

Section 9. Adverse Event Reporting and Safety Monitoring

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9 Introduction

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-037.

9.1 Adverse Event Reporting and Safety Monitoring

Please also refer to Protocol Section 8 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 (FGGT)
 - Addendum 2: Male Genital Grading Table for Use in Microbicide Studies
 - Addendum 3: Rectal Grading Table for Use in Microbicide Studies (Clarification dated May 2012)
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, January 2010

- DAERS Reference Guide for Site Reporters and Study Physicians
- Investigators Brochure for PC-1005 Gel (current version and any subsequent updates)

9.1.1 Adverse Events

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

For MTN-037, the ICH-E6 definition is applied to all participants, 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 Baseline Medical History Log (whether they are ongoing at enrollment or not). If any condition is ongoing at the time of enrollment, it is a baseline medical history 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 IoR to complete AE Log CRFs. 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.

9.1.2 Serious Adverse Events (SAEs) / Expedited Adverse Events (EAEs)

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 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.

SAEs are a subset of all AEs. For each AE identified in MTN-037, 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.

All AEs that meet the definition of “serious” (SAEs), regardless of relationship to study product, are expedited adverse events (EAEs). Seriousness is the only consideration in determining whether an AE meets the definition of an EAE. EAEs require additional reporting for rapid review and assessment by DAIDS (see section 8.2). In some cases, DAIDS may be required to report an EAE to the US FDA.

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

Expedited Adverse Events (EAEs) should be reported per the Manual for Expedited Reporting of Adverse Events to DAIDS, version 2.0; January 2010.

For MTN-037, the “SAE (Serious Adverse Event) Reporting Category” will be used to report EAEs.

All EAEs must be reported to the DAIDS Regulatory Support Center (RSC) using the internet-based DAIDS Adverse Experience Reporting System (DAERS). All EAEs must be reported within three reporting days of site awareness of the EAE. All EAEs must also be reported on the AE Log CRF; a specific question on the AE Log CRF denotes whether the AE is also being reported as an EAE.

When completing the AE Log CRF and DAERS report, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness and consistency.

All AE descriptions and details (e.g., AE verbatim term, onset date, severity grade, relationship to study product, and status/outcome) must be recorded consistently across both documents.

All EAEs submitted to the DAIDS RSC will be compared with AE Log CRFs received at the MTN SDMC to ensure that all reports that should have been received by both DAIDS Safety Office and the SDMC have been received and that the details recorded on each form are consistent.

If an EAE that was previously reported to the DAIDS RSC resolves and then later recurs at a level requiring expedited reporting, the second occurrence must be reported as a new EAE report (and on a new AE LOG CRF (new log line in the study database), if not already completed).

For each EAE reported to DAIDS, sites are required to submit an updated report to DAIDS as soon as significant additional information becomes available. Note that updates made to EAE reports should also be made to the corresponding AE Log CRF, as applicable. Similarly, any updates made to an AE Log CRF should also be made to the corresponding EAE report, as applicable. 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 AE (this is particularly important for new information addressing cause of death if the initial assignment was “pending”)
- Any change in the assessment of the severity grade of the AE

- An update including the final or stable outcome, unless the initial SAE submitted had a final or stable outcome noted already

Note that although assessment of a change in the severity grade or the relationship between the AE and the study product does not require a new EAE form, it must be reported on a new AE Log CRF to the SDMC (as described previously).

9.2 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in MTN-037. The guidance below should be followed when assigning AE terms/descriptions:

- When there is evidence of rectal bleeding, this AE should be documented as ‘rectal bleeding’. Do not use the terms ‘anal bleeding’ or ‘hematochezia’.
- 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.
- Whenever possible, use specific terms to indicate the anatomical location of the AE (e.g., “rectal ulcer,” “vaginal” instead of “genital”).
- Use medical terms and correct spelling of such terms
- Do not use abbreviations, unless the abbreviations are for accepted laboratory findings (e.g. “AST increased”, “SGOT decreased”)
- 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.
- 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 gel leakage by itself is not an AE and should not be reported on an AE Log CRF. However, any untoward effect the gel or gel leakage has on a participant – for example, “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.
- The Rectal Grading Table requires biopsy confirmation in order to report an AE under the diagnosis of “proctitis.” If a biopsy is not done or is pending, report each associated symptom (e.g., abdominal pain) as a separate AE on its own AE Log CRF.
- Seasonal allergies should be graded according to the “estimating severity grade” row of the Toxicity Table (not the “acute systemic allergic reaction” row).
- Any event that occurs as a result of a study-related procedure should be recorded as an AE.
 - Specify in AE text description if the AE is related to a procedure (iatrogenic).
 - For example, “rectal bleeding due to rectal biopsy” or “anal fissure due to applicator trauma.” This information must be documented in the AE text on the AE Log CRF (and not in the comments section) in order for the AE to be properly coded and appear correctly in the safety reports.
 - For example, if a participant experiences rectal bleeding that is more than expected as a result of the biopsy, then “rectal bleeding due to rectal biopsy” should be submitted as an AE.

AEs not listed in any of the above-mentioned grading tables should be graded according to the “estimating severity grade” row 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 adverse events per the “estimating severity grade” row (i.e. for AEs not listed specifically in the FGGT or DAIDS Toxicity table), ‘intervention’ should be defined as outlined in the “Glossary and Acronyms” section of the Toxicity Table 2.0: “medical, surgical or other procedures 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) vs. provider-recommended (Grade 2). Importantly, clinicians should note that grading is dependent on participant-reported impact of symptoms on his/her life, and whether intervention (defined as above) is indicated, regardless of whether the treatment was actually provided or taken by the participant. It is at the discretion of clinician to determine whether intervention was indicated for the reported AE. In the event that a (provider-recommended) intervention was indicated but not taken, the treatment should be marked as “other” rather than ‘medications’ and additional details should be included in the line provided. The AE severity grade, per the toxicity table, would be assigned 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 row of the Toxicity Table. If culture and/or microscopy are done per site standard of care, Grade 1 and Grade 2 UTI can be graded per the UTI row of the applicable male or female microbicide grading tables.
- Abnormal Pap smear findings should be initially reported and graded based on the “Pap” row of the FGGT (see below). AGC and AGC-favor neoplastic are not specifically mentioned in the “Pap” row, but should be assigned severity grades 1 and 2, respectively. If abnormal cytology uncovered at screening is followed by a biopsy during follow-up, sites should report an AE for the histologic diagnosis IF the biopsy result is a higher grade than the baseline pap smear. For example, consider a participant who has an LGSIL pap result (grade 1) at screening and undergoes a colposcopy with biopsy at month 6. If the biopsy result is grade 1, no AE need be reported; HOWEVER, if the biopsy result is grade 2 or higher, an AE should be submitted using the histologic diagnosis (CIN II, for example).

PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Intraepithelial Neoplasia by biopsy (VIN, CIN, VAIN)	None	Intraepithelial Neoplasia 1 (IN1)	Intraepithelial Neoplasia 2 (IN2)	Carcinoma in situ (CIS)	Invasive carcinoma
Pap (use this category <u>only</u> if treatment performed without diagnostic testing, otherwise use biopsy category above)	nl PAP	ASCUS or LSIL	HSIL	Carcinoma in situ or Carcinoma	NA

Procedures 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 adverse event, “appendicitis” would, with “appendectomy” documented as a treatment provided for the adverse event. 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 form. 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.

9.2.1 Reporting Genital, Genitourinary, and Reproductive System AEs

Vaginal Discharge: Vaginal discharge by participant report and vaginal discharge as observed by the clinician should be graded per the appropriate rows in the FGGT. The verbatim term from the FGGT should be used to distinguish if vaginal discharge was clinician observed versus participant reported.

** Note – if vaginal 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 discharge by participant report' as the AE term.

Vaginal bleeding: For MTN-037, genital bleeding that is different from baseline ((i.e. longer, heavier, more/less frequent per participant assessment) and not attributable to contraceptive use or her menstrual cycle (per clinician assessment) should be captured as an AE. Record the newly-identified bleeding within the AE Log CRF. Grade and term the episode per the applicable Toxicity Table category, "Abnormal Uterine Bleeding Unrelated to Pregnancy" or the "Unexplained Infrequent Bleeding" row of the DAIDS FGGT (menorrhagia, metrorrhagia, or postcoital bleeding). Note that *shorter* than baseline menses is not included in the FGGT, and should not be considered an AE

In the event a baseline bleeding condition resolves during follow-up (e.g. a participant with amenorrhea at baseline resumes her menstrual cycle after stopping her contraceptive method), document the resolution in chart notes, but do not update the Baseline Medical History Log CRF. If the change in bleeding is determined to be related to a participant's contraceptive method, then per protocol this is not reportable as an AE.

Recurrent bleeding AEs in follow-up: Once a bleeding AE has been reported, each subsequent bleeding episode should be assessed to determine whether the episode is consistent with previously reported bleeding AEs, or if it is the first of its kind. Clinician discretion should be used to determine if a new AE needs to be documented or if a previously reported AE is ongoing.

- As needed, update the AE Log CRF to be 'ongoing' The dates of each irregular bleeding episode do not need to be recorded on the AE Log CRF, but should be captured in source documentation.
- If reviewing files in retrospect within Medidata Rave, inactivate any AE Log CRFs completed for bleeding episodes that can be subsumed under the AE that was initially reported for the event. When/if any AEs are inactivated, clearly document the rationale in the relevant source documents.
- If applicable, review and update the Concomitant Medications CRF "Taken for a reported AE?" and "Applicable Adverse Event #" to ensure that no deleted/inactivated AEs are indicated on the form.

If a participant has an ongoing (recurrent) bleeding AE, a pelvic exam is not required each time the participant reports the same ongoing bleeding, provided that the clinician assesses the bleeding to be consistent with the bleeding captured by the ongoing AE. If the AE increases in severity per the DAIDS Grading Table, a new AE Log CRF should be completed to document this change in severity.

When reporting genital bleeding events, reference should be made to the points below, which standardize the terminology that should be used when reporting AEs involving genital bleeding.

- Bleeding at the time of BD™ Luer-Lok™ Tip syringe with cap and rectal administration tip use, speculum, anoscope, or flexible sigmoidoscope insertion/removal and/or biopsy collection that is

judged by the clinician to be within the range of normally anticipated will not be reportable as an AE. If the bleeding is of greater quantity or longer duration than considered normal by the clinician, it should be considered an AE. If applicable, bleeding should be reported using the term cervical friability. The severity of cervical friability should be graded per the cervical edema and friability row of the DAIDS FGGT.

- If both Menorrhagia and Metrorrhagia are present, a single adverse event should be reported as “Menometrorrhagia” and graded per the Menorrhagia row of the FGGT.
- Bleeding that is associated with an observed abnormal pelvic exam finding should be considered an AE and should be documented and reported if applicable using the term associated with the exam finding, with the anatomical location noted. For example, if a vaginal laceration is observed on exam, with blood emanating from the finding, the term “vaginal laceration” should be used to document the AE. The fact that blood or bleeding was present should be documented on the Pelvic Exam Diagrams form and the Pelvic Exam CRF, and may also be noted in the comments section of the AE Log CRF, but the term “metrorrhagia” should not be used to document the AE.
- The term metrorrhagia should be used to refer to vaginal bleeding that meets AE reporting criteria that is not menses related and is not associated with an observed pelvic exam finding. For example, the term could be used to report bleeding of variable amounts occurring between regular menstrual periods such as spotting between menses, ovulation bleeding, and breakthrough bleeding. This term should also be used to report blood-tinged discharge and blood observed in the vagina with no identified source. Note that bleeding determined to be related to a participant’s contraceptive method is not reportable as an AE.
- If a participant reports genital bleeding after sexual intercourse, this event should be recorded as “postcoital bleeding” and graded per the “Postcoital Bleeding” row of the DAIDS Female Genital Grading Table.

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 STI diagnosis is based on clinical evaluation and confirmed, when appropriate/possible, by laboratory result(s).

- 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 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 it thought to be due to prior herpes diagnosis/infection.
 - Suspected genital herpes outbreak should be reported using the term marked on the Pelvic Exam CRF or the Anorectal 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” anal condyloma” if applicable and include the anatomical location of the warts (e.g., cervical, vaginal, perianal).
- **Syphilis:** a Grade 2 Syphilis adverse event 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-037 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 female participants:

- **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.”
- **Candidiasis:** Only report symptomatic infections that are confirmed with KOH wet prep and report these as “vulvovaginal candidiasis.”
 - In the absence of a laboratory-confirmed STI or RTI diagnosis, use the term “vulvovaginitis” when 2 or more of the genital/vaginal signs or symptoms listed below are present. Grade the AE as per the “Vulvovaginitis” row in the FGGT. 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 2 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 FGGT. Comment on the individual signs/symptoms in the “Comments” field of the AE Log CRF.
 - dyspareunia
 - erythema
 - edema
 - tenderness
 - discharge

9.2.2 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 pelvic, or anorectal, 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 (i.e., “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 (i.e, ‘anal pain’, ‘proctalgia’ or ‘rectal pain’).

9.2.3 Reporting Pelvic Examination Findings as AEs

In general, and unless otherwise specified in this manual, report pelvic exam findings using terminology corresponding to the FGGT and provided within the Abnormal Findings section of the Pelvic Exam CRF.

All AEs should be documented per the term marked on the Pelvic Exam form. Always include the specific anatomical location of pelvic exam findings (e.g., cervical, vaginal, vulvar) in the AE term.

9.2.4 Reporting Laboratory Abnormalities as AEs

If an abnormal laboratory test result is reported as an AE, separate from any clinical diagnosis associated with the result, the type of test performed and the direction of the abnormality should be reported (e.g. elevated ALT). The specific value or the severity grade of the result should not be reported as part of the AE term.

Laboratory values that fall outside of a site’s normal range but are below severity grade 1 are not considered AEs. These out of range, but below grade 1, values are not documented as pre-existing conditions (on the Baseline Medical History Log CRF) or adverse events (on the AE Log CRF) unless requested by the IoR or designee. These laboratory results can be identified as “NCS” (Not Clinically Significant) in the source documentation, if determined by a study clinician.

When assigning severity grades, note that some sites may have normal reference ranges that overlap with the severity grade ranges. Thus, it is possible for a participant to have a result that falls within the site’s normal range, but is still gradable per the Toxicity Table. Assign the severity grade based on the Toxicity Table severity grade ranges, regardless of whether or not the lab result falls within the site’s normal reference range.

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

9.2.5 HIV and AE Reporting

HIV infection is not included in the 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 these sign(s)/symptom(s) as a single AE using ONLY the term “seroconversion illness” for the AE term 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 comment section.

Complete the other items on the AE Log CRF per the general form instructions. The onset date should be completed using the date on which the participant first reported experiencing the first sign/symptom 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 the associated signs/symptoms have resolved or returned to baseline per participant report, and medications for the symptoms are no longer indicated. Mark any medications 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 eCRF. Inactivate the applicable AE Log line within Medidata Rave.

9.2.6 Reporting Sexual Assault

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

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, response to reports of sexual assault should include first line support—listening and offering comfort, help, and information/referrals to connect him/her 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 and STI prophylaxis/treatment should be offered. Plans for continued follow-up and care should be outlined to check in on the participant’s well-being and uptake of referrals, as appropriate.

9.3 Adverse Event Severity Grading

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in MTN-037 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:

- 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 (FGGT)
 - Addendum 2: Male Genital Grading Table for Use in Microbicide Studies
 - Addendum 3: Rectal Grading Table for Use in Microbicide Studies (Clarification dated May 2012)

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

9.4 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. When an AE is assessed as "Not Related" to the study product, an alternative etiology, diagnosis, or explanation (for example, "not biologically plausible") must be provided in the AE "Comments" field. When an AE is assessed as "Related" to the study product, a rationale must be provided in the "Comments" field. Note that 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 adverse event 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 later, after the AE is first reported, that would change the assessment. If the relationship status is changed later, 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'.

Per protocol, study staff who apply gel rectally are not to be the same staff who assess the participant's safety. This assessment should be completed prior to gel administration at applicable visits. At a minimum, site staff should inquire whether the participant has experienced any symptoms or discomfort since the last visit (by participant report is acceptable).

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

All AEs identified in MTN-037 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 1 month. All AEs grade 2 or higher judged to be related to study product should be reduced to Grade 1 or resolved prior to administering the next study gel dose in the series (Visit 5 and 7). In the event an AE has not returned to Grade 1 or resolved at the time a dosing visit is scheduled to occur, the PSRT should be consulted prior to administering the next dose.

- 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 should be selected “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 at 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 the specifications of Protocol Section 9. 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 reported initially on the AE Log, it must be reported as a new AE at the increased severity 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 “recovered/resolved.” 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 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.

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

All AE Log forms 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 record.

For AEs that are ongoing at the Final Contact Visit (V9) when the participant terminates the study, 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 final contact visit. AEs that require reassessment after the participant's termination visit include the following:

- New AEs and 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/EAEs

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

For AEs that are continuing 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. Sites may notify the Protocol Safety Physicians (mtn037safetymd@mtnstopshiv.org) team for guidance in such situations. The requirements for submission of follow-up information on EAEs are specified in Section 4.3 of the *Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0 dated January 2010)*.

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 PSRT at the time of reassessment. The MTN-037 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.

9.7 Reporting Recurrent Adverse Events

If an AE previously reported on an AE Log CRF resolves and then recurs later, 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 his/her baseline condition, it would not be considered an AE. For example, if a participant reports that they have three (3) migraines a month before the study, and they continue at the same frequency and severity during the study, these migraines should not be reported as AEs.

An exception to this rule, 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.

9.8 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 in the participant's chart. The IoR will report any social harm, in his/her judgment, to be serious or unexpected to the PSRT and IRB according to local requirements. Social harms that result in serious adverse events (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-037 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. If the social harm is associated with an AE that meets criteria for expedited reporting to the DAIDS RSC, report it as an EAE. Also report the issue or problem to all IRBs/ECs responsible for oversight of MTN-037, 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.

9.9 Safety Distributions from DAIDS

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

- Updated Investigators Brochures
- IND Safety Reports
- Other safety memoranda and updates

Each distribution will include a cover memo providing instructions on how the document is to be handled. In all cases, a copy of the distribution must be filed in on-site essential document files and study staff responsible for clinical oversight of study participants should be made aware of any newly available safety information. In many cases, the distribution will need to be submitted to site IRBs/ECs. Safety distributions do not require IRB/EC approval, however acknowledgement of receipt is desirable. Submission letters/memos for IRB/EC submissions should specify the name and date of all documents submitted.

9.10 Safety Monitoring, Review, and Oversight

Please refer to Protocol Section 8 for a complete description of the participant safety monitoring procedures in place for MTN-037. SSP Section 14 is a reference for 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-037. 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 and EAE reports to DAIDS, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- Staff at the MTN SDMC will review clinic and laboratory data received at the SDMC and apply clinical data queries to data requiring confirmation, clarification, or further follow-up by site staff. These queries will be applied directly in the study database for site staff to resolve (within the database) on an ongoing basis throughout the period of study implementation. In addition, Protocol Safety Physicians may contact site staff directly, if needed, for additional clarification of safety data.
- The DAIDS RSC, DAIDS RAB Safety Specialist, and DAIDS PSP Medical Officer will review all EAE Forms received and follow up on these reports with site staff, the Protocol Team, and drug regulatory authorities when indicated.
- The PSRT will routinely review safety data reports prepared by the SDMC for the study. The PSRT will meet monthly conference call to discuss cumulative study safety data and any potential safety concerns.
- The MTN Study Monitoring Committee (SMC) also will 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 by arm of the study. While site staff are not typically involved in these reviews, site staff should be aware that the SMC may make recommendations to DAIDS and/or the MTN leadership that could affect the study and sites in significant ways. These decisions are based on a detailed review of the available study data and careful consideration of ongoing participant safety.

9.10.1 MTN-037 Protocol Safety Review Team

Roles and Responsibilities of the PSRT

The roles and responsibilities of the MTN-037 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports. Once the SDMC begins receiving follow-up safety data, the PSRT will convene via regularly scheduled monthly conference calls. The frequency of calls may be adjusted throughout the period of study implementation as agreed upon by the PSRT. Should any safety concerns be identified by the PSRT, these will be referred to the Protocol Team and MTN Study Monitoring Committee (SMC) as appropriate.
2. Respond to queries regarding product use management, including permanent discontinuation of study product use.
3. Respond to queries regarding adverse event (AE) assessment, reporting, and/or management.
4. Respond to investigator notification of participant withdrawal from the study
5. Respond to queries regarding study eligibility and/or re-joining a study participant who previously withdrew consent

PSRT Composition

The following individuals comprise the core members of the MTN-037 PSRT:

- Craig Hendrix, Protocol Chair
- Katie Bunge, MTN Protocol Safety Physician
- Devika Singh, MTN Protocol Safety Physician
- Jeanna Piper, DAIDS Medical Officer
- George Creasy, Population Council Medical Director
- Mohcine Alami, Global Head of Safety for Population Council

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 a MTN Safety Physician, must take part in all calls to reach quorum. If these members are not present, the call may be deferred until the next scheduled call time unless a PSRT member requests an immediate call.

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.

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

PSRT Communications

Site consultation with the PSRT will be facilitated using the MTN-037 PSRT Query Form, which is available in the Study Implementation Materials section of the MTN-037 web page. Site staff will email completed query forms to the Protocol Safety Physicians (mtn037safetymd@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. This 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 MTN Safety Physician.