptoms, and findings identified prior to random assignment are documented on the **Pre-Existing Conditions CRF**. If a condition is ongoing at the time of randomization, it is a pre-existing condition. If this 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.

9.7 Adverse Event Relationship to Study Product

When assessing an AE's relationship to study product (AE Log CRF item 4), the site clinician should only consider the most recent study product regimen (daily oral, daily rectal, or RAI rectal) the participant used prior to the AE onset date. If an AE onset date falls during a washout period, the site clinician should assess the AE's relationship to the study product used during the last completed period in which the participant received 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.

Note: When an AE is assessed as "not related", an alternative etiology, or explanation should be provided in the 'Comments' section of the CRF. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required.

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

All AEs identified in MTN-017 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 (all AE Log CRF with an "ongoing" status and evaluate and document their current status.)
- For all AEs, outcomes must be reported on Adverse Experience Log (AE-1) CRF.
- In many cases, the final outcome of a reportable AE will not be available when the AE Log CRF is first completed. In such cases, the AE Log CRF should be updated when the final outcome becomes available. All updated AE Log CRFs must be re-faxed to DataFax at that time.

Per protocol section 7.2.1, all AEs grade 2 or higher judged to be related to study product are required to have resolved and/or stabilized prior to a participant initiating Period 2 (Visit 5) and Period 3 (Visit 8). In the event an adverse event has not resolved within 7 days following the

Period 1 End (Visit 4) or the Period 2 End (Visit 7), the PSRT should be consulted regarding progression into the next dosing period.

Clinical management and follow-up of AEs detailed in Section 9 of the MTN-017 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 scheduled study visits (at a minimum) until resolution or stabilization has been documented. More frequent evaluations 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 or frequency (worsens) after it has been reported on an AE Log CRF, it must be reported as a new AE on a new Adverse Experience Log (AE-1) CRF at the increased severity or frequency. In this case, the outcome of the first AE will be documented as "severity/frequency increased" on the applicable AE Log CRF. The outcome date of the first AE and the onset date of the new (worsened) AE on the AE Log CRF will be the date upon which the severity or frequency increased (see instructions on the back of the AE Log CRF for additional instructions).

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

A subset of AEs must be followed after a participant's termination visit. AEs that require reassessment after the participant's termination visit include the following:

- All Grade 2 or higher AEs that are ongoing at the termination visit
- All AEs deemed related to study product

For AEs that are continuing at the termination visit but do not meet the criteria above, it is left to the discretion of the IoR or designee as to whether the AE needs to be followed. The PSRT can be consulted as needed.

At a minimum, an AE that requires reassessment after the termination visit 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. If the AE has not resolved or stabilized at the time of reassessment, 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 entire study has ended (not only participant participation), all AEs requiring re-assessment will 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-017 PSRT 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 chart notes and communicated to the PSRT. No updates should be made to any AE Log CRFs on which the AEs were reported; rather, the AE Log CRFs should reflect the status of the AEs at the time of termination.

9.10 Reporting Recurrent Adverse Events

If a reportable AE that was previously reported on an AE-1 CRF resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new AE Log CRF as applicable.

9.11 Social Harms

In addition to medical AEs, participants may experience social harms. Social harms are non-medical adverse consequences that occur as a result of an individual's 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.

Site staff will routinely ask participants about social harms at each regularly scheduled visit, and will be prompted to do so via the visit checklist. If a social harm is reported, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section. Each social harm is reported on a separate Social Impact Log CRF which is faxed to SCHARP.

Site staff must follow up on all social harms until their resolution or the end of the study. Any ongoing or unresolved social harm requires consultation with the PSRT.

Prior to study initiation, study staff should discuss as a group, and with community representatives, what social harms are most likely to be encountered by participants 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, study staff 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.

9.11.1 Addressing Reports of Social Harm

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 participants' description of the problem and ask questions to elicit as much detail as possible about the problem, including the participants' perception of the severity of the problem. Record all pertinent details in signed and dated chart notes.
- Ask the participant for his/her thoughts on what can/should be done to address the problem, including what s/he 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 him/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 9.1) report the AE on 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 EAE as described in Section 9.2.
- Social harms determined to be serious or unexpected should be reported to the PSRT. Report the issue or problem to all IRBs/ECs responsible per IRB/EC guidelines.
- Consult the MTN-017 PSRT for further input and guidance as needed.

9.12 MTN-017 Safety Monitoring, Review, and Oversight

Primary safety monitoring and safeguarding of study participants is of utmost importance and is the responsibility of study staff, under the direction of the IoR. The IoR and designated study staff are responsible for submitting case report forms to the MTN SDMC and EAE reports to DAIDS, to ensure relevant safety data are available in a timely manner.

Safety monitoring procedures for MTN-017 are as follows:

- Clinical Affairs Safety Associates 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.
- The DAIDS RSC, DAIDS RAB Safety Specialist, and DAIDS PSB Medical Officer and CONRAD representative will review all EAE Forms received and follow up on these reports with site staff, the MTN-017 Protocol Team, and drug regulatory authorities when indicated.
- The PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns including any adverse social impacts involving physical or other harm to the participant and/or the participant's child(ren). The safety data reports will be prepared by the MTN SDMC.
- Protocol Safety Physicians will routinely review safety data reports prepared by the MTN SDMC and may contact site staff directly, if needed, for additional clarification of safety data.
- The MTN Study Monitoring Committee (SMC) will periodically review study data with a focus on performance indicators such as participant accrual and retention, protocol adherence, intervention adherence, and data quality.

Please refer to Section 8 of the MTN-017 protocol and Section 15 of the MTN Manual of Operations for further information on participant safety monitoring procedures.

9.13 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 and/or the MTN Leadership and Operations Center (LOC), and may include:

- Updated Investigators Brochures or 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.

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.

9.14 Appendices

Section Appendix 9-1: Resources for Safety and AE Reporting to DAIDS for the clinical research sites

- [Protocol, Version 1.0 dated 17 July 2012](#) (and any subsequent protocol Clarification Memos, Letters of Amendment, and Amendments issued after Version 1.0)
- [Division of AIDS \(DAIDS\) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1, December 2004, Clarification August 2009](#)
- [Addendum 3: Rectal Grading Table for Use in Microbicide Studies \(Clarification dated May 2012\)](#)
- [Manual for Expedited Reporting of Adverse Events to DAIDS \(Version 2.0 \(DAIDS EAE Manual\), dated January 2010\)](#)
- [DAERS Reference Guide for Site Reporters and Study Physicians](#)
- [DAIDS Identification and Classification of Critical Events: Site Responsibilities Policy](#)
- [DAIDS Critical Events Manual, Version 1.0 dated May 2012](#)
- [Investigator's Brochure for Tenofovir Gel](#) (current version and any subsequent updates)
- [Package Insert for Truvada](#) (current version and any subsequent updates)

Section Appendix 9-2: Roles and Responsibilities of the PSRT

PSRT Roles and Responsibilities

The roles and responsibilities of the MTN-017 Protocol Safety Review Team (PSRT) are listed below.

- 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 or SMC as appropriate.
- Respond to notifications, requests and/or queries regarding:
 - participant unblinding
 - *Note: 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.*
 - product use management
 - *Note: The protocol specifies a number of situations in which study product use should be temporarily held, permanently discontinued and/or resumed. Site staff will implement these holds, discontinuations, and/or resumptions in the absence of required consultation with the PSRT. In other situations, however, product use must be managed in accordance with PSRT consultation.*
 - adverse event (AE) assessment, reporting, and management
 - participant withdrawal from the study
 - participant study eligibility

PSRT Composition

The following individuals comprise the MTN-017 PSRT:

- Ross Cranston, Protocol Chair and Pittsburgh IoR
- Javier Lama, Protocol Co-Chair
- Jill Schwartz, CONRAD Representative
- Ken Ho, MTN Safety Physician
- Devika Singh, MTN Safety Physician
- Jeanna Piper, DAIDS Medical Officer
- Yevgeny Grigoriev, MTN SDMC Clinical Affairs Safety Associate

The PSRT will also be comprised of the study investigators or other site staff as designated. Representatives from the MTN Leadership and Operations Center (LOC) -FHI 360], the SDMC [SCHARP] and MTN LC may participate in PSRT reviews, discussions and other communications. The Protocol Safety Physician will serve as the chair of the PSRT. Ideally, all PSRT members will take part in routine PSRT conference calls.

Quorum: At a minimum, a Protocol Chair, the DAIDS Medical Officer (or designee, if the DAIDS Medical Officer is not available), and a MTN 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 an immediate call.

PSRT Communications

A group email address will be used to facilitate communication with the PSRT.

Site consultation with the PSRT will be facilitated using the MTN-017 PSRT Query Form, which is available in the [Study Implementation Materials](#) section of the MTN-017 web page.

Site staff are requested to email completed query forms to the Protocol Safety Physicians (mtn017safetymd@mtncstopshiv.org) for review. The Protocol Safety Physician will include a draft response to the query and distribute the draft response to the PSRT for review and agreement. All members of the PSRT are encouraged to review the information provided by the site in the query form upon receipt of the completed form from the Protocol Safety Physician. All members are asked to contribute to the consensus response drafted. Recommendations on the consensus response from all members of the PSRT will be taken into consideration prior to finalization of the response. However, the final determination of the consensus response rests with the Protocol Safety Physician, the Protocol Chair(s) and the DAIDS Medical Officer.

Once a final consensus response is reached and incorporated into the query form, the Protocol Safety Physician will notify the site and email the final query form back to the site for review and implementation. The final query form must be filed in the participant's binder.

This process is expected to occur within three (3) business days. When necessary, site requests which require an immediate response can usually be accommodated for within one (1) business day. An emergency safety telephone number (+001-412-641-8947) is also available to site staff. This telephone uses a US number (toll call from outside the US) and is carried by the Protocol Safety Physician 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. If the Safety Physician does not answer, a voicemail should be left with the call back number. Questions that can wait for email communication should be handled using the PSRT query process described above.