Section 8. Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-030/IPM 041. Please also refer to Section 8 of the protocol and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table)
- Addendum 1-DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT)
- Manual for Expedited Reporting of Adverse Events to DAIDS
- DAERS Reference Guide for Site Reporters and Study Physicians
- Investigator's Brochure for Dapivirine-Levonorgestrel Vaginal Ring

8.1 Definitions and General Reporting Guidance

8.1.1 Adverse Event (AE)

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

For MTN-030/IPM 041, this definition applies to each and every participant, beginning at the time of enrollment/randomization through when she terminates from the study.

8.1.2 Reporting Adverse Events

Per Section 8.3 of the MTN-030/IPM 041 protocol, study staff will report on the AE Log CRF all AEs reported by or observed in enrolled study participants regardless of severity, presumed

relationship to study product or expectedness. However, changes in genital bleeding during follow-up *will not be* reportable as an AE, unless also deemed to be a Serious Adverse Event (see Section 8.1.3).

Each site's SOP for source documentation should define the extent to which the AE Log CRF will be used as the source document for the data elements on the form.

Documentation of site-specific delegation of duties should designate study staff authorized by the IoR to complete the AE Log CRF. Regardless of who initially completes the form, a clinician listed on the site's FDA Form 1572 should review each AE Log CRF to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

If, at any time, site staff have questions about participant safety or reporting clinical events, they should send an email to the MTN-030/IPM 041 Safety Physicians at mtn030safetymd@mtnstopshiv.org.

8.1.3 Serious Adverse Events (SAEs)

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

1. Results in death,
2. 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. When determining whether a grade 4 event meets the ICH definition of "life threatening", consider the event in the context of any related symptoms the participant may have experienced.
3. Requires inpatient hospitalization or prolongation of 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) or admission for diagnosis or therapy of a condition that existed before randomization (i.e., enrollment for MTN-030) AND has not increased in severity or frequency since baseline.
4. Results in persistent or significant disability/incapacity,
5. Is a congenital anomaly/birth defect,
6. Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition 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 and that "important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definition above" should also be considered serious. SAEs are a subset of all AEs. For each AE identified, an authorized study clinician must determine whether the AE meets the definition of a SAE. The AE Log CRF includes an item to record this information.

All AEs that meet the definition of "serious" (SAEs), regardless of relationship to study product, are expedited adverse events (EAE) and require additional reporting for rapid review and assessment by DAIDS.

8.1.4 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-030/IPM 041, 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. The definition of a "reporting day" is as follows:

- Monday through Friday
- Saturday and Sunday are not considered reporting days.
- Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday
- A reporting day starts at 12:00 AM (midnight) and ends at 8:59 PM local time (in the site's time zone).
- The day site personnel become aware that an AE has met the definition of an EAE shall count as day 1 if that day occurs on a reporting day (i.e., Monday through Friday). This is true, regardless of the time of the day site personnel become aware of the EAE. If the day site personnel become aware of the EAE is a non-reporting day (i.e., Saturday or Sunday), then the next reporting day shall count as day 1.

All EAEs must also be reported on the AE Log CRF. The AE Log CRF includes an item to record if the AE is also being reported as an EAE. When completing the AE Log CRF and DAERS report or EAE form, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness and consistency. All AE descriptions and details (e.g., AE verbatim term, onset date, severity grade, relationship to study product, and status/outcome) must be recorded consistently across all documents to the extent possible. All EAEs submitted to the DAIDS Safety Office 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).

In the event that DAERS cannot be accessed (e.g., due to poor internet connectivity), paper-based EAE reporting should be used, per instructions provided in the Manual for Expedited Reporting of Adverse Events to DAIDS. Completed paper EAE Forms may be faxed or digitally scanned and emailed to the DAIDS RSC via email. The EAE Form and form completion instructions are available on the DAIDS RSC web site (http://rsc.tech-res.com). Contact details for submission of EAE Forms to the RSC are provided in the Manual for Expedited Reporting of Adverse Events to DAIDS.

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 documenting the AE, as applicable (i.e., for changes that occur on study, prior to participant study termination). 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.
- Results of re-challenge with the study product, if performed

Note: A new EAE form does not need to be submitted for any change in the assessment of the severity grade or the relationship between the AE and the study product. However, an increase in severity must be reported as a new AE to the SDMC.

8.2 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in MTN-030/IPM 041. The guidance below should be followed when assigning AE terms/descriptions:

- Whenever possible, a diagnosis should be assigned. 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., "vaginal" instead of "genital" or "uterine cervix" instead of "cervical").
- Use medical terms (e.g., "ulcers" instead of "sores")
- Ensure correct spelling
- Do no use abbreviations, unless the abbreviations are for accepted laboratory findings (e.g., "AST increased", "SGOT decreased")

Procedures per se should not be reported as adverse events; rather the underlying condition which leads to a procedure may be considered an adverse event. Any associated procedures may be considered treatments for the adverse event. For example, while "appendectomy" would not be considered an adverse event, "appendicitis" would, with "appendectomy" documented as a treatment provided for the adverse event. In addition, 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, if a participant experiences dizziness from a blood draw, then "dizziness due to blood draw" should be submitted as an AE.

Do not include information on 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. Including text such as "after ring insertion" or "at site of ring placement" affects the way the AE is MedDRA-coded, and thus, how it will appear in safety reports.

When reporting an AE which are due to ring removal or insertion, please follow the guidance below:

- If the AE is **due to the act** of study ring insertion or removal, include this information in the AE text description. For example, use AE text of "pelvic pain due to ring removal" or "vulvar laceration due to ring insertion" rather than just "pelvic pain" or "vulvar laceration."
    - It is important to specify in the AE text description if an AE is due to the act of study ring insertion or removal, as these AEs are assigned unique coding terms within the standardized MedDRA coding system.
- If an AE is **not** due to the act of study ring insertion or removal, do not include mention of the ring in the AE text description.
- If the text present in the "Comments" field indicates that the AE is due to the act of ring insertion or removal, this same text needs to be present in the AE text description for MedDRA coding purposes. If not, this may result in a clinical data query asking that this information be added to the AE text description so that the AE is described completely and accurately.

Sites should include text in the “Comments” field explaining why the AE has been judged “related” to study product use.

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.

8.2.1 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 (see below). The verbatim term from the FGGT should be used to distinguish if vaginal discharge was first observed by the site clinician or reported by the participant.

PARAMETER	Grade 0 NORMAL	Grade 1 MILD	Grade 2 MODERATE
Vaginal discharge by participant report	Participant's usual amount of discharge, regardless of color or quantity	Mild-moderate increase in amount above participant baseline - no sanitary protection required	Profuse increase in discharge requiring pad use or other hygienic intervention
Vaginal discharge as observed by clinician (red or brown discharge should be reported under bleeding, not discharge)	Slight amount of discharge, any color	Mild-moderate increase in amount	Significant increase in amount with pooling in vagina on examination

Note – if vaginal discharge is both reported by a participant and observed during pelvic examination, only report the one with the highest severity grade. If they are the same grade, report ”vaginal discharge by participant report” as the AE term. Grade 3 and 4 vaginal discharge are listed as “NA” in the FGGT, and thus are not pictured here.

Genital bleeding: Genital bleeding other than menstrual bleeding, often referred to as intermenstrual bleeding (IMB), is a common occurrence among reproductive age women, and often is of physiologic or benign etiology. The Vaginal Bleeding Assessment CRF is completed at all scheduled follow-up visits, and is used to assess for and document any and all vaginal bleeding events experienced by participants. Genital bleeding events are not reportable as adverse events for MTN-030/IPM 041, unless they are also deemed to be SAEs. Vaginal and/or cervical bleeding associated with speculum insertion and/or specimen collection is likewise not considered to be an adverse event.

If bleeding is associated with an observed abnormal pelvic exam finding, sites should document the abnormal exam finding and its anatomical location. For example, if a vaginal laceration is observed on exam, and there is bleeding attributable to the laceration, the term “vaginal laceration” should be used to document the AE. The fact that blood or bleeding was present should be documented on the site’s pelvic exam source document (e.g., Pelvic Exam CRF and/or Pelvic Exam Diagrams), and may also be noted in the comments section of the AE Log CRF.

8.2.2 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). For example, symptomatic bacterial vaginosis and symptomatic vulvovaginal candidiasis should not be reported as AEs based on participant symptoms alone.

- Bacterial vaginosis: Only report symptomatic infections that are confirmed with saline wet mount testing and fulfilling Amsels criteria as AEs, using the term "symptomatic bacterial vaginosis."
- Candidiasis: Only report symptomatic infections that are confirmed with KOH wet prep and/or culture as AEs, using the term "vulvovaginal candidiasis."
- Chlamydia: Report all infections using the term "genitourinary chlamydia infection."
- Gonorrhea: Report all infections using the term "genitourinary gonorrhea infection."
- Suspected genital herpes outbreaks: Because herpes testing is not required in MTN-030/IPM 041, each suspected genital herpes outbreak should be reported as an AE using the term marked on the Pelvic Exam CRF describing the lesion, together with the anatomical location (e.g., "vulvar ulceration", or "vaginal blister").
- Genital herpes: The criterion for diagnosing genital herpes per the FGGT is below. 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 it thought to be due to prior herpes diagnosis/infection.

PARAMETER	Grade 0 NORMAL	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	Grade 4 POTENTIALLY LIFE-THREATENING
Genital herpes	No lesions	Characteristic ulcerative or vesicular lesions confirmed by culture, PCR, Tzanck prep or other diagnostic test of lesion or previous type-specific serology, covering < 25% of vulva, vagina, or cervix	Same criteria as mild but covering 25-50% of vulvar, vaginal, or cervical surface	Same criteria as mild but covering > 50% of vulvar, vaginal, or cervical surface	Symptoms of significant systemic involvement, e.g., encephalitis, hepatitis

- Genital warts: Report all new outbreaks of genital warts as AEs, regardless of whether infection with HPV was known to be pre-existing before enrollment. Report the AE using the term "condyloma" and include the anatomical location of the warts (e.g., cervical, vaginal, vulvar, perianal). Grade according to the "Condyloma" row of the FGGT.
- Syphilis: Per the FGGT, 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. Report all syphilis adverse events, using the term "syphilis infection" (no anatomical location is required when reporting syphilis infections).
- Trichomoniasis: Report only Grade 2 infections per FGGT, using the term "vaginal trichomoniasis". Trichomoniasis may be diagnosed by positive wet mount, culture, PCR, Trichomoniasis or other licensed test (excluding Pap smear) showing T. vaginalis, regardless of symptoms.

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. 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. Comment on the individual signs/symptoms in the “Comments” field of the AE Log CRF.

- dyspareunia
- erythema
- edema
- tenderness
- discharge

8.2.3 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 or reproductive in nature.

If abdominal pain is assessed as gastrointestinal in nature and no other overarching or unifying diagnosis is available, the term “abdominal pain” or “lower abdominal pain” should be used as the AE term (text description) 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 reproductive in nature and a specific anatomic location is known, the term reported on the AE Log CRF should be described as such (e.g., “uterine adnexal pain”, “ovarian pain”).

If the pain cannot be localized to a specific organ, it should be described on the AE Log CRF using terms that identify a reproductive or genitourinary anatomical location (e.g., “pelvic pain”, “urinary tract pain”).

8.2.4 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 or adverse events unless requested by the Investigator of Record (IoR) or designee. 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 study CRFs (specifically, the STI Tests, HIV Tests, Hormone Tests, Pregnancy Test, and Local Laboratory Results CRFs). Sites should document other results if any, in visit chart notes, or in other designated site-specific documents. Throughout a participant's study follow-up period, 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.

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-030/IPM 041 must be graded on a five-point scale:

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

Severity is not the same as seriousness, which is based on the outcome or action associated with an event, as described in Section 8.1.3.

The severity of all AEs identified in MTN-030/IPM 041 will be graded using:

- DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT)
- If not identified in the FGGT, the DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table), Version 2.0, dated November 2014

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).

AEs listed in both the FGGT and the Toxicity Table should be graded according to the FGGT. AEs not listed in the FGGT should be graded according to the Toxicity Table. AEs not listed in the FGGT or the Toxicity Table should be graded according to the "estimating severity grade" row of the Toxicity Table, shown below.

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

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

- Genital petechiae and genital ecchymosis should be considered Grade 1 as neither requires treatment.

- 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.
- If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, and the diagnosis is not specifically listed in the Toxicity Table, assign the AE the highest severity grade among each of the associated signs and symptoms. Record the diagnosis as the AE term and record each associated sign and symptom in the AE Log comments section.
- Seasonal allergies should be graded according to the "Estimating Severity Grade for Parameters Not Identified in the Grading Table" row of the Toxicity Table (not the "acute systemic allergic reaction" row).
- When grading using the "Estimating Severity Grade for Parameters Not Identified in the Grading Table" row of the Toxicity Table, note that if the condition requires treatment, it must automatically be graded at Grade 2 or higher.
- If urinary tract infections (UTI) are diagnosed on the basis of symptoms alone, they must be graded according to the "Estimating Severity Grade for Parameters Not Identified in the Grading Table" 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 FGGT. In either case, document the AE using the AE term "Urinary Tract Infection".
- It is preferable that abnormal Pap smear findings are reported and graded based on results of a biopsy, using the "Intraepithelial Neoplasia by biopsy" row of the FGGT (below). However, if further evaluation of the Pap smear finding is not performed, or is scheduled to be performed at a later date, then abnormal Pap smear findings should be graded according to the "Pap" row of the FGGT (see below).

  Note: AGC and AGC-favor neoplastic are not specifically mentioned in the "Pap" row, but should be assigned severity grades 1 and 2, respectively.

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 only if treatment performed without diagnostic testing, otherwise use biopsy category above)	nl PAP	ASCUS or LSIL	HSIL	Carcinoma in situ or Carcinoma	NA

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.

Please note that where no cause for the event is apparent, the relationship does not default to "related". There must be at least a reasonable possibility of a causal relationship for "related" to be marked. In addition, if the AE is **due to the act** of study ring insertion or removal, then the "related" category should be utilized.

Study staff must give a reason for their determination of the relationship of the AE to the study product.

- When an AE is assessed as "Not Related" to the study product, an alternative etiology, diagnosis, or explanation (e.g., "not biologically plausible") should be provided in the "Comments" field on the AE Log CRF.

- When an AE is assessed as "Related", a rationale (e.g., "due to the act of ring insertion") should be provided in the "Comments" field on the AE Log CRF. 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. Refer to section 8.2 of this SSP manual section for detailed guidance on reporting AEs due to the act of study ring insertion or removal.

If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required. When reporting an AE that is the result of a study-related procedure other than study ring insertion or removal, mark the "Relationship to Study Product" as "Not Related" and explain in the "Comments" field that the event is the result of a study-related procedure (specify).

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

Each AE identified in MTN-030/IPM 041 must be followed clinically through study participation until the AE resolves (returns to baseline) or improves to a Grade 2 or lower assessment.

At each follow-up visit, an authorized study clinician should review each previously identified, ongoing AE 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 outcome should be marked "recovering/resolving" until the 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 when the condition returns to its severity grade at baseline (i.e., at the time of enrollment/randomization). For clinical events that are AEs, clinical management and follow-up of the AE should proceed per the specifications of section 9 of the protocol. If, however, a clinical AE is not addressed in section 9 of the protocol, at a minimum, follow-up evaluations should be performed at scheduled study visits until resolution, or the condition has improved to a Grade 2 or lower assessment. 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 or frequency (worsens) after it has been reported on an AE Log CRF, it must be reported as a new AE, at the increased severity or frequency, 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 or frequency increased.

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

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. The IoR or designee must establish a clinically appropriate follow-up plan for the AE.

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

- 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

At a minimum, the above listed AEs 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. 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 should send an informational query regarding the case to the Protocol Safety Review Team (PSRT) (see Appendix 8-1) at the time of reassessment. The MTN-030/IPM 041 PSRT may advise on whether any additional follow-up is indicated on a case by case basis.

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 may be communicated to the PSRT, if applicable. However, no updates should be made to any AE Log forms based on re-assessments that occur after a participant has terminated the study.

8.6.1 Reporting Recurrent Adverse Events

If an AE previously reported on an AE Log CRF resolves and then recurs at a later date, 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 her baseline condition, it would not be considered an AE. For example, if a woman reports that she has 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. See section 8.2.2 of this SSP manual section for further details.

8.7 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 that any social harms are reported during the study, study staff should fully document in participant chart notes (and/or another designated source document) the issues or problems, and make every effort to facilitate their resolution as described in this section. There is no CRF for the reporting of social harms. The IoR will report any social harm that is, in his/her judgment, deemed serious or unexpected, to the PSRT and IRB according to local requirements. Study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm.

Prior to study initiation, study staff teams at each site should discuss as a group, and with community representatives, what issues and problems are most likely to be encountered by participants at their site, and should agree upon how these issues and problems should be handled, if reported. Roles and responsibilities should be defined for all staff members, such that each staff member is aware of what actions he/she can appropriately take, and what actions should be referred to other members of the team.

During study implementation, staff teams at each site should continue to discuss actual participant experiences, successful and unsuccessful response strategies, and other lessons learned among themselves and with community representatives. Based on these discussions and lessons learned, procedures for responding to issues and problems should be reassessed and updated as needed throughout the study.

The following are suggested strategies for responding to social harms that may be adapted and tailored to best meet participant needs at each site:

- When first responding to an issue or problem, actively listen to the participant's description of the problem and ask questions to elicit as much detail as possible about the problem, including the participant's perception of the severity of the problem. Record all pertinent details in signed and dated chart notes.
- Ask the participant to articulate her thoughts on what can/should be done to address the problem, including what she would like study staff to do in response to the problem (if anything).
- Discuss with the participant any additional or alternative strategies that you might suggest to address the problem and collaborate with her to develop a plan to try to address the problem. Document the plan in signed and dated chart notes.
- Take all possible action to try to address the problem, per the plan agreed upon with the participant. Document all action taken, and outcomes thereof, in signed and dated chart notes.
- As with medical AEs, follow all problems to resolution or return to baseline status.
- 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-030/IPM 041, if required per IRB/EC guidelines.
- Consult the Protocol Safety Review Team (PSRT) for further input and guidance as needed.

8.8 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 Leadership 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. Also, in all cases, study staff responsible for clinical oversight of study participants should be made aware of any newly available safety information. In many cases, the distribution will need to be submitted to 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.

8.9 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-030/IPM 041 protocol for a complete description of the participant safety monitoring procedures in place for MTN-030/IPM 041. Section 13 of this manual describes the reports prepared by the MTN SDMC in support of MTN-030/IPM 041 safety monitoring procedures.

Participant safety is of the utmost importance in MTN-030/IPM 041. 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 case report forms to the MTN SDMC and EAE reports via DAERS to the RSC, 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 PSB Medical Officer, will review all EAE Forms received for MTN-030/IPM 041 and follow up on these reports with site staff, the MTN-030/IPM 041 Protocol Team, and drug regulatory authorities when indicated.
- The Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared by the SDMC for the study. The PSRT will meet via monthly conference calls (or on an as needed basis) to discuss cumulative study safety data and any potential safety concerns.
- The MTN Study Monitoring Committee (SMC) also will periodically review study data with a focus on performance indicators, such as participant accrual and retention, protocol adherence, and data quality. While site staff are not typically involved in these reviews, site staff should be aware that the SMC may make recommendations to DAIDS and/or the MTN leadership that could affect the study and sites in significant ways. These decisions are based on a detailed review of the available study data and careful consideration of ongoing participant safety.

Appendix 8-1: MTN-030/IPM 041 Protocol Safety Review Team

Roles and Responsibilities of the PSRT

The roles and responsibilities of the MTN-030/IPM 041 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 MTN-030/IPM 041 PSRT:

- Sharon Achilles, Protocol Chair
- Beatrice Chen, Protocol Co-Chair
- Katie Bunge, MTN Protocol Safety Physician
- Devika Singh, MTN Protocol Safety Physician
- Ken Ho, MTN Protocol Safety Physician
- Jeanna Piper, DAIDS Medical Officer
- Annalene Nel, IPM Medical Officer

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 or Protocol Co-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-030/IPM 041 PSRT Query Form, which is available in the Study Implementation Materials section of the MTN-030/IPM 041 web page. Site staff will email completed query forms to the Protocol Safety Physicians (mtn030safetymd@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 Protocol Chair(s).

An emergency safety telephone number (412-641-8947) is also available to site staff. This telephone is carried by the Protocol Safety Physicians 24 hours a day, seven days a week. It is intended for use in emergencies only, in which immediate consultation with a Protocol Safety Physician is needed. If the Safety Physician does not answer, a voicemail should be left with the call back number. Questions that can wait for email communication should be handled using the above-described PSRT query process.