

Section 11. Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-013/IPM 026. Please also refer to Section 8 of the protocol and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table), dated December 2004 (Clarification August 2009)
- Addendum 1-DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT), dated November 2007
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2 (DAIDS EAE Manual), dated January 2010
- DAERS Reference Guide for Site Reporters and Study Physicians
- Investigator's Brochure for Dapivirine/Maraviroc Vaginal Ring, Version 2.0 dated 14 July 2011

11.1 Definitions and General Reporting Guidance

11.1.1 Adverse Event (AE)

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice 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-013/IPM 026, the same definition is applied to all participants in all four study groups, beginning at the time of random assignment. Study staff must document in source documents and case report forms all AEs reported by or observed in study 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)
- Action taken with study product

Ongoing 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 Section 10 of this manual, and reported on the Pre-Existing Conditions case report form. Pre-existing conditions must be graded and are assigned severity grades just as AEs. If a pre-existing condition worsens (increases in severity or frequency) after randomization, the worsened condition is considered an AE and is reportable on the AE Log form. If a pre-existing condition resolves after randomization, but then recurs at a later date, the recurrence is considered an AE. Procedures per se should not be reported as adverse events; rather the underlying condition which leads to a procedure may be considered an adverse event. Any associated procedures may be considered treatments for the adverse event. For example, while “appendectomy” would not be considered an adverse event, “appendicitis” would, with “appendectomy” documented as a treatment provided for the adverse event. In addition, any event that occurs as a result of a study-related procedure should be recorded as an AE. For example, if a participant experiences vaginal pain as a result of the pelvic exam, the vaginal pain should be submitted as an AE.

11.1.2 Reporting Adverse Events

Per Section 8.3 of the MTN-013/IPM 026 protocol, study staff will report on case report forms (AE log form), all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. Due to some of the clinical procedures, study participants may experience some expected AEs. These may include bruising from a blood draw or small amount of vaginal bleeding from pelvic examination, for example. Expected AEs should also be captured on the AE Log form.

AE severity will be graded per the *DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dates August 2009)* and the *Female Genital Grading Table for Use in Microbicide Studies (FGGT- Addendum 1 to the above mentioned table)*. The FGGT should serve as the primary source for grading AEs. If the affected body system is not listed in the FGGT, the Toxicity Table should be used.

The Adverse Experience Log form is used to report AEs to the MTN SDMC. All sites are strongly encouraged to use an AE tracking tool to ensure that all AEs are source documented.

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

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

If, at any time, site staff has questions about participant safety or reporting clinical events, they should send an email to the MTN-013/IPM 026 Safety Physicians at mtn013safetymd@mtnstopshiv.org

11.1.3 Serious Adverse Events (SAEs)

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

1. Results in death,
2. Is life-threatening,
3. Requires inpatient hospitalization or prolongation of existing hospitalization,
4. Results in persistent or significant disability/incapacity,
5. Is a congenital anomaly/birth defect,
6. Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition 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 and 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 also be considered serious. SAEs are a subset of all AEs. For each AE identified, an authorized study clinician must determine whether the AE meets the definition of SAE. The AE Log case report form includes an item to record this information.

11.1.4 Reporting Adverse Events in an Expedited Manner (EAE Reporting)

Expedited Adverse Events (EAEs) are AEs that meet criteria specified in the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0 dated January 2010) as requiring additional reporting for rapid review and assessment by DAIDS and IPM. In some cases, IPM may be required to report an EAE to the US Food and Drug Administration (FDA).

All EAEs must be reported to the DAIDS Regulatory Support Center (RSC) using the internet-based DAIDS Adverse Experience Reporting System (DAERS). All EAEs must be reported within three reporting days of site awareness of the EAE. The definition of a “reporting day” is those that count towards the 3-day timeline provided for reporting of EAEs to DAIDS. The criteria are as follows:

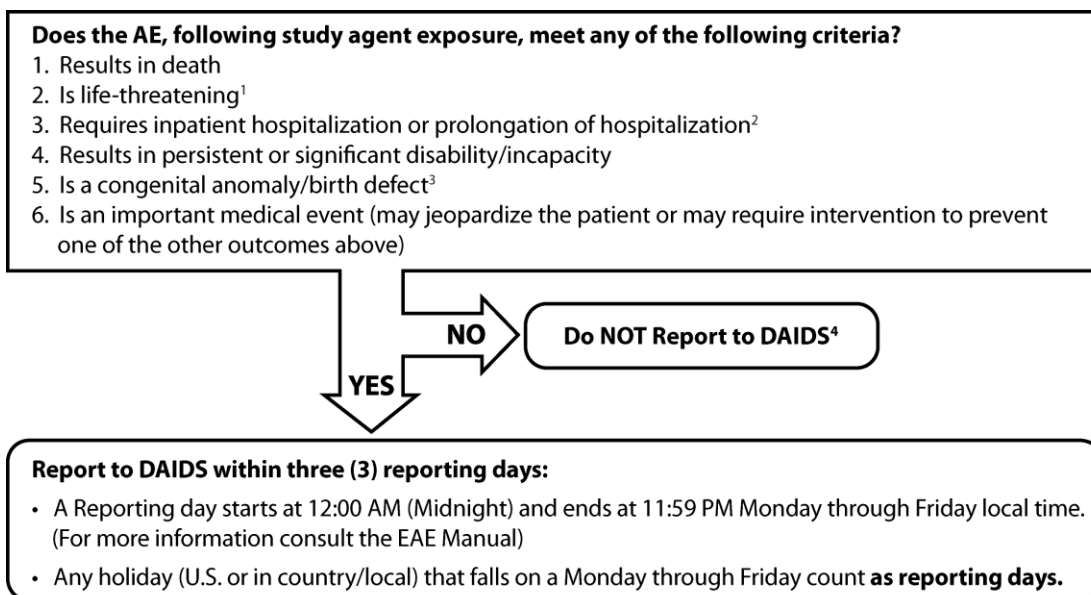
- Monday through Friday count as reporting days.
- Saturday and Sunday are not considered reporting days.
- Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday counts as a reporting day.
- A reporting day starts at 12:00 AM (midnight) and ends at 11:59 PM local time (in the 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.

For questions or other communications regarding submission of EAE Reports, see below.

| | |
|---------------|--|
| Website: | http://rsc.tech-res.com |
| Office Phone: | 301-897-1709 or toll free in the US: 800-537-9979 |
| Office Fax: | 301-897-1710 or toll free in the US: 800-275-7619 |
| Office Email: | DAIDSRSCSafetyOffice@tech-res.com |
| Office Hours: | Monday through Friday, 8:30 AM to 5:00 PM ET |

All EAEs must also be reported on the AE Log form. The AE Log case report form includes an item to record if the AE is also being reported as an EAE. When completing AE Log form and DAERS report or EAE form, 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 EAEs submitted to the DAIDS Safety Office will be compared with AE Log forms received at the MTN SDMC to ensure that all reports that should have been received by both DAIDS Safety Office and the SDMC have been received and that the details recorded on each form are consistent.

Figure 11-1
Expedited Adverse Event Reporting Requirements for MTN-013/IPM 026



Contact Information for the DAIDS Safety Office:

Website: <http://rcc.tech-res.com> • **E-mail:** RCCSafetyOffice@tech-res.com
Office Phone: 1-800-537-9979 (U.S. only) or +1-301-897-1709 • **Fax:** 1-800-275-7619 (U.S. only) or +1-301-897-1710
(Office Phone and Fax are accessible 24 hours per day)
Mailing Address: DAIDS Safety Office 6500 Rock Spring Drive, Suite 650, Bethesda, MD 20817

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.

11.2 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in MTN-013/IPM 026. 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 specific value or 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:

1. Use a diagnosis whenever possible.
2. Use specific medical terms whenever possible
3. Use correct spelling for all terms; and,
4. 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.

11.3 Adverse Event Severity

The term severity is used to describe the intensity of an AE. It is important to remember that severity and seriousness are not the same. The severity of an AE does not determine whether an event meets the criteria for seriousness. Importantly, severity is not the same as seriousness, which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning (ICH E2A). The severity of all AEs identified in MTN-013/IPM 026 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

The severity of all AEs identified in MTN-013/IPM 026 will be graded using:

- DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT)
- If not identified there, the DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table), dated December 2004 (Clarification dated August 2009) will be utilized.

The DAIDS Toxicity Tables can be accessed on the DAIDS RSC web site (<http://rsc.tech-res.com/safetyandpharmacovigilance/>).

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

- If the severity of an AE falls into more than one grading category on 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 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 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).
- If a participant reports an adverse event that is not identified in the DAIDS AE grading table, use the category “Estimating Severity Grade” located on Page 3 of the Toxicity Table. This category should only be used for reporting clinical events. Do not use this category for reporting laboratory results.
- 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. 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.

11.4 Adverse Event Relationship Assessment

One of the following relationship categories must be assigned to each 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.

When an AE is assessed as “not related” to the study products, an alternative etiology, diagnosis or explanation should be provided in the “Comments” line on the AE Log form. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required. When recording an AE that is the result of a study-related procedure, mark the “Relationship to study product” as “Not Related” and provide an explanation in the “Comments” section that the event is a ‘result of a study-related procedure’.

11.5 Adverse Event Outcomes and Follow-Up Information

All AEs identified in MTN-013/IPM 026 must be followed clinically until they resolve (return to baseline) or stabilize (persist at a certain severity grade (above baseline)).

At each follow-up visit, an authorized study clinician should review all previously identified ongoing AEs and evaluate and document their current status in participants chart notes. Outcomes must also be reported on the AE Log case report form. In many cases, the final outcome of an AE will not be available when the AE 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 clinical events that are AEs, clinical management and follow-up of the AE should proceed per the specifications of section 9.4 and 9.5 of the protocol. If, however, a clinical AE is not addressed in section 9.4 and 9.5 of the protocol, at a minimum, follow-up evaluations should be performed at scheduled study visits until resolution or stabilization has been documented.

If an AE increases in severity or frequency (worsens) after it has been reported on an AE Log form, it must be reported as a new AE, at the increased severity or frequency, on a new AE Log 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.

The requirements for submission of follow-up information on EAEs are specified in Section 4.3 of the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0 dated January 2010). As specified therein, for the circumstances listed below regarding an EAE reported to DAIDS, the site is required to submit an updated report to DAIDS as soon as significant additional information becomes available. Requirements include:

- An updated report documenting the stable or resolved outcome of the AE, unless the initial report included a final outcome,
- Any change in the assessment of the severity grade of the AE or the relationship between the AE and the study agent, or
- Additional significant information on a previously reported AE (e.g., cause of death, results of re-challenge with the study agent(s)).

Note: If Information regarding an EAE is updated (i.e., onset date, relationship to study product), the corresponding AE Log case report form should also be updated and resubmitted if any data recorded on the AE Log form has been updated. It should also be noted that if a previously reported AE increases in severity grade, a new AE Log page for the new (higher grade) AE should be completed and submitted.

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

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. 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 within 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. Sites should notify the Protocol Safety Physicians (mtn013safetymd@mtncstopshiv.org) team for guidance in such situations. The requirements for submission of follow-up information on EAEs are specified in Section 4.3 of the *Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0 dated January 2010)*.

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 only; however, no updates should be made to any case report forms based on the re-assessments.

11.6 Reporting Recurrent Adverse Events

If an AE that was previously reported on an AE Log form resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new AE Log case report form and applicable source documents. Likewise, if a resolved EAE that was previously reported to DAIDS later recurs at a level requiring expedited reporting, the EAE must be reported as a new EAE Report to the DAIDS Safety Office.

An important clarification of this guidance relates to genital herpes and genital warts. Genital herpes and genital warts are associated with chronic viral infections — HSV-1/2 and HPV — and periodic symptomatic outbreaks — genital ulcers and genital warts.

- If infection with HSV-1/2 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.
- 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 AE Log form.

11.7 Social Harms

In addition to medical AEs, participants 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. There is no CRF for the reporting of social harms. The Investigator of Record will report any social harm, in his/her judgment, to be serious or unexpected to the PSRT and IRB according to local requirements. Study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm.

Note: 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. If the issue or problem meets criteria for expedited reporting to the DAIDS Safety Office, report it as described in Section 11.1.3 above. Also report the issue or problem to all responsible IRBs, if required per IRB guidelines.
- Ask the participant to articulate 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 return to baseline.
- Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.
- Consult the Protocol Safety Review Team (PSRT) for further input and guidance as needed. As is the case with medical AEs, data collected on social harms will be monitored by the PSRT.

11.8 Safety Distributions from DAIDS

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

- Updated Investigators Brochures and/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. 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.

11.9 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-013/IPM 026 protocol for a complete description of the participant safety monitoring procedures in place for MTN-013/IPM 026. Section 15 of this manual is a reference for a description of the reports prepared by the MTN SDMC in support of MTN-013/IPM 026 safety monitoring procedures.

Participant safety is of the utmost importance in MTN-013/IPM 026. 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 and IPM, 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.
- The DAIDS PSP Medical Officers and the IPM Medical Safety Physician will review all EAE Forms received for MTN-013/IPM 026 and follow up on these reports with site staff, the protocol team, and drug regulatory authorities when indicated.
- The Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared by the SDMC for the study. As described further in Section Appendix 11-1, the PSRT will meet via conference call to discuss cumulative study safety data and any potential safety concerns.
- The MTN Study Monitoring Committee (SMC) also will periodically review study data with a focus on performance indicators such as participant accrual and retention, protocol adherence, and data quality. While site staff are not typically involved in these reviews, site staff should be aware that the SMC 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.

Section Appendix 11-1
MTN-013/IPM 026 Protocol Safety Review Team Plan

Roles and Responsibilities of the PSRT

Per the MTN-013/IPM 026 protocol, the roles and responsibilities of the MTN-013/IPM 026 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, and the MTN Study Monitoring Committee (SMC), as appropriate.
2. Respond to queries regarding product use management including temporary hold or permanent discontinuation of study product.

The protocol specifies a number of situations in which study product use should be temporarily held, permanently discontinued and/or resumed; designated site staff may 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. (Protocol Section 9.3 and 9.4)

3. Respond to queries regarding adverse event (AE) assessment, reporting, and/or management.
4. Respond to investigator notification of participant withdrawal from the study
5. Respond to queries regarding study eligibility, participant evaluability, and/or re-joining of study participant's which previously withdrew consent (Protocol Section 9.8)

PSRT Composition

The following individuals comprise the MTN-013/IPM 026 PSRT:

- Beatrice Chen, Protocol Chair
- Lori Panther, Protocol Co-Chair
- Katie Bunge, MTN Protocol Safety Physician
- Devika Singh, MTN Protocol Safety Physician
- Ken Ho, MTN Protocol Safety Physician
- Lydia Soto-Torres, DAIDS Medical Officer (MO)
- Ludo Lavreys, IPM Representative
- Mercy Kamupira, IPM Medical Safety Physician (Back-up)
- Majia Anderson, SDMC Clinical Affairs Safety Associate

Ideally, all members of the PSRT will participate in routine conference calls. At a minimum, the DAIDS Medical Officer (or designee if DAIDS MO is not available), the Protocol Chair and/or co-Chair, a MTN Safety Physician, must take part in all calls to reach quorum.

If these 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 (FHI360) Clinical Research Managers, SDMC Project Managers, Statistical Research Associates, and Site Investigators and study coordinators 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).

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

PSRT Communications

An email distribution lists (mtn013safetymd@mtnstopshiv.org) will be used to facilitate communication with the MTN safety physicians. All communications with the safety physicians from study sites should be sent to the above email address. The safety physicians will then coordinate the distribution of all safety data summary reports from the SDMC, discussion of PSRT queries from study sites, and all query responses from members of the PSRT will be distributed via the MTN-013/IPM 026 PSRT distribution list (mtn013psrt@mtnstopshiv.org).

A standard PSRT query form be used to elicit sufficient information to allow the PSRT to make an informed determination and respond to each query. Site consultation with the safety physicians will be expedited using the *MTN-013/IPM 026 PSRT Query Form*, which is located in Section Appendix 11-2 of this manual as well as available in the Study Implementation Materials section of the MTN-013/IPM 026 web page.

The Protocol Safety Physicians will review the query form, draft a response and/or add their recommendations to the document, and distribute the query form to members of the PSRT for review and comment. All members of the PSRT should review the query within 48 hours. After PSRT consensus, the safety physician will inform the site of PSRT decision, send the final PSRT response to the site and then file the resolved query online on the PSRT Query Message Board.

The PSRT Query Message Board is for the sole use of the MTN-013/IPM 026 PSRT and is password-protected. Access to the message board is limited to members of the SCHARP ATLAS group and to users who are subscribed to the PSRT alias list (mtn013psrt@mtnstopshiv.org).

To ensure a timely PSRT response, the MTN Safety Physician and DAIDS Medical Officer have ultimate responsibility for providing a final response to the query (via email) within three business days after receipt of the query (unless a more urgent response is requested by the site). All members of the PSRT are encouraged to review the information provided by the site and to offer their advice; however, final determination rests with the MTN Safety Physicians and the DAIDS Medical Officer on behalf of the PSRT.

Note: The site that submitted the query typically will not comment on the draft response.

Section Appendix 11-2
Sample MTN-013/IPM 026 Protocol Safety Review Team Query Form

Instructions: Email form to the MTN-013/IPM026 Safety Physicians:
mtn013safetymd@mtnstopshiv.org

IMPORTANT: Complete all required fields so the PSRT has all information needed to respond to your query.

Site: **Query Date (dd-MMM-yy):**
Completed by: **Email address:**

PTID: **Participant Age (in years):**

Reason for query: Consultation on AE assessment/management/reporting
 Consultation on product use management
 Consultation on participant eligibility and/or evaluability
 Other, specify:

Is this query a request for the PSRT to consult on an adverse event (AE)?

- Yes → continue completing this page
 No → skip to Comments on page 2

AE of concern:

AE onset date (dd-MMM-yy): **AE severity grade at onset:**

Relatedness to study product:

- Related
 Not related

Current study product administration:

- No change
 On hold
 Permanently discontinued
 Not applicable

Has this AE been reported on a SCHARP AE Log form?

- Yes
 No

Has this AE been assessed more than once?

- Yes
 No → skip to Comments on page 2

Has this AE been reported as an EAE?

- Yes
 No

Has this AE been reported as an SAE?

- Yes
 No

Date of most recent assessment (dd-MMM-yy):

Status of AE at most recent assessment:

- Continuing, stabilized (severity grade unchanged)
- Continuing, improving → severity grade decreased to
- Continuing, worsening → severity grade increased to
- Resolved

Comments: Provide additional details relevant to this query. *If product use has been held, include date of last reported product use prior to the hold (per participant report).*

End of Form for Site Staff. Email completed form to the MTN-013/IPM 026 Protocol Safety Physicians, mtn013safetymd@mtnstopshiv.org. If an email response is not received from the PSRT within 3 business days, re-contact the Protocol Safety Physicians, copying the following distribution list (mtn013mgmt@mtnstopshiv.org) for assistance as soon as possible.

FOR PSRT USE ONLY — PROVIDE RESPONSE TO QUERY HERE

PSRT Responding Member:

PSRT Response Date (dd-MMM-yy):

PSRT Comments: