Section 11. Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-008. Please also refer to Section 8 of the MTN-008 protocol and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events
- Female Genital Grading Table for Use in Microbicide Studies
- Manual for Expedited Reporting of Adverse Events to DAIDS
- DAERS Reference Guide for Site Reporters and Study Physicians
- Investigators Brochure for tenofovir gel

11.1 Definitions and General Reporting Guidance

11.1.1 Adverse Event (AE)

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

The MTN-008 protocol specifies that any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. is considered an AE.

Study staff must document in source documents all AEs reported by or observed in MTN-008 participants, beginning at the time of enrollment, regardless of severity and presumed relationship to study product. Source documentation for all AEs should include the following:

- AE term/diagnosis
- Severity grade
- Onset date
- Outcome
- Outcome date
- Treatment (if any)
- Date reported to site
- Relationship to study product
- Action taken with study product as a result of the AE
- Whether the AE is serious per ICH guidance (see Section 11.1.3)
- Whether the AE is a worsening of a pre-existing condition (see Section 11.1.1)

Study staff also must follow all AEs to resolution or stabilization. As a general operational guideline, "resolution" is defined as returning to the condition or severity grade that was present at baseline (i.e., at the time of enrollment) and "stabilize" is defined as persistence at a certain severity grade (above baseline) for 30 days.

The Adverse Experience Log case report form (see Section 13) is used to report all AEs that occur among MTN-008 study participants to the MTN Statistical and Data Management Center (SDMC) via DataFax. The site SOP for source documentation should define the extent to which this form will be used as a source document. Site-specific delegation of duties documentation should designate study staff authorized by the Investigator or 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 exposure to study drug are considered pre-existing conditions. Such conditions should be documented per the screening and enrollment visit guidance provided in Sections 4, 7, and 10 of this manual, and reported on the Pre-Existing Conditions case report form. If a pre-existing condition worsens (increases in severity or frequency) after enrollment, the worsened condition is considered an AE.

11.1.2 Serious Adverse Event (SAE)

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,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event 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

SAEs are a subset of all AEs. For each AE identified in MTN-008, 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 determination.

11.1.3 Expedited Adverse Event (EAE)

Expedited adverse events (EAEs) are AEs that meet criteria specified in the study protocol as requiring additional reporting for rapid review and assessment by DAIDS. In some cases, DAIDS may be required to report the EAE to the US Food and Drug Administration (FDA). All EAEs must be reported to the DAIDS Safety Office within three reporting days of site awareness of the EAE. Reporting days is defined as Monday-Friday, excluding weekends but including holidays. The day site personnel become aware that an AE has met the definition of an EAE counts 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 site personnel become aware of the EAE on a non-reporting day, (i.e., Saturday or Sunday), then the next reporting day will be day 1. All SAEs must be reported in an expedited manner to the DAIDS RSC Safety Office, regardless of relationship to study product. Figure 11-1 summarizes the SAE Reporting Category algorithm for MTN 008.

All EAEs must be reported using the internet-based DAIDS Adverse Event Reporting System (DAERS). Information on the use of DAERS is available at: http://rsc.tech-res.com/safetyandpharmacovigilance/. DAERS incorporates a report printing function that should be used to print all EAE reports —including modifications and updates — for filing in participant study notebooks. Automated email messages confirming submission of EAE reports also should be printed and filed with the print-out of the associated EAE report. In the event that DAERS cannot be accessed (e.g., due to poor internet connectivity), paper-based EAE reporting should be used, per instructions provided in the *Manual for Expedited Reporting of Adverse Events to DAIDS*. Completed paper EAE Forms may be faxed or digitally scanned and emailed to the DAIDS RSC via email. Contact details for submission of EAE Forms to the RSC are provided in the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2, January 2011*.

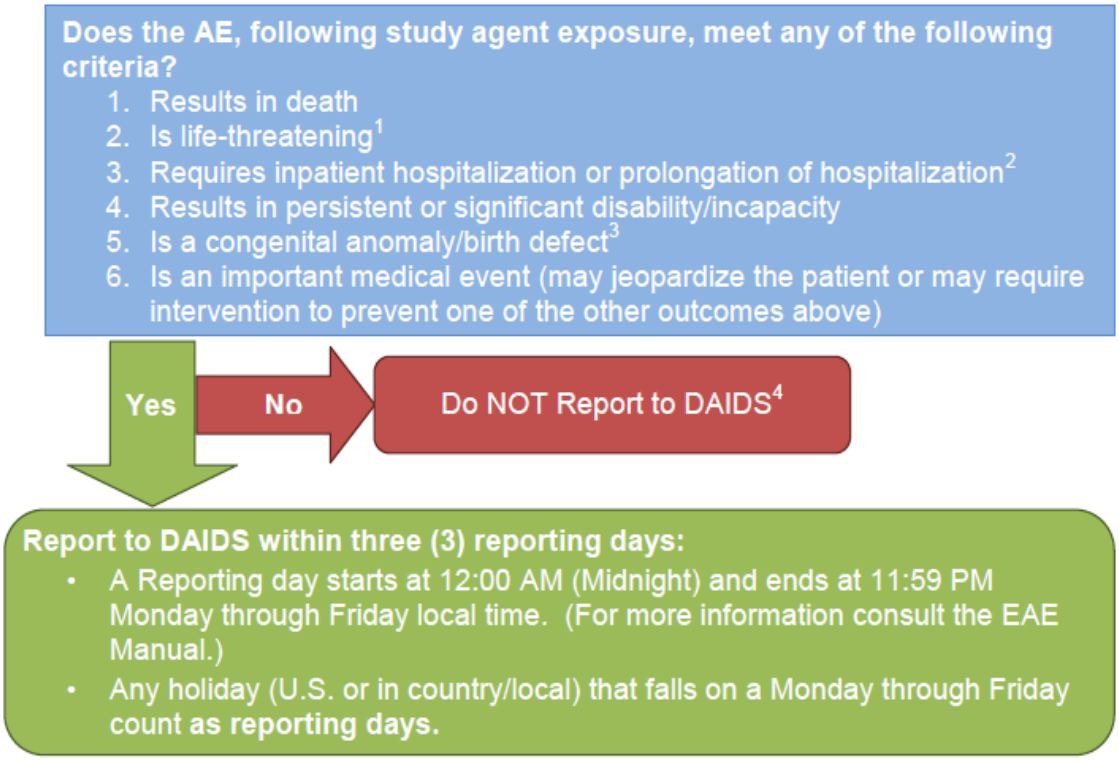
DAERS also may be used to modify or update an EAE report or to withdraw an EAE report that was submitted in error.

The process of EAE reporting via DAERS involves a designated "Study Reporter" creating an electronic EAE report and a designated "Study Physician" reviewing the EAE report, signing the EAE report with an electronic signature, and submitting the EAE report to the DAIDS RSC. The IoR or designee is responsible for designating on the designation log at least one other physician, who is listed on the FDA form 1572, at the site who can perform the assessment and signature. This will ensure uninterrupted coverage of AE/EAE monitoring and reporting in the event that the IoR is unavailable.

All EAEs must also be reported as AEs on Adverse Experience Log case report forms. Note that while AEs are not routinely reported for infant offspring of study participants in the pregnancy cohorts, congenital anomalies/birth defects identified in infant offspring are recoded as AEs since they are required to be reported as EAEs.
When completing Adverse Experience Log case report forms and EAE Forms, 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 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.

For each participant, EAE reporting is undertaken for the duration of the participant's study participation, from enrollment to post-delivery assessment or Day 14 Visit, whichever is longer, for the Pregnancy Cohort and through the Day 14 Visit for the Lactation cohort.

Figure 11-1: SAE (Serious Adverse Event) Reporting Category Flow Chart



Information for the DAIDS Safety Office
Website: http://rcc.tech-res.com • Email: 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 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 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 births 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.

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

11.2 Adverse Event Terminology

Both the Adverse Experience Log case report form and the DAIDS 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 relevant, a precise anatomical location should be included in the term or description. This is especially important in MTN-008 for distinguishing pelvic exam findings that may be observed on the vulva, in the vagina, or on the cervix.

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.

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., decreased hematocrit, elevated ALT). The severity grade of the result should not be reported as part of the AE description since the grade is captured elsewhere on the form.

Further tips and guidelines for assigning AE terms are as follows: use specific medical terms whenever possible (e.g., “ulcers” instead of “sores”), use correct spelling for all terms, and do not use abbreviations. When reporting an AE that is associated with an underlying condition, include the underlying condition in the AE term or description. For example, if a participant is experiencing pain related to an underlying cancer diagnosis, include the cancer diagnosis in the AE term or description. Additional guidance for reporting AEs is provided in Figure 11-2 of this section.

Figure 11-2
Reporting Hospitalization as AEs

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

For example:

- Fetal conditions (i.e. breech, fetal distress, meconium staining, non reassuring fetal heart tones) which result in a cesarean section should not be captured as adverse events. Even though a cesarean section for a fetal condition may prolong the mother's hospitalization, because the underlying problem is not maternal, it should not be captured as an adverse event.

- Maternal conditions (i.e. hemorrhage, preeclampsia, etc.) which result in a cesarean section should be captured as adverse events. If the condition is considered immediately life-threatening or the condition and its resultant surgery result in a prolonged hospitalization, the adverse event should be considered a serious adverse event.

- If the cesarean was performed for failure to progress in labor (no matter what the underlying cause- cervical dystocia, contracted maternal pelvis, large fetus, poor contraction pattern) the event should be captured as an adverse event but the preferred term should be "cephalo-pelvic disproportion." This AE will be serious if the cesarean results in a prolonged hospitalization.

- A scheduled cesarean section performed because of a history of cesarean section, should **not** result in an adverse event as the indication for the cesarean section (uterine scar due to a previous cesarean section) would be a preexisting condition.

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

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

11.3 Adverse Event Severity

The term severity is used to describe the intensity of an AE. The severity of each AE identified in MTN-008 must be graded on a five-point scale:

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

Severity is not the same as seriousness, which is based on the outcome or action associated with an event, as described in Section 11.1.2.

The MTN-008 specifies that the Female Genital Grading Table for Use in Microbicide Studies will be the primary tool for grading adverse events for this protocol, with the exception of asymptomatic bacterial vaginosis which will not be a reportable AE. Adverse events not included in that table 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 both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized. In cases where an AE is not listed in both tables, DAIDs AE Grading Table, the "estimating severity grade" row should be used for grading. Both the FGGT and the Toxicity Table can be accessed on the DAIDS RSC web site (http://rsc.tech-res.com/safetyandpharmacovigilance/). Copies also are provided at the end of this section

Hypertensive Disorders occurring during pregnancy will be graded as follows:

Grading Scale for Hypertensive Disorders of Pregnancy

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Hypertensive disorder of Pregnancy	Pregnancy-induced hypertension	Mild preeclampsia	Severe preeclampsia	HELLP syndrome, eclampsia, or life-threatening sequelae of preeclampsia (e.g., pulmonary edema)

11.4 Adverse Event Relationship to Study Product

For each AE identified in MTN-008, an authorized study clinician must assess the relationship of the AE to study product, based on the temporal relationship of the AE to administration of product, product pharmacology and other information provided in the Investigator's Brochure, and clinical judgment. 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 assessing relationship, the study products that should be considered are the two vaginal gels (tenofovir gel, and placebo gel), and the applicator in which the gels are packaged. For participants assigned to gel, any AEs thought to be related to an applicator should be documented as such by choosing "related" and using descriptive text, comments, or other notations to indicate that the presumed relationship is with the applicator.

11.5 Adverse Event Outcomes and Follow-Up Information

Each AE identified in MTN-008 must be followed clinically until the AE resolves (returns to baseline) or stabilizes. In addition to performing other protocol-specified procedures, at each follow-up visit an authorized study clinician should review all previously reported ongoing AEs to evaluate their current status. To assist study sites in following unresolved AEs, the MTN SDMC will generate listings of such AEs throughout the period of study implementation (see also Section 15 of this manual).

In many cases the final outcome of an AE will not be available when the Adverse Experience Log case report 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.

If an AE increases in severity or frequency (worsens) after it has been reported on an Adverse Experience Log case report form, it must be reported as a new AE, at the increased severity or frequency, on a new Adverse Experience Log case report form. In this case, the outcome of the first AE will be documented as "severity/frequency increased." The outcome date of the first AE and the onset date of the new (worsened) AE will both be the date upon which the severity or frequency increased. However, it is not necessary to submit a new AE log for an event when its severity improves to a lower range. For example, a grade 3 increased ALT is submitted, but later the event improves to a grade 2 range; the higher severity grade range – the grade 3 AE log, can cover the lower severity grade range, the grade 2 increased ALT event, till resolution.

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

Site staff are not required to report the outcome of EAEs to the DAIDS Safety Office, unless outcome information is specifically requested by DAIDS. However, 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 adverse event (this is particularly important for new information addressing cause of death if the initial assignment was "pending")
- Results of re-challenge with the study product, if performed

See also the Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, January 2010 for further information on reporting EAEs.

11.6 Reporting Recurrent Adverse Events

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

An important clarification of this guidance for MTN-008 relates to genital herpes and genital warts. Both of these conditions are associated with chronic viral infections — HSV-2 and HPV — and periodic symptomatic outbreaks — herpetic ulcers and genital warts.

- If infection with HSV-2 or HPV occurred before enrollment, the infection is considered a pre-existing condition: report on the Pre-Existing Conditions form.

- For HPV, genital warts present before enrollment also are considered a pre-existing condition: report on the Pre-Existing Conditions form.

- If infection with HSV-2 or HPV is newly diagnosed after enrollment, the infection is considered an AE: report on an Adverse Experience Log form. Since HSV-2 and HPV infections cannot be cured, they should be reported as AEs only once per participant.

- If any new symptomatic outbreaks occur after enrollment, each outbreak is considered an AE and should be reported separately on an Adverse Experience Log form.

11.7 MTN-008 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-008 protocol and Section 14 of the MTN Manual of Operations for a complete description of the participant safety monitoring procedures in place for MTN-008. Also refer to Section 15 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN-008 safety monitoring procedures.

Participant safety is of paramount importance in MTN-008. 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 EAE reports 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 clinical 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.

- The DAIDS Safety Office, DAIDS RAB Safety Specialist, and DAIDS PSB Medical Officer will review all EAE reports received for MTN-008 and follow up on these reports with site staff, the MTN-008 Protocol Team, and drug regulatory authorities when indicated.

- The MTN-008 Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared for MTN-008 by the MTN SDMC. As described further in Section 11, Section 11-9, the PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns.

- The MTN Study Monitoring Committee (SMC) also will periodically review MTN-008 study data with a focus on performance indicators such as participant accrual and retention, safety data, protocol adherence, intervention 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 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.

11.8 Safety Distributions from DAIDS

As noted in Section 1 of this manual, study sites will receive product- and safety-related information throughout the period of study implementation. This information will be distributed by DAIDS, through its Regulatory Compliance Center and/or the MTN Coordinating and Operations Center, and may include:

- Updated Investigator's Brochures
- IND Safety Reports
- SMC review summaries
- Other safety memoranda and updates

Each distribution will include a cover memo providing instructions on how the document is to be handled. In all cases, a copy of the distribution must be filed in the study site Essential Document files for MTN-008. 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 the study site IRB/EC. 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 MTN-008 Protocol Safety Review Team Plan

11.9.1 Roles and Responsibilities of the PSRT

Per the MTN-008 protocol, the roles and responsibilities of the MTN-008 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports (protocol Section 8.1). Once the SDMC begins receiving study 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 MTN Study Monitoring Committee (SMC).

2. Respond to Investigator queries regarding temporary or permanent discontinuation of product use. The protocol specifies a limited number of situations in which study participants must discontinue participation; Investigators will implement these discontinuations in the absence of consultation with the PSRT. In other situations, however, discontinuation or withholding of product must be undertaken in consultation with the PSRT.

3. Respond to Investigator queries regarding study eligibility and general AE management and reporting (not necessarily related to product use; protocol Section 10).

4. Respond to Investigator requests for participant withdrawal from the study (protocol Section 10).

11.9.2 PSRT Composition

The following individuals currently comprise the MTN-008 PSRT:

- Richard H Beigi, Protocol Chair
- Katie Bunge, MTN Safety Physician
- James Dai, Protocol Statistician
- Jeanna Piper DAIDS Medical Officer
- Heather Watts, NICHD Medical Officer
- Devika Singh, MTN Safety Physician
- Jenny Tseng, SCHARP 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 three members must take part in all calls. The quorum must consist of:

- Protocol Chair
- DAIDS Medical Officer (or designee) and
- One of the MTN Safety Physicians

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 Manager also will participate in and facilitate PSRT calls and reviews.

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

The SDMC will generate and post on a designated website standard safety data reports for the PSRT a week prior to each monthly PSRT conference call. Overall, there are two sets of tabulations for safety reports, one containing mothers' data and the other containing infants' data. Each set of the safety reports is sorted by cohort and group, Lactation Cohort or Pregnancy Cohort, Group1 or 2. The safety reports that are distributed for PSRT review include the following data:

- Cumulative DAIDS EAE and/or ICH-Serious AE Listing Summary of Uncoded AEs by Verbatim Term and Severity
- Adverse Experiences by Body System/MedDRA Preferred Term and Severity (Limited to New or Modified AEs only) Adverse Experiences by Body System/MedDRA Preferred Term and Relationship to Study Product (Limited to New or Modified AEs only)
- Adverse Experiences by Body System/MedDRA Preferred Term and Severity
- Adverse Experiences by Body System/MedDRA Preferred Term and Relationship
- Pregnancy history and outcomes
- Product hold and discontinuation

An individual safety history of participants is also available based on PSRT's ad hoc request. The report includes the following data elements: demographics, enrollment, product hold log, hematology, chemistry, AEs, pre-existing conditions, concomitant medications, estimated date of delivery, type of cohort, and gestational age.

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

11.9.4 PSRT Communications

Initial PSRT queries from the sites will be sent directly via email to mtn008safetymd@mtnstopshiv.org. All safety data summary reports from the SDMC, and all query responses from the PSRT will be distributed via the following MTN-008 PSRT alias list: mtn008psrt@mtnstopshiv.org. A standard PSRT query form, which is available in the Study Implementation Materials section of the MTN-008 web page, will be used to elicit sufficient information to allow the PSRT to respond to each query. To ensure a timely PSRT response, the MTN safety physicians have ultimate responsibility for providing a final response to the query (via email) within three business days after receipt of the query. 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 Protocol Chair.

PSRT query board is also available via Atlas at SCHARP to provide all PSRT members a tool for the PSRT communication and documentation.

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

To document calls made to the emergency safety telephone number, near the time of the call (either before or after) site staff will complete the site section of the MTN-008 Emergency Phone Contact form (available in the Study Implementation Materials section of the MTN-008 web page) and email the form to the Protocol Safety Physicians. Within 24 hours after the call, the responding Protocol Safety Physician will complete the remainder of the form and email the completed version to site staff, copied to the study management team.