

Section 8. Adverse Event Reporting and Safety Monitoring

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8 Introduction

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-035.

8.1 Adverse Event Reporting and Safety Monitoring

Please refer to protocol section 8 (Assessment of Safety) and the following resources relevant to AE assessment and reporting:

- [DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017](#) (DAIDS Toxicity Table)
 - [Addendum 1: Female Genital Grading Table for Use in Microbicide Studies](#), dated November 2007
 - [Addendum 2: Male Genital Grading Table for Use in Microbicide Studies](#), dated November 2007
 - [Addendum 3: Rectal Grading Table for Use in Microbicide Studies](#) (Clarification dated May 2012)

8.1.1 Adverse Events

The [International Conference on Harmonisation Consolidated Guidance for Good Clinical Practice \(ICH-E6\)](#) defines an adverse event (AE) as “[a]ny untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product....”

For MTN-035, the ICH-E6 definition is applied to all participants in all study groups, beginning at the time a participant is randomized through study termination.

Study staff must document all AEs reported by or observed in study participants, regardless of severity and presumed relationship to study product.

Relevant medical conditions, problems, signs, symptoms, and findings identified prior to random assignment are considered pre-existing conditions. Such conditions should be documented on the Medical History Log CRF (whether they are ongoing at enrollment or not). If any condition is ongoing at the time of enrollment, it is a baseline medical condition regardless of its medical significance. If this condition worsens (increases in severity or frequency per the DAIDS grading table) after enrollment, the worsened condition is considered an AE. If a baseline medical history condition resolves after enrollment, but then recurs at a later date, the recurrence is considered an AE.

Each site's SOP for source documentation should define the extent to which the AE Log CRF 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 the AE Log CRF. Regardless of who initially completes these forms, a clinician listed on the site's DAIDS IoR Form should review them to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

8.1.2 Serious Adverse Events (SAEs)

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

- Results in death,
- Is life-threatening,
 - NOTE:** The term "life threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. A grade 4 severity grading on the Toxicity Table does not necessarily mean that an event is life-threatening. For example, when determining whether a grade 4 laboratory event meets the ICH definition of "life threatening", consider the event in the context of any related symptoms the participant may have experienced.*
- Requires in-patient hospitalization or prolongs an existing hospitalization,
 - The following types of hospitalizations are not considered Adverse Events, serious or otherwise:
 - Any admission unrelated to an AE (e.g., for labor/delivery)
 - Admission for diagnosis or therapy of a condition that existed before randomization AND has not increased in severity or frequency since baseline.
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above

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

SAEs are a subset of all AEs. For each AE identified in MTN-035, an authorized study clinician must determine whether the AE meets the definition of SAE. The AE Log CRF includes a specific question to record this determination.

8.2 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in MTN-035. The guidance below should be followed when assigning AE terms/descriptions:

- Do not include information on severity grade, relatedness to study product or timing of study product use in the AE term/description. Limit the AE text to the medical description and anatomical location, when needed.
- Whenever possible, a diagnosis should be assigned to describe a cluster of signs and/or symptoms.
 - Document associated signs and/or symptoms related to a diagnosis in the comments section of the AE Log CRF.
- When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, each individual sign and symptom must be identified and documented as an individual AE.
- Do not use abbreviations
- When there is evidence of rectal bleeding, this AE should be documented as ‘rectal bleeding’. Do not use the terms ‘anal bleeding’ or ‘hematochezia’.
- Seasonal allergies should be graded according to the “Estimating Severity Grade” parameters of the DAIDS Toxicity Table (not the “Acute Allergic Reaction” row of the “Systemic” table).
- Whenever possible, use specific terms to indicate the anatomical location of the AE (e.g., “rectal” instead of “genital”).
- Use medical terms (e.g. “ulcers” instead of “sores”).
- Use correct spelling.
- If an STI result warrants AE reporting, document the STI diagnosis, and not the test result, in the AE term/description. For example, report an AE of chlamydia as “rectal chlamydia”, and not “positive NAAT/chlamydia result”.
- The presence of study product leakage by itself is not an AE and should not be reported on an AE Log CRF. However, any untoward effect the leakage has on a participant (e.g., “perianal irritation” or “anorectal discomfort”) should be reported as an AE on an AE Log CRF.
- “Genital ulcer disease” is not a codable event. Rather, an STI diagnosis should be reported in the AE term/description. If there is no STI diagnosis, the AE should be reported as “ulcers” with the anatomical location (e.g., “anal” or “rectal”) specified.
- Any event that occurs as a result of a study-related procedure should be recorded as an AE.
 - Specify in the AE text description if the AE is related to a procedure (iatrogenic).
 - For example, “rectal bleeding due to anoscope insertion” or “anal fissure due to enema tip insertion”. This information must be documented in the AE text on the AE Log CRF (and not in the comments section) for the AE to be properly coded and appear correctly in the safety reports.

Any lab value that is severity grade 1 or higher, according to the DAIDS Toxicity Table, regardless of where the testing took place, should be reported as an AE and documented within the AE Log CRF. Lab results from outside sources should be filed in participant charts as source documentation, if available. Even when source documentation from an outside lab is not immediately available, self-reported lab-based AEs (for example, a participant was told by an outside health care provider that she tested positive for gonorrhea) should be captured within the AE Log CRF (and confirmed by on-site testing as soon as possible). In contrast, CRFs that capture local laboratory results should only be used to document lab results from protocol-specified tests run at site-approved labs. AEs not listed in any of the above-mentioned grading tables should be graded according to the “Estimating Severity” parameters of the DAIDS Toxicity Table.

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

- If the severity of an AE falls into more than one grading category on the toxicity table, assign the higher of the two grades to the AE.
- When grading AEs per the “Estimating Severity” parameters (i.e. for AEs not listed specifically in the Female Genital Grading Table, Male Genital Grading Table, Rectal Grading Table or DAIDS Toxicity Table), “intervention” should be defined as outlined in the “Glossary and Acronyms” section of the toxicity table: “[m]edical, surgical or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.” If a participant reports treatment, the clinician must obtain further information as to whether it was self-initiated (grade 1) versus provider-recommended (grade 2). Importantly, clinicians should note that grading is dependent on participant-reported impact of symptoms on her life, and whether intervention (as defined above) is indicated, regardless of whether the treatment was actually provided or accepted by the participant. It is at the clinician’s discretion whether intervention is indicated for the reported AE. If a clinician recommends intervention but the participant does not accept it, the treatment should be marked as “other” rather than “medications” and additional details should be included in the line provided. The assigned AE severity grade, per the toxicity table, should be grade 2.
- Urinary tract infection (UTI), which is expected to be diagnosed on the basis of symptoms should be graded according to the “Estimating Severity” parameters of the toxicity table. If culture and/or microscopy are done per site standard of care, grade 1 and grade 2 UTI can be assigned per the UTI parameter of the applicable toxicity table.
- Procedures per se should not be reported as AEs; rather the underlying condition which leads to a procedure may be considered an AE. Any associated procedures may be considered treatments for the AE. For example, while “appendectomy” would not be considered an AE, “appendicitis” would, with “appendectomy” documented as a treatment provided for the AE. Also, planned procedures or surgeries are not AEs. Rather, the underlying diagnosis or condition that warrants the procedure or surgery may be a reportable AE. Any adverse experiences resulting from a planned procedure or surgery are AEs and should be reported on an AE Log CRF. The AE term/description should specify the procedure as the cause of the AE. For example, a throat infection that resulted from the tonsillectomy should be reported as an AE of “throat infection due to tonsillectomy”.
- 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.
- Fecal urgency, bloating and flatulence associated with rectal procedures deemed to be within the range of normally expected will also not be reportable as AEs.
- For individuals who can get pregnant, fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs, but will be captured on the Pregnancy Outcome CRF. Also, untoward maternal conditions that either result in or result from fetal losses are reported as reproductive system AEs.
- COVID-19: If a participant is suspected or confirmed to have COVID-19, “COVID-19” should be reported as the AE term. Grade based on the “estimating severity grade” row of the toxicity table. It is not necessary to include details on whether suspected or confirmed in the comments.

8.2.1 Reporting Genital, Genitourinary, and Reproductive System AEs

Discharge: Vaginal or urethral Discharge by participant report or observed by the clinician should be graded per the appropriate rows in the FGGT or MGGT. The verbatim term from the FGGT or MGGT should be used to distinguish if discharge was clinician observed versus participant reported. If discharge is present both by history and on examination, only report the one with the most severe grade. If they are the same grade, report 'vaginal' or 'urethral' discharge by participant report' as the AE term.

Vaginal odor: Per the FGGT, odor is listed as a symptom and should be documented as an AE if different from baseline and not due to a larger diagnosis. This is based on participant report of the symptom only and grading based on the participant's perception of severity.

STIs/RTIs: The following terminology should be used only if an STI diagnosis is based on clinical evaluation and confirmed, when appropriate/possible, by laboratory results.

- **Chlamydia:** Report genital infections using the term "genitourinary chlamydia infection." Report rectal infections using the term "rectal chlamydia."
- **Gonorrhea:** Report genital infections using the term "genitourinary gonorrhea infection." Report rectal infections using the term "rectal gonorrhea."
- **Genital herpes:** Note that laboratory testing is required in order to use the term "genital herpes" for AE reporting. Such testing is not required per protocol and should only be done if clinically indicated. Any new lesion/ulcer observed during the study should be reported as an AE even if thought to be due to a prior herpes diagnosis/infection.
 - A suspected genital herpes outbreak should be reported using the term marked on the Anorectal Exam CRF (if applicable, the Pelvic Exam CRF) describing the lesion together with the anatomical location (e.g., anal ulcer, perianal ulcer, vulvar ulceration, vaginal blister).
- **Genital warts:** Report all outbreaks of genital warts as AEs, regardless of whether infection with HPV was known to be pre-existing before enrollment/randomization. Report the AE using the term "external" or "internal" and "condyloma" and include the anatomical location of the warts (e.g., cervical, vaginal, perianal).
- **Syphilis:** a grade 2 syphilis AE is defined as a positive treponemal test along with a positive non-treponemal test and no previous treatment OR a four-fold rise in titer on the non-treponemal test after previous treatment, regardless of symptoms, or non-oral lesions positive by darkfield exam for treponemes. Additionally, a confirmed positive treponemal test with a negative non-treponemal test without a prior history of treatment also constitutes a grade 2 syphilis adverse event. Report all syphilis adverse events, using the term "syphilis infection" (no anatomical location is required when reporting syphilis infections). Contact the MTN-035 PSRT in the event a participant has a positive treponemal test and a negative non-treponemal test, as this could represent late latent syphilis.

For participants with a vagina or neovagina:

- **Bacterial Vaginosis (BV):** Only report symptomatic infections that are confirmed with saline wet mount testing and that fulfill Amsel's criteria as AEs, using the

term “symptomatic bacterial vaginosis.” Asymptomatic BV will not be a reportable AE, but a diagnosis will be captured on the STI Test Results CRF.

- **Candidiasis:** Only report symptomatic infections that are confirmed with KOH wet prep and/or culture as AEs, using the term “vulvovaginal candidiasis.” Asymptomatic candida will not be a reportable AE, but a diagnosis will be captured on the STI Test Results CRF.
 - In the absence of a laboratory-confirmed STI or RTI diagnosis, use the term “vulvovaginitis” when two or more of the genital/vaginal signs or symptoms listed below are present. Grade the AE as per the “Vulvovaginitis” row in the DAIDS Female Genital Grading Table (Addendum 1). Comment on the individual signs/symptoms in the “Comments” field of the AE Log CRF.
 - pain
 - itching
 - erythema
 - edema
 - rash
 - tenderness
 - discharge
 - Similarly, use the term “cervicitis” when two or more of the genital/vaginal signs or symptoms listed below are present in the absence of a laboratory-confirmed STI/RTI. Grade the AE as per the “Cervicitis” row in the DAIDS Female Genital Grading Table (Addendum 1). Comment on the individual signs/symptoms in the “Comments” field of the AE Log CRF.
 - dyspareunia
 - erythema
 - edema
 - tenderness
 - discharge

8.2.2 Reporting Abdominal Pain as an AE

When reporting abdominal pain as an AE, pain that is gastrointestinal in nature must be differentiated from pain that is genitourinary, anorectal, or pelvic in nature.

If abdominal pain is assessed as gastrointestinal in nature and no other overarching or unifying diagnosis is available, the term “abdominal pain” should be used to describe the AE on the AE Log CRF.

If the pain is assessed as genitourinary and a specific anatomic location is known, the term reported on the AE Log CRF should be described as such (e.g., “bladder pain”).

If the pain is assessed as pelvic in nature and a specific anatomic location is known, the term reported on the AE Log CRF should be described as such (e.g., “adnexal pain”, “uterine pain”). Pain associated with menstruation is reproductive in nature and the term reported on the AE Log CRF should be described using the term “dysmenorrhea”.

If the pain cannot be localized to a specific organ but is believed to be gynecologic in origin it should be described on the AE Log CRF using terms that identify a reproductive or genitourinary anatomical location (e.g., ‘pelvic pain’).

If the pain is assessed as anorectal in nature and a specific anatomical location is known, the term on the reported on the AE Log CRF should be described as such (e.g., ‘anal pain’, ‘proctalgia’ or ‘rectal pain’).

8.2.3 Reporting Pelvic and Genital Examination Findings as AEs

In general, and unless otherwise specified in this manual, report pelvic and genital exam findings using terminology corresponding to the DAIDS Female Genital Grading Table and Male Genital Grading Table, respectively, and provided within the “Abnormal Findings” section of the corresponding CRF.

All AEs should be documented per the term marked on the Genital Exam Checklist. Always include the specific anatomical location of pelvic or genital exam findings in the AE term.

8.2.4 HIV and AE Reporting

HIV infection is not included in the DAIDS Toxicity Table and is not considered an AE for data collection or reporting purposes. Thus, if a participant seroconverts during study participation, “HIV” or “HIV infection” should not be reported as an AE or written anywhere on an AE Log CRF.

If a participant seroconverts and develops one or more signs or symptoms of acute HIV-infection, it is appropriate to report the sign(s)/symptom(s) as a single AE using ONLY the AE term “seroconversion illness” on the AE Log CRF. Use the comments section of the AE Log CRF to describe each HIV-related sign/symptom (e.g., fatigue, pharyngitis) and to note the alternative etiology as due to “acute HIV”. To avoid generating a clinical query, please ensure that the term “acute” is included when describing the required alternative etiology in the comments section.

Complete the other items on the AE Log CRF per the general form instructions. The onset date recorded should be completed using the date on which the participant first reported experiencing signs/symptoms of acute HIV infection. If there is more than one HIV-related sign/symptom, record the highest severity grade. A seroconversion illness AE is considered “resolved” when all associated signs/symptoms have resolved or returned to baseline, per participant report, and medications for the symptoms are no longer indicated. Mark any medication(s) indicated and taken for the associated symptoms, if applicable.

If one or more signs/symptoms, reported on separate AE Log entries, are later attributed to acute HIV infection, update the AE term for the earliest reported sign/symptom AE to the “seroconversion illness” diagnosis and list any other signs or symptoms in the comments section of this AE Log CRF. Inactivate the applicable AE Log line within Medidata Rave.

8.2.5 Reporting Sexual Assault

Any physical and/or psychological sequelae that result from a sexual assault reported during the study and that meet AE reporting criteria should be reported on the AE Log CRF. Each physical and/or psychological sequelae should be reported as its own AE, with the description of the physical and/or psychological sequelae as the AE text (i.e., do not mention sexual assault) and with sexual assault survivor (and additional details, if applicable), referenced in the “Comments” section of the AE Log CRF. In this instance, do not complete a separate AE log form for ‘sexual assault survivor’ as the AE term.

In the event that a participant reports a sexual assault that did not result in physical and/or psychological sequelae, the sites should report the event as a “Sexual Assault Survivor” as the AE text.

Sites should specify “survivor” when reporting a sexual assault event (e.g. “sexual assault survivor”), to clarify survivor of the assault and not perpetrator of the assault. Note that site staff should accept participant report of sexual assault rather than probing regarding this issue for the purposes of AE reporting. Sites should consult the PSRT if there are any questions about classification or documentation of a sexual assault.

Participants who disclose any form of violence by an intimate partner (or other family member) or sexual assault by any perpetrator should be offered immediate support, care, and referrals according to site-specific SOPs regarding intimate partner violence and sexual assault response. Generally, the response to reports of sexual assault should include first line support—listening and offering comfort, help, and information/referrals to connect the participant to services and social support—as well as offering the participant an opportunity to provide a complete history of events, and receive relevant physical evaluations and treatment and/or referral for any injuries. Emergency contraceptive (if indicated) and STI prophylaxis/treatment should be offered. Plans for continued follow-up and care should be outlined to check on the participant’s well-being and uptake of referrals, as appropriate.

8.3 Adverse Event Severity Grading

The term “severity” is used to describe the intensity of an AE. The severity of all AEs identified in MTN-035 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.

The severity of all AEs identified and/or reported will be graded using the following grading tables as noted in section 8.1 above.

The DAIDS Toxicity Tables can be accessed on the DAIDS RSC web site (<http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>)

8.4 Adverse Event Relationship Assessment

One of the following relationship categories must be assigned to each AE:

- Related: There is a reasonable possibility that the AE may be related to the study product.
- Not related: There is not a reasonable possibility that the AE is related to the study product.

For both “related” and “not related” assignments, a rationale (such as alternative etiology or explanation) is required to be provided within the “Comments” section provided for each AE. Recording “no other cause identified” is not adequate. Although an AE’s relationship status defers to clinician discretion, some clinical explanation is helpful in understanding the nature of the AE and in determining a more complete safety profile of the study product.

The relationship status of an AE may be changed if new information becomes available at a later date, after the AE is first reported, that would change the assessment. If the relationship status is changed at a later date, for example, due to receipt of a new test result that confirms a diagnosis, update the “Relationship to Study Product” item. Then, review the entire form for completeness and add additional rationale in the “Comments” field.

When recording an AE that is the result of a study-related procedure, the “Relationship to study product” should be selected as “Not Related” and an explanation provided in the “Comments” section that the event is a “result of a study-related procedure”.

8.5 Adverse Event Outcomes and Follow-Up Information: During Study Participation

All AEs identified in MTN-035 must be followed clinically at each scheduled visit until they resolve (return to baseline) or stabilize. “Stabilization” is defined as continuing at the same severity grade for one month.

The PSRT must be consulted regarding progression to the next product use sequence prior to initiation of study product use for Periods 2 and 3, for any participant who has unresolved pelvic, genital or anorectal AEs grade 3 or higher, and any other AE that, in the opinion of the IoR, would preclude the participant from continuing to the next product use period.

- At each follow-up visit, an authorized study clinician should review all previously identified ongoing AEs and evaluate and document its current status.
- Outcomes must also be reported on the AE Log CRF.
- In many cases, the final outcome of an AE will not be available when the AE Log CRF is first completed. In such cases, the status/outcome selected should be “recovering/resolving” until the final outcome becomes available or the participant terminates the study (whichever is earlier) at which point the “Outcome” on the form should be updated.

As noted above, “resolution” of an AE is generally defined as returning to the condition or severity grade that was present at baseline (i.e. at the time of randomization) and “stabilize” is defined as persistence of a certain severity grade (above baseline) for one month. For clinical events that are AEs, clinical management and follow-up of the AE should proceed per protocol section 9 (Clinical Management). More frequent evaluations may be performed at any time if required to properly monitor and/or manage participant safety, at the discretion of the IoR or designee. It is acceptable for AE follow-up/evaluation to be conducted over the phone, as clinically appropriate.

If an AE increases in severity per the DAIDS Toxicity Table after it has been initially reported on the AE Log, it must be reported as a new AE at the increased severity grade, per the DAIDS toxicity table, on a new AE Log CRF (i.e. a new log line in the study database). 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 on which the severity, per the DAIDS Toxicity Table, increased (see instructions for these items within the CRF Completion Guidelines for additional guidance).

Resolution dates for any AE requiring treatment should be based on the date when all associated symptoms resolve or when treatment is completed (whichever occurs later). For asymptomatic STIs, the resolution date is the date the participant completes treatment.

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

All AE Log CRFs completed for each participant should be reviewed at Visit 8 to confirm they were evaluated by qualified and designated staff, and that the relationship status, AE grade, and outcome are accurately documented in the participant's record.

For AEs that are ongoing at the termination visit, the status/outcome of the AE should be updated to "not recovered/resolved" on the AE Log CRF."

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

- AEs that are found to have increased in severity at the termination visit
- AEs deemed related to study product
- All grade 3 or higher AEs that are ongoing at the termination visit
- SAEs

The IoR or designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the AE must be re-assessed by study staff within 30 days after the termination visit; additional evaluations may also take place at the discretion of the IoR or designee.

For AEs that are ongoing at the termination visit but do not meet the criteria above, it is left to the discretion of the IoR or designee as to whether the AE needs to be followed. In such situations, sites may notify the Protocol Safety Physicians (mtn035safetymd@mtntopshiv.org) team for guidance.

If not resolved or stabilized at the time of reassessment, additional assessments should occur at the following frequency:

- If the study is ongoing, continue to reassess at least once per month while the study is ongoing until resolution/stabilization.
- If the entire study has ended (not only participant participation), all AEs requiring re-assessment will be re-assessed at least once within 30-60 days after the study end date. The site is to send an informational query regarding the case to the MTN-035 PSRT (mtn035psrt@mtntopshiv.org) at the time of reassessment. The PSRT also may advise on whether any additional follow-up is indicated on a case-by-case basis.

Documentation: for AEs that are re-assessed after the termination visit, information on the status of the AE at the time of re-assessment will be recorded in chart notes, and must be communicated to the PSRT using the PSRT query form or by email. However, no updates should be made to any CRF based on the re-assessments. The AE Log CRF should reflect the status of the AEs at the time of termination and should remain unchanged.

8.7 Reporting Recurrent Adverse Events

If an AE previously reported on an AE Log CRF resolves and then recurs, the second occurrence must be reported as a new AE on a new AE Log CRF (new log line in the study database).

Some participants may have chronic, episodic, pre-existing conditions. In these situations, if the participant experiences an episode of the condition during follow-up that has not increased in severity or frequency from the baseline condition, it would not be considered an AE. For example, if a participant reports having three migraines a month before study participation, and this continues at the same frequency and severity during the study, the migraines should not be reported as AEs.

An exception, however, relates to HSV ulcer outbreaks or HPV genital wart outbreaks. Any new outbreak will be considered an AE, even if the participant has a pre-existing herpes or HPV diagnosis/infection.

8.8 Social Harms

In addition to medical AEs, participants may experience social harms — non-medical adverse consequences — as a result of their participation in the study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends. They also could experience stigma or discrimination from family members and members of their community.

In the event a social harm occurs, study staff should fully document the issue(s) or problem(s) and make every effort to facilitate resolution. Social harms will also be documented on the Social Impact log CRF and supplemental information may be documented in the participant's chart. The IoR will report any social harm that s/he judges to be serious or unexpected to the PSRT and IRB according to local requirements. Social harms that result in SAEs should be considered "serious or unexpected." Social harms that are not SAEs but may be considered serious or unexpected include serious threats of physical harm, significant psychological duress, or discontinued provision of food, housing or financial support. Determination of whether a social harm is serious or unexpected is at the discretion of the IoR or designee; the MTN-035 PSRT can always be consulted as needed. 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 should discuss as a group 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, study staff teams 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.
- Ask the participant to articulate his/her thoughts on what can/should be done to address the problem, including what s/he would like study staff to do in response to the problem (if anything).
- Discuss with the participant any additional or alternative strategies that you might suggest to address the problem, and collaborate with the participant 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.
- If the reported social harm is associated with an AE, report the AE on an AE Log CRF. Also report the issue or problem to all IRBs/ECs responsible for oversight of MTN-035, if required per IRB/EC guidelines.
- Consult the PSRT for further input and guidance as needed. As is the case with medical AEs, data collected on social harms will be monitored by the PSRT.

8.9 Safety Monitoring, Review, and Oversight

Please refer to protocol section 8 (Assessment of Safety) for a complete description of the participant safety monitoring procedures in place for MTN-035. SSP section 14 provides a description of the reports prepared by the MTN SDMC in support of safety monitoring procedures.

Participant safety is of the utmost importance in MTN-035. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study staff, under the direction of the IoR. The IoR and designated study staff also are responsible for submitting CRFs to the MTN SDMC, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- The MTN SDMC will review clinical and laboratory data received at the SDMC and issue clinical data queries for data requiring confirmation, clarification, or further follow-up by sites. These queries will be issued directly in the study database for site staff to resolve (within the database) on an ongoing basis throughout study implementation. In addition, protocol safety physicians may contact site staff directly, if needed, for additional clarification of safety data.
- The PSRT will routinely review study safety data reports prepared by the SDMC. The PSRT will hold monthly conference calls to discuss cumulative study safety data and any potential safety concerns.
- The MTN Study Monitoring Committee (SMC) will also conduct interim reviews of study progress, including rates of participant accrual and retention, completion of study endpoint assessments, study or lab issues, and in a closed report, safety data per study arm. 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 MTN leadership that could affect the study and sites in significant ways. These decisions are based on a detailed review of the available study data and careful consideration of ongoing participant safety.

Section Appendix 8-1 MTN-035 Protocol Safety Review Team Plan

Responsibilities of the PSRT

The responsibilities of the MTN-035 PSRT are to:

1. Conduct regular reviews of standardized study safety data reports. Once the SDMC begins receiving follow-up safety data, the PSRT will convene via regularly-scheduled monthly conference calls. The frequency of calls may be adjusted throughout the period of study implementation as agreed upon by the PSRT. Should any safety concerns be identified by the PSRT, these will be referred to the Protocol Team and SMC, as appropriate.
2. Respond to queries regarding product use management, including temporary holds and permanent discontinuation of study product.
3. Respond to queries regarding AE assessment, reporting, and/or management.
4. Respond to investigator notification of participant withdrawal from the study.

Respond to queries regarding study eligibility and/or re-joining a study participant who previously withdrew consent

PSRT Composition

The following comprise the MTN-035 PSRT:

- Protocol Chair
- MTN Protocol Safety Physician(s)
- DAIDS Medical Officer (MO)
- Representative(s) from CONRAD

Ideally, all members of the PSRT will participate in routine conference calls. At a minimum, the DAIDS Medical Officer (or designee if DAIDS MO is not available), the Protocol Chair, and MTN Safety Physician, must take part in all calls to reach quorum. If these members are not present, the call may be deferred until the next scheduled call time unless a PSRT member requests an immediate call.

MTN LOC (FHI 360) Clinical Research Managers, SDMC Clinical Data Manager, and site investigators and study coordinators may attend PSRT calls as observers and/or discussants.

The SDMC Clinical Safety Associate (CSA) serves as the primary liaison between the PSRT and the SDMC. The CSA will participate in the PSRT calls, and, based on PSRT discussion and request, will place clinical queries in the study database and communicate with sites as needed. The CSA will also bring to the calls for discussion any data trends or issues observed in the context of routine study clinical data reviews.

PSRT Communications

Site consultation with the PSRT will be facilitated using the MTN-035 PSRT Query Form, which is available in the Study Implementation Materials section of the MTN-035 web page. Site staff will email completed query forms to the Protocol Safety Physicians (mtn035safetymd@mtnstopshiv.org) who will work with the PSRT to prepare a consensus response to the query, and then email the final response to the site. A group email address (mtn035psrt@mtnstopshiv.org) will be used to facilitate communication with the PSRT. All PSRT communications will be facilitated using this email address. The PSRT review process is expected

to occur within three business days. When necessary, site requests for responses within one business day can usually be accommodated. All members of the PSRT are encouraged to review the information provided by the site in the query form and to contribute to the response; however, final determination rests with the Protocol Chair.