

Section 11. Adverse Event Reporting and Safety Monitoring

11.1 Definitions

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-007. Please also refer to Section 8 of the MTN-007 Protocol Version 2.0 dated 13 August 2010 and the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0 dated January 2010).

11.1.1 Adverse Event

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines an adverse event (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.

The MTN-007 protocol specifies that any untoward medical occurrence experienced by a participant after enrollment, which begins at the time of random assignment, is considered an AE, regardless of the study group to which the participant is assigned (i.e. “gel” or “no gel”).

In MTN-007, all AEs are reportable. That means that all AEs should be recorded on the Adverse Experience (AE) Log case report form (Section 13) and the form should be faxed to the MTN Statistical and Data Management Center (SDMC) via DataFax. All AEs should also be documented in source documents. Each site’s SOP for source documentation (see Section 3) should define the extent to which the AE Log form will be used as a source document. Site-specific delegation of duties documentation should designate study staff authorized by the Investigator of Record (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.

Medical conditions, problems, signs, symptoms and findings identified prior to randomization are considered pre-existing conditions. Such conditions should be documented in the source documents (Section 3), which may include the Baseline Medical and Menstrual History non-DataFax form, the Rectal Exam form, lab forms, etc., and reported on the Pre-Existing Conditions case report form (Section 13). Pre-existing conditions must be graded because if the condition worsens after randomization; the worsened condition is considered an AE and is reportable on the AE Log form. Pre-existing conditions are assigned severity grades just like AEs (see Section 11.3 below), so the clinician can evaluate and document if the condition worsens after study enrollment (increases in frequency or severity), in which case it would be reported as an AE.

11.1.2 Serious Adverse Event

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

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongs an existing hospitalization
 - *Note:* Per ICH SAE definition, hospitalization itself is not an adverse event, but is an outcome of the event. Thus, hospitalization in the absence of an adverse event is not regarded as an AE, and is not subject to expedited reporting. The following are examples of hospitalization that are not considered to be AEs:
 - Protocol-specified admission (e.g., for procedure required by study protocol)
 - Admission for treatment of target disease of the study, or for pre-existing condition (unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator)
 - Diagnostic admission (e.g., for a work-up of an existing condition such as persistent pretreatment lab abnormality)
 - Administrative admission (e.g., for annual physical)
 - Social admission (e.g., placement for lack of place to sleep)
 - Elective admission (e.g., for elective surgery)
- Results in persistent or significant disability/incapacity
- 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 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 in MTN-007, an authorized study clinician must determine whether the AE meets the definition of SAE. The Adverse Experience Log case report form includes an item (item 8) to record this information. Throughout the entire follow-up period, all SAEs – regardless of relatedness – will be recorded on the Adverse Experience Log CRF.

11.1.3 Expedited Adverse Event

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 the CONRAD and the DAIDS Medical Officers (MOs). For MTN-007, the AEs that must be reported in an expedited fashion include all SAEs occurring in participants assigned to “gel”, starting at the Treatment 1 Visit up through the participant’s Follow Up Phone Assessment/Termination Visit, regardless of the relationship to the study agent(s). All EAEs must be reported to the DAIDS Regulatory Support Center (RSC) Safety Office, also known as the DAIDS Safety Office, via DAIDS Adverse Event Reporting System (DAERS). Once the Termination Visit has been completed, if the site becomes aware of any suspected, unexpected serious adverse reactions (SUSAR) and/or pregnancy outcomes that meet criteria for expedited reporting, these events will also be expeditiously reported.

EAE reporting is undertaken for participants assigned to a “gel” group only. No EAEs are reported for participants assigned to the “no gel”, also referred to as “no treatment”, group.

All EAEs must be reported using the DAERS internet-based reporting system. If an EAE report needs to be modified or updated, or an EAE report submitted in error needs to be withdrawn, this can also be done through DAERS. For questions about DAERS, contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself. Information about DAERS is also available on the RSC website at <http://rsc.tech-res.com>. All EAEs will be reported via DAERS Reporting System within three (3) reporting days of site awareness (the site’s recognition that the event fulfills the criteria for expedited reporting) to the DAIDS Safety Office through their Regulatory Support Center (RSC) according to the procedures specified in the DAIDS EAE manual.

If the site cannot use DAERS to report an AE on an expedited basis, the AE must be documented on the DAIDS Expedited Adverse Reporting Form (EAE Reporting Form) and submitted as specified by the DAIDS EAE Manual. This form may be found on the Regulatory Support Center (RSC) website at <http://rsc.tech-res.com>.

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 Adverse Experience Log case report form. The AE Log case report form includes an item (item 9) to record if the AE is also being reported as an EAE. When completing AE Log CRFs 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. For SAEs experienced by no gel participants as well as experienced by gel participants prior to the Treatment 1 Visit (and as such, not reported as EAEs), information from the AE Log CRF will be forwarded by the MTN SDMC to the DAIDS MO.

11.2 Adverse Event Terminology

Both the Adverse Experience Log case report form and the DAERS report or EAE form require site staff to assign a term or description to each AE. Whenever possible, a diagnosis should be reported, rather than a cluster of signs and/or symptoms. 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 reported as an individual AE. When relevant, an anatomical location should be included in the term or description.

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 (such as elevated ALT). The severity grade of the result should not be reported as part of the AE description since the grade is captured elsewhere (item 3) on the form.

Further tips and guidelines for assigning AE terms are as follows: use medical terms whenever possible, use correct spelling for all terms, and do not use abbreviations. Additional instructions on completion of AE Log forms can be found in Section 13 (both on the back of the AE Log form and in Section 13.6).

11.3 Adverse Event Severity

The term severity is describes as the intensity of an AE (that is, the grade or level for a specific event such as mild, moderate, severe, or life-threatening. 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 DAIDS AE Grading Table Version 1.0, December 2004 (Clarification dated August 2009), Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies) will be the primary tools for grading adverse events for this protocol. Adverse events not included in those tables will be graded by the DAIDS AE Grading Table, Version 1.0 December 2004 (Clarification dated August 2009). In cases where an AE is covered in multiple tables, Addendum 3 (Rectal Grading Table for Use in Microbicide Studies) will be the grading scale utilized. The grading tables are available at <http://rsc.tech-res.com/safetyandpharmacovigilance/default.aspx>.

There are 5 severity grades that can be assigned to AEs, which are defined as follows:

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

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

- For the grading of clinical AEs not specified in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events or in the protocol, sites are to use the 'Estimating Severity Grade' on page 3 of the of the DAIDS grading table
- If the severity of an AE could fall under either one of two grades (e.g., the severity could be a grade 2 or a 3), the higher of the two grades should be assigned
- If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, assign the highest severity grade of each of the signs and symptoms to the AE
- Seasonal allergies should be graded according to the 'Estimating Severity Grade' row of the Toxicity Table
- Glycosuria should be graded per the "proteinuria" row of the Toxicity Table

11.3.1 Assigning Severity Grades for Laboratory Assays on Case Report Forms

For some lab assays, the severity grade range is calculated using a value from the DAIDS Toxicity Table and a local normal range. When grading laboratory values for which the Toxicity Table specifies the use of a multiple of the upper limit of normal (ULN), ‘normal’ values are defined according to local age-adjusted institutional values.

For example, Grade 1 for total bilirubin is 1.1–1.5 times the site lab upper limit of normal (ULN). There will be times when the calculated severity range will have more significant digits than the reported lab value, which can lead to confusion regarding which severity grade to assign.

When working with calculated severity grade ranges, remember the following:

1. Rounding is permitted only when recording lab values on a CRF in order to match the level of precision allowed on the CRF.
 2. When calculating a severity grade range, never round on interim steps.
 3. Always compare the severity grade range to the value that was recorded on the CRF (not the lab-reported value).
 4. If the calculated severity grade range has more significant digits than the lab value, do not round the calculated range values. Instead, treat all missing digits in the lab value as zeros.
- Example: Total bilirubin = 1.4 mg/dL, site ULN = 1.3 mg/dL

	DAIDS Toxicity Table Grade Range	Site-specific Grade Range
Grade 1	1.1–1.5 x ULN	1.43–1.95 mg/dL
Grade 2	1.6–2.5 x ULN	2.08–3.25 mg/dL

The site-specific grade range is accurate to the hundredths place (because $1.1 \times 1.3 = 1.43$ and $1.5 \times 1.3 = 1.95$, etc.). Treating the hundredths place of the total bilirubin value as a zero gives us a value of 1.40.

The lab value (1.40) falls below the minimum calculated value for Grade 1 (1.43). Do not assign a severity grade or report as an Adverse Experience.

5. If the lab value falls between two calculated severity grade ranges, assign it the higher grade as stated in the DAIDS Toxicity Table General Instructions (page 1).
- Example: Total bilirubin = 2.0 mg/dL, site ULN = 1.3 mg/dL

As in the example above, the site-specific grade range is accurate to the hundredths place. The hundredths place of the total bilirubin value is treated as a zero, giving us a value of 2.00.

The lab value (2.00) falls between the maximum calculated value for Grade 1 (1.95) and the minimum for Grade 2 (2.08). Therefore, this value should be assigned the higher grade (Grade 2).

11.4 Adverse Event Relationship Assessment

For each AE identified in MTN-007, the study clinician must assess the relationship of the AE to the study product, based on the temporal relationship of AE onset to study drug administration, the pharmacology of the study product and his/her clinical judgment. The categories of relatedness that will be used to assess the relationship of all AEs to study product are:

- Related: There is a reasonable possibility that the AE may be related to the study agent(s)
- Not related: There is not a reasonable possibility that the AE is related to the study agent(s)

When assessing relationship, the study products in MTN-007 that should be considered are the three gels and the applicators in which these gels are packaged. For participants assigned to gel, any AE thought to be related to an applicator should be documented as such by choosing the “Related” category and using descriptive text, comments, or other notations to indicate that the presumed relationship is with the applicator. For participants assigned to “no gel” (no treatment), this item will always be “Not Related” and using descriptive text or comments noting relationship is not related because participant is “no gel.”

11.5 Follow-up Information on Adverse Event

All AEs identified in MTN-007 must be followed clinically until the AE resolves (returns to baseline) or stabilizes. In addition to performing protocol-specified assessments, at each visit, an authorized study clinician should review all previously reported ongoing AEs to evaluate and document in the participant’s chart notes the current status.

A new Adverse Experience Log CRF is NOT required when submitting follow-up information for a previously reported AE. Rather, the existing CRF is updated and resubmitted. However, if an AE increases in severity or frequency (if it worsens), it must be reported as a new AE on a new AE Log form. The onset date on the AE Log form will be the date that the severity or frequency increased. Note that a decrease in severity should not be reported as a new AE. For additional instructions, see Section 13.

The requirements for submission of follow-up information on EAAs 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 EAA 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.

11.6 Outcome of Adverse Events, Review of AE Reports, and Study Physician Assessment and Signature

The site must follow the progress of each reported adverse event and record eventual outcomes in the source documentation. In many cases the final outcome of an AE will not be available when the AE Log form is first completed and faxed to SCHARP DataFax. In such cases, the AE Log form should be updated when the final outcome becomes available. If the AE is still continuing at the time of the Follow-up Phone Assessment Visit/Termination Visit, item 6 (“Status/Outcome”) of the AE Log form should be updated to “Continuing at end of study participation”. Any AE continuing at the Follow-up Phone Call Assessment Visit/Termination Visit should be followed clinically until resolution or stabilization, and this should be documented in chart notes only (the AE Log form should not be updated once the participant has terminated from the study).

Site staff should carefully review ALL documentation regarding an adverse event to ensure consistency and accuracy. This includes the source documentation, the AE Log CRF and the EAE Form. Site staff should be sure that onset dates, severity grades and all other details are consistent. All EAE Forms received at the DAIDS Safety Office 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 Safety Office and the SDMC have been received and that the details recorded on each form are consistent.

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 Lab 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.

A study clinician listed on the FDA Form 1572 must assess each participant and record the details of all adverse events in the source documentation and complete or carefully review the information transcribed onto the AE Log CRF.

A study physician listed on the FDA Form 1572 must review and verify the data on the DAERS report or EAE form for accuracy and completeness. This physician also makes the site's final assessment of the relationship between the study product and the adverse event. This physician must electronically sign the completed DAERS report or EAE form. If necessary, to meet timely reporting requirements, sites can submit an expedited adverse event report without a completed signature page. However, the completed signature page, and necessary corrections or additions, must be submitted within the next 3 reporting days.

11.7 Reporting Recurrent Adverse Events

If a resolved adverse event that was previously reported on the AE Log CRF later recurs, the AE is considered a new adverse event and a new AE Log CRF must be completed.

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.

11.8 Social Harms

In addition to medical adverse events, participants may experience social harms – any non-medical adverse consequence experienced as a result of a person's participation in a 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 harm occurs, 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. However, in addition to documenting the social harm in the source files, the Investigator of Record will report any social harm, in his/her judgment, to be serious or unexpected to the IRB on at least an annual basis. Study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm.

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 his/her thoughts on what can/should be done to address the problem, including what he/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 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 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 MTN-007 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 MTN-007 PSRT.

11.9 Safety Distributions from DAIDS

Sites will receive product- and safety-related information throughout the period of study implementation from DAIDS through its Regulatory Support Center and/or the MTN Coordinating and Operations Center. The information distributed may include:

- Safety Reports and Memos
- Updated Investigator Brochures and Package Inserts
- Other safety updates and documents.

Each distribution will indicate in the cover note how the information is to be handled. In many cases, this information must be submitted to all responsible IRBs for their information and retained in the site regulatory files. It is important for all relevant clinical staff to be provided copies of this information or be notified of their receipt and have access to them for careful review. Safety distributions do not require IRB approval; however, acknowledgement of receipt is desirable. Cover letters for these (and all) IRB submissions should specify the name and date of all attachments.

11.10 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-007 protocol for a complete description of the participant safety monitoring procedures in place for MTN-007. Also refer to Section 15 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN-007 safety monitoring procedures.

Participant safety is of utmost concern. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study site staff, under the direction of the IoR. The IoR and designated site staff also are responsible for submitting case report forms to the MTN SDMC and DAERS report or EAE form to the DAIDS Safety Office, 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 (clinical 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.
- The DAIDS PSP Medical Officer and CONRAD Medical Officer will review all DAERS report or EAE form received for MTN-007 and follow up on these reports with site staff, the MTN-007 Protocol Team, and drug regulatory authorities when indicated.
- The MTN-007 Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared for MTN-007 by the MTN SDMC. The PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns (See Section Appendix III for more details).

Management of study product dosing (temporarily holding or permanently discontinuing either study product dosing) relative to the occurrence of toxicities must follow the standard toxicity management procedures. Site staff should seek the advice and counsel of the PSRT on these matters.

11.11 Protocol Safety Review Team (PSRT)

11.11.1 Roles and Responsibilities of the PSRT

Per the MTN-007 protocol, the roles and responsibilities of the MTN-007 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports (protocol Section 8). Once the SDMC begins receiving study follow-up safety data, the PSRT will convene via regularly scheduled conference calls for the first six months of the study. Thereafter, 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 MTN Study Monitoring Committee (SMC).

2. Respond to Investigator queries regarding permanent discontinuation of product use (protocol Section 9.4). The protocol specifies criteria for permanent discontinuation of further study product use. These situations include, but are not limited to consultation on:
 - (a) Study product-related toxicity requiring discontinuation of study product(s)
 - (b) Request by participant to terminate study product(s)
 - (c) Clinical reasons determined by the physician
 - (d) HIV infection
 - (e) Pregnancy or Breastfeeding

When the IoR discontinues study product(s) due to study product-related toxicity, or any other clinical reason that is not specified in the protocol as criteria for permanent discontinuation, the PSRT should be notified immediately.

There are other situations when the IoR would discontinue product and then submit a PSRT query form to notify the PSRT of product discontinuation and obtain further product use management guidance, such as:

- (a) Study product-related toxicity per Sections 9.3 and 9.5 of the MTN-007 protocol.
 - (b) Use of a prohibited medication
 - (c) Participants are unable or unwilling to comply with required study procedures;
 - (d) Otherwise might put participant at risk or the safety and well-being of the participant may be compromised by continuing product use.
3. Respond to Investigator queries regarding study eligibility and general AE management and reporting (not necessarily related to product use).
4. Respond to Investigator requests for participant withdrawal from the study (protocol Section 9.6).

11.11.2 PSRT Composition

The following individuals currently comprise the MTN-007 PSRT:

- Ian McGowan, Protocol Chair
- Kenneth Mayer, Protocol Co-Chair
- Jeanna Piper, DAIDS PSP Medical Officer
- Jill Schwartz, CONRAD Medical Officer
- Katherine Bunge, MTN Safety Physician
- Devika Singh, MTN Safety Physician
- Yevgeny Grigoriev, SDMC Clinical Affairs Safety Associate

Ideally all of the above-listed PSRT members will take part in routine PSRT conference calls; however a quorum of at least two members, the DAIDS PSP Medical Officer (or designee) and an MTN Safety Physician, must take part in all calls.

If a quorum is not present, the call may be deferred until the next scheduled call time unless a quorum member requests a more immediate call.

The MTN CORE (FHI) Clinical Research Managers and SDMC (SCHARP) Project Managers will also participate in and facilitate PSRT calls and reviews. The DAIDS PSP Program Officer(s), MTN CORE Pharmacist and Co-Sponsors also may attend calls as observers.

11.11.3 Routine Safety Data Summary Reports: Content, Format and Frequency

The SDMC will generate and distribute standard safety data reports to the PSRT via e-mail within a week prior to each PSRT conference call. Tabulations will be generated for all study participants combined (i.e., across all study regimen groups). Pending final confirmation from the PSRT, the following events will be included in the standard safety data reports, regardless of relationship to study product:

- Cumulative listing of all study expedited adverse events (EAEs) and serious adverse events (SAEs)
- Summary of uncoded adverse event coding progress
- New adverse events by body system/MedDRA preferred term and severity
- New adverse events by body system/MedDRA preferred term and relationship to study product
- Cumulative adverse events by body system/MedDRA preferred term and severity
- Cumulative adverse events by body system/MedDRA preferred term and relationship to study product
- Summary of pregnancies and pregnancy outcomes

During PSRT conference calls, the DAIDS Medical Officer will summarize any additional DAERS report or EAE form received at the DAIDS Safety Office after the cut-off date for inclusion in the SDMC PSRT report.

11.11.4 PSRT Communication

An email distribution list will be used to facilitate communication with the PSRT. Queries and communications with the PSRT should be sent via email to mtn007safetyMD@mtnstopshiv.org. All safety data summary reports from the SDMC, all PSRT queries from study sites, and all query responses from the PSRT will be distributed via this alias.

A standard PSRT query form (Appendix III) will be used to elicit sufficient information to allow the PSRT to make an informed determination and respond to each query. The Protocol Safety Physicians will review the PSRT query form, add their recommendations to the document, and post the updated document to the message board. Please note that site staff should NOT post queries directly to ATLAS; rather, they must e-mail the queries to the Protocol Safety Physicians per instructions on the PSRT Query Form. The PSRT Query Message Board is for the sole use of the MTN-007 PSRT. Through SCHARP/ATLAS, the PSRT member can configure her or his preferences to receive e-mail notifications automatically from the message board when a new query or response is posted.

Note: Replying to an e-mail notification from Atlas DOES NOT add the response into the discussion on ATLAS. To post a response, you must log into Atlas, navigate to the appropriate query discussion page, and post your response. The MTN-007 PSRT Query Message Board 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 (mtn007psrt@mtnstopshiv.org).

Once all responses have been submitted and discussed, the Safety Physician will inform the site of PSRT decision and then file the resolved query online. If a PSRT member cannot access the Message Board via a mobile device, they are to email the safety physicians to inform them of their problem and the Safety Physicians will return the email with the query attached. 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.

In the event that the protocol team or PSRT has serious safety concerns, the protocol team or PSRT will request a review of the data by the MTN Study Monitoring Committee (SMC). 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 study sites in significant ways. These decisions are based on detailed review of the available study data and careful consideration of ongoing participant safety and study viability.

Section Appendix I

(DAIDS Female Genital and Rectal Grading Tables for Use in Microbicide Studies)

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events,
December 2004, Addenda 1 and 3 can be found at:

<http://rsc.tech-res.com/safetyandpharmacovigilance/>

Section Appendix II

DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events
(Clarification dated August 2009)

This table can be found at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

Section Appendix III
MTN 007 Protocol Safety Review Team Query Form

Instructions: Email completed form to MTN Safety Physicians at mtn007safetymd@mtnstopshiv.org. It is important to complete all 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: Product use consultation:
 Should use of study product be permanently discontinued?
 Request for consultation on AE management
 Request to withdraw participant from the study
 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

Primary 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

Permanently discontinued

Not Applicable

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

Yes

No

Has this AE been reported as an SAE?

Yes

No

Has this AE been reported as an EAE?

Yes

No

Has this AE been assessed more than once?

Yes

No → skip to Comments on page 2

MTN 007 Protocol Safety Review Team Query Form (Continued)

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 discontinued, include date of last reported product use prior to the discontinuation (per participant report).

End of Form for Site Staff. Email completed form to the MTN-007 Protocol Safety Physicians at mtn007safetymd@mtnstopshiv.org. If an email response is not received from the PSRT within 3 business days, re-contact the Protocol Safety Physicians and/or the MTN CORE (mtn007mgmt@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):

Query Outcome:

- Approved
- Not approved
- Not applicable

PSRT Comments: