Section 11. Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in HPTN 059. Please also refer to Section 6 of the HPTN 059 protocol and the Manual for Expedited Reporting of Adverse Events to DAIDS in Section 17.2 of the SSPs.

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 HPTN 059 protocol specifies that any untoward medical occurrence experienced by a study participant after randomization is considered an AE, regardless of the study group to which the participant is assigned.

The Adverse Experience Log case report form (see Section 13) is used to report all AEs that occur among HPTN 059 study participants to the HPTN Statistical and Data Management Center (SDMC) via DataFax. Each site's 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 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 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 (see Section 13.6). If a pre-existing condition worsens (increases in severity or frequency) after randomization, 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, or
- Is a congenital anomaly/birth defect.

ICH guidance (E2A) also states that medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious 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 usually be considered serious.

SAEs are a subset of all AEs. For each AE identified in HPTN 059, 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 Regulatory Compliance Center (RCC) within three business days of site awareness of the EAE. Reports must be submitted to the RCC by 11:59 PM Eastern Time on third business day. For example, if a site becomes aware of an EAE/SAE on Wednesday (day 1), the EAE/SAE report must be submitted to the RCC by 11:59 pm Eastern Time on Friday (day 3). All questions regarding submission of EAEs/SAEs should be directed to the RCC Safety Office at:

Telephone:	301-897-1709
	800-537-9979
E-Mail:	RCCSafetyOffice@tech-res.com

Although seriousness (defined in Section 11.1.2) is a consideration in determining whether an AE meets the definition of EAE, the terms SAE and EAE are not synonymous. The two terms refer to two different, but overlapping, subsets of AEs. For HPTN 059, the subset of AEs that are considered EAEs includes some AEs that are serious and some that are not serious.

The Manual for Expedited Reporting of Adverse Events to DAIDS defines levels of EAE reporting that may be used in DAIDS-sponsored studies. **For HPTN 059 the "intensive" reporting level will be followed.**

All EAEs must be reported on a DAIDS Expedited Adverse Event (EAE) form. Copies of the form and form completion instructions are available at http://rcc.tech-res-intl.com.

All participants will be followed for EAEs 12 weeks post product use per Section 6.4.1 of the protocol.

Pregnancy outcomes that meet criteria for expedited reporting such as congenital anomalies, birth defects, or fetal losses regardless of relationship to study gel (refer to Manual for Expedited Reporting of Adverse Events to DAIDS) occurring among participants known to be pregnant at study exit will be reported as EAEs on the EAE form.

Note: Sites should attempt to obtain on and report on the SCHARP AE Log form all pregnancy outcomes (whether they occur on-study or after study exit) for all pregnancies that occur on-study.

A study physician listed on the site's FDA Form 1572 must review and verify all data recorded on the DAIDS EAE Form for accuracy and completeness. This physician also must make the final assessment of the relationship between the EAE and study product and sign the completed form. If necessary to meet required reporting timeframes, an EAE Form may be submitted to the DAIDS Safety Office without a completed signature page. However, the completed signature page, and any necessary corrections or additions, must be submitted to the DAIDS Safety office within the next three business days.

As noted above, **EAE Forms must be submitted to the DAIDS Safety Office as soon as possible, but no later than three business days after the site's recognition that the event fulfills the criteria for expedited reporting**. The DAIDS Safety Office fax number is shown on the first page of the EAE Form. Completed forms also may be digitally scanned and submitted to the DAIDS Safety Office via email. Contact details are as follows:

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

With the exception of congenital anomalies and birth defects identified among infants born to study participants, all EAEs also must be reported on Adverse Experience Log case report forms. 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 HPTN 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.

11.1.3.1 EAE Reporting for Spontaneous Abortions

For participants who experience a spontaneous abortion during the course of the study, the severity of the event will be graded per the guidance for "Estimating Severity Grade" of the DAIDS Toxicity Table, which takes into consideration the functional status of the woman who experiences a spontaneous abortion. For example, a participant who does not experience any symptoms but is found to have a negative pregnancy test after having a prior positive pregnancy test should have a Grade 1 assigned to that spontaneous abortion. A participant who experiences severe symptoms (such as hemorrhaging) will be assigned a Grade 3 or Grade 4 to her spontaneous abortion.

Determination of whether the spontaneous abortion meets the ICH definition of "serious" will depend on the outcome of the woman who experiences the abortion, specifically whether the spontaneous abortion:

- results in a participant's death
- is life threatening to the participant
- requires that the participant be hospitalized
- results in persistent or significant disability/incapacity.

Note**: The severity of the grade assigned to spontaneous abortions will not impact EAE reporting of the event. **ALL spontaneous abortions observed among women will be reported as EAEs regardless of the grade.

11.1.3.2 EAE Reporting Requirements

EAE reporting requirements are presented in Table 11-1.

Table 11-1
Expedited Adverse Event Reporting Requirements for HPTN 059

Type of Adverse Event	Intensive EAE Reporting
Results in death	Report as EAE regardless of relationship to study product
Is a congenital anomaly or birth defect or fetal loss	Report as EAE regardless of relationship to study product
Results in persistent or significant disabilities or incapacities	Report as EAE regardless of relationship to study product
Requires or prolongs hospitalization or requires intervention to prevent significant/permanent disability or death	Report as EAE if relationship to study product is: • Definitely related • Probably related • Possibly related • Probably not related
Is life-threatening (includes all Grade 4 AEs)	Report as EAE if relationship to study product is: • Definitely related • Probably related • Possibly related • Probably not related

Table 11-1 continued
Expedited Adverse Event Reporting Requirements for HPTN 059

Other Grade 3 AEs	Report as EAE if relationship to study product is: • Definitely related • Probably related • Possibly related Probably not related
Other Grade 1 and Grade 2 AEs	Do not report as EAE

In addition to the events listed above, the following also should be reported as EAEs:

- AEs that may be related to study product (i.e., definitely, probably, possibly, or probably not related) that the IoR believes are of sufficient concern to be reported on an expedited basis to DAIDS. This includes AEs that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent a serious AE.

- Serious AEs that are not related to study product but could be associated with study participation or procedures.

- Unexpected serious AEs that may be related to study product (i.e., definitely, probably, possibly, or probably not related) that occur after the participant's study exit visit.

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, an anatomical location should be included in the term or description. This is especially important in HPTN 059 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 should be anemia, elevated liver enzymes should be hepatitis, and decreased platelets thrombocytopenia). 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.

11.3 Adverse Event Severity

The term severity is used to describe the intensity of an AE. The severity of each AE identified in HPTN 059 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.

HPTN Protocol 059 version 2.0, dated 13 March, 2006, specifies that all AEs, except vulvovaginits and cervicitis, will be graded severity using the DAIDS Table for Grading Adult and Pediatric Adverse Events, dated 28 December 2004, which can be found in Appendix 11-1 and at the following web site: http://rcc.tech-res-intl.com.

Refer to Protocol Section 6.3, Table 2, for severity grading for Vulvovaginitis and Cervicitis.

11.4 Adverse Event Relationship to Study Product

For each AE identified in HPTN 059, 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 Brochures, and clinical judgment. One of the following relationship categories must be assigned to each AE:

- Definitely Related: The AE and administration of study gel are related in time, and a direct association can be demonstrated.

- Probably Related: The AE and administration of study gel are reasonably related in time, and the AE is more likely explained by study gel than other causes.

- Possibly Related: The AE and administration of study gel are reasonably related in time, and the AE can be explained equally well by study gel as by other causes.

- Probably Not Related: A potential relationship between the AE and study gel could exist (i.e., the possibility cannot be excluded), but the AE is more likely explained by causes other than study gel.

- Not Related. The AE is clearly explained by another cause not related to study gel.

Note: The HPTN 059 study products are comprised of the gel and the applicator used to insert the gel into the vagina. Any AEs thought to be related to an applicator should be documented as such by choosing one of the "related" categories and using descriptive text, comments, or other notations to indicate that the presumed relationship is to the applicator.

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

11.5 Adverse Event Outcomes and Follow-Up Information

Each AE identified in HPTN 059 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 HPTN 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.

Site staff is not required to report the outcome of EAEs to the DAIDS Safety Office, unless outcome information is specifically requested by DAIDS. However, if an EAE increases in severity to a higher grade than previously reported, it must be reported to the DAIDS Safety Office as a new EAE on a new EAE Form.

EAE follow-up information also must be reported to the DAIDS Safety Office 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

In these circumstances, the required follow-up information should be reported on a new EAE Form as a Follow-Up Report. See also Section 5.1 of the Manual for Expedited Reporting of Adverse Events to DAIDS.

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 HPTN 059 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, genital HSV-1, or HPV occurred before randomization, the infection is considered a pre-existing condition: report on the Pre-Existing Conditions form.

- For HPV, genital warts (exterior to the labia minora) that are present before randomization also are considered a pre-existing condition: report on the Pre-Existing Conditions form. (Genital warts located interior to or on the labia minora that are present at baseline are an exclusion criteria).

- If infection with HSV-2, genital HSV-1, or HPV is newly diagnosed after randomization, the infection is considered an AE: report on an Adverse Experience Log form. Since HSV-2, genital HSV-1, and HPV infections cannot be cured, they should be reported as AEs only once per participant.

- If any new symptomatic outbreaks occur after randomization, each outbreak is considered an AE: report on an Adverse Experience Log form.

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 on a new EAE Form.

11.7 Social Harms

In addition to medical AEs, participants in HPTN 059 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 harm to the participant occurs, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section.

The HPTN 059 Follow-Up Behavior Assessment form actively ascertains, whether participants have had "any problems as a result of being in the study." In addition to responding to this standardized questionnaire, participants also may spontaneously report study-related issues and problems to study staff at any study visit.

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/ECs, if required per IRB/EC 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 stabilization.

- Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.

- Consult the HPTN 059 Protocol Safety Review Team (PSRT) for further input and guidance as needed.

As is the case with medical AEs, data collected regarding social harms will be monitored by the HPTN 059 PSRT and the NIAID Vaccine and Prevention Data and Safety Monitoring Board (DSMB), as described below.

11.8 HPTN 059 Safety Monitoring, Review, and Oversight

Please refer to Section 6 of the HPTN 059 protocol and Section 14 of the HPTN 059 Manual of Operations for a complete description of the participant safety monitoring procedures in place for HPTN 059. Also refer to Section 15 of this manual for a description of the reports prepared by the HPTN SDMC in support of HPTN 059 safety monitoring procedures.

Participant safety is of paramount importance in HPTN 059. 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 HPTN SDMC and EAE Forms 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 HPTN 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.

- The DAIDS Safety Office, DAIDS RAB Safety Specialist, and DAIDS PSB Medical Officer will review all EAE Forms received for HPTN 059 and follow up on these reports with site staff, the HPTN 059 Protocol Team, and drug regulatory authorities when indicated.

- The HPTN 059 Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared for HPTN 059 by the HPTN SDMC. As described further in Section 11-10, the PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns. To preserve blinding, data reviewed by the PSRT will be pooled across the four study treatment groups.

- In the unlikely event that the protocol team has serious safety concerns that lead to a decision to permanently discontinue study gel for all participants and stop accrual into the study, the protocol team will request an unblinded review of the data by the NIAID Data and Safety Monitoring Board (DSMB) before recommending that the study be stopped. Members of the NIAID DSMB will be independent investigators with no financial interest in the outcomes of this study.

The HPTN Study Monitoring Committee (SMC) also will periodically review HPTN 059 study data with a focus on performance indicators such as participant accrual and retention, protocol adherence, intervention adherence, and data quality. While site staff is not typically involved in these reviews, site staff should be aware that the SMC may make recommendations to DAIDS and/or the HPTN 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.

11.9 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 HPTN Coordinating and Operations Center, and may include:

- Updated Investigator's Brochures
- IND Safety Reports
- PSRT 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 HPTN 059. 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 all study 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.

11.10 Roles and Responsibilities of the Protocol Safety Review Team (PSRT)

Per the HPTN 059 protocol, the roles and responsibilities of the HPTN 059 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports (protocol Section 6.1). 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 HPTN Study Monitoring Committee (SMC) and/or DAIDS Vaccine and Prevention Data and Safety Monitoring Board (DSMB), as appropriate.

2. Respond to Investigator queries regarding temporary or permanent discontinuation of product use (protocol Section 4.6). The protocol specifies a limited number of situations in which study participants must discontinue product use; Investigators will implement these discontinuations in the absence of consultation with the PSRT. In other situations, however, discontinuation of product must be undertaken in consultation with the PSRT. These situations involve participants who:

   (a) experience an AE that meets criteria for expedited reporting to DAIDS that is judged possibly related to product use
   (b) have a pelvic exam finding involving deep epithelial disruption, generalized erythema or edema, vaginitis, suspected cervicitis, and intermenstrual bleeding/spotting (refer to Protocol Appendix II)
   (c) are unable or unwilling to comply with required study procedures; or
   (d) otherwise might be put at undue risk to their safety and well-being by continuing product use.

3. Respond to Investigator queries regarding product resumption following occurrence of an AE judged probably or definitely related to study product that meets criteria for expedited reporting (protocol Section 4.6).

4. Respond to Investigator queries regarding study eligibility and general AE management and reporting (not necessarily related to product use; protocol Section 10.3).

5. Respond to Investigator requests for participant withdrawal from the study (protocol Section 3.6).

6. Respond to Investigator requests for participant unblinding (protocol Section 7.5). There are no circumstances under which it is expected that unblinding will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants.

However, if an Investigator feels that specific product knowledge is necessary to protect participant safety, the Investigator may notify the PSRT to consider and rule upon the request.

11.10.1 PSRT Composition

The following individuals currently comprise the HPTN 059 PSRT:

- Sharon Hillier, Protocol Chair, PSRT Chair
- Craig Hoesley, Site Investigator of Record
- Smita Joshi, Site Investigator of Record
- Jessica Justman, Site Investigator of Record
- Lydia Soto-Torres, DAIDS PSB Medical Officer
- Benoît Mâsse, Protocol Statistician
- Bryna Harwood, Protocol Safety Physician
- Nancy Connolly, Protocol Safety Physician

Ideally all of the above-listed PSRT members or their designees 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:

- Either the PSRT Chair or Alternate Chair
- The DAIDS PSB Medical Officer (or designee) and
- The Protocol Statisticians

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 HPTN CORE (FHI) Clinical Research Managers, SDMC (SCHARP) Project Manager, SDMC (SCHARP) Statistical Research Associate, and SDMC (SCHARP) Clinical Affairs staff also will participate in and facilitate PSRT calls and reviews. The DAIDS PSB Program Officer(s), DAIDS PAB Protocol Pharmacist, and Pharmaceutical Co-Sponsors also may attend calls as observers.

11.10.2 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 4-5 days prior to each PSRT conference call. Tabulations will be generated for all study participants combined (i.e., across all treatment 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:

- Grade 2 and higher genital bleeding events
- Grade 3 and higher liver, hematology, and coagulation laboratory events
- Other Grade 3 and higher clinical and laboratory events (with the exception of creatinine)
- Grade 2 or higher creatinine laboratory event
- Other adverse events that meet criteria for expedited reporting to DAIDS
- Abnormal Colposcopic findings
- Pregnancies and pregnancy outcomes

Reports will include summary information regarding the number and frequency events that meet the criteria above organized by body system (using MedDRA terms) and severity and will include information on relatedness. Each distribution will consist of one set of reports listing cumulative data and one set listing only new events reported since the last distribution.

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

11.10.3 PSRT Communications

When a query is generated at a site, the site will complete the Protocol Safety Review Team query form illustrated Appendix 11-3, and submit the completed query form to the HPTN 059 Protocol Safety Physicians. The Safety Physicians will create a draft response and forward the draft response to the PSRT via the PSRT email alias list within 48 hours.

The PSRT will be given 24 hours to review the draft response and provide any comments to the Protocol Safety Physicians. Once a final version of the response is approved by all PSRT members, the response will be forwarded to the site.

A standard PSRT query form (below) will be used to elicit sufficient information to allow the PSRT to respond to each query. To ensure a timely response, the PSRT response, the Protocol Safety Physicians has 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 Safety Physicians.

Appendix 11-1
DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

Appendix 11-2
Manual for Expedited Reporting of Adverse Events to DAIDS (May 6, 2004)

Appendix 11-3
HPTN 059 Protocol Safety Review Team Query Form (Page 1 of 2)

Instructions: Email completed form to brynah@uic.edu **and** nconnolly@mail.magee.edu. IMPORTANT: Complete all required fields so the PSRT has all information needed to respond to your query.

Site:
Completed by:
PTID:
Enrollment Date (dd-MMM-yy):

Query Date (dd-MMM-yy):
Email address:
Participant Age (in years):

Reason for query:
- ☐ Product use consultation:
  - ☐ Should use of study gel be temporarily discontinued?
  - ☐ Should use of study gel be permanently discontinued?
  - ☐ Should use of study gel be resumed?
- ☐ Request for consultation on AE management
- ☐ Request to withdraw participant from the study
- ☐ Request to unblind participant's gel assignment
- ☐ 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 gel:
☐ Definitely related
☐ Probably related
☐ Possibly related
☐ Probably not related
☐ Definitely not related

Current study gel 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 reported as an EAE?
☐ Yes
☐ No

Has this AE been assessed more than once?
☐ Yes
☐ No → skip to Comments on page 2

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 gel use has been held, include date of last reported gel application prior to the hold (per participant report).

End of Form for Site Staff. Email completed form to the HPTN 059 Protocol Safety Physicians (brynah@uic.edu **and** nconnolly@mail.magee.edu). If an email response is not received from the PSRT within 3 business days, re-contact the Protocol Safety Physicians and/or HPTN CORE Protocol Specialists (ecyrus@fhi.org) for assistance.

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: