Section 8. Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-024/IPM 031. 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 Vaginal Ring

8.1 Definitions and General Reporting Guidance

8.1.1 Adverse Event (AE)

The International Conference on Harmonisation 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-024/IPM 031, the same definition is applied to both study groups, beginning at the time of random assignment through when she terminates from the study. Study staff must document in source documents and case report forms all AEs reported by or observed in study participants, beginning at the time of random assignment, regardless of severity and presumed relationship to study product.

Ongoing medical conditions, problems, signs, symptoms, and findings identified prior to random assignment are considered pre-existing conditions. Such conditions should be documented on the Pre-Existing Conditions case report form. Pre-existing conditions must be graded and are assigned severity grades just as AEs. If a pre-existing condition worsens (increases in severity or frequency) after randomization, the worsened condition is considered an AE and is reportable on the AE Log CRF. If a pre-existing condition resolves after randomization, but then recurs at a later date, the recurrence is considered an AE.

8.1.2 Reporting Adverse Events

Per Section 8.3 of the MTN-024/IPM 031 protocol, study staff will report on the AE Log CRF all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. Due to some of the clinical procedures, study participants may experience some expected AEs. These may include bruising from a blood draw or small amount of vaginal bleeding from pelvic examination, for example. Expected AEs should also be captured on the AE Log CRF.

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 these data elements.

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 these forms, 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 has questions about participant safety or reporting clinical events, they should send an email to the MTN-024/IPM 031 Safety Physicians at mtn024safetymd@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 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 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). EAEs 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-024/IPM 031, 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 those that count towards the 3-day timeline provided for reporting of EAEs to DAIDS. The criteria are as follows:

- Monday through Friday count as reporting days.
- Saturday and Sunday are not considered reporting days.
- Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday counts as a reporting day.
- 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.

For questions or other communications regarding submission of EAE Reports, see below.

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

All EAEs must also be reported on the AE Log CRF. The AE Log case report form includes an item to record if the AE is also being reported as an EAE. When completing 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., onset date, severity grade relationship to study product) must be recorded consistently across all documents. 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 a new AE-1 CRF, 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.

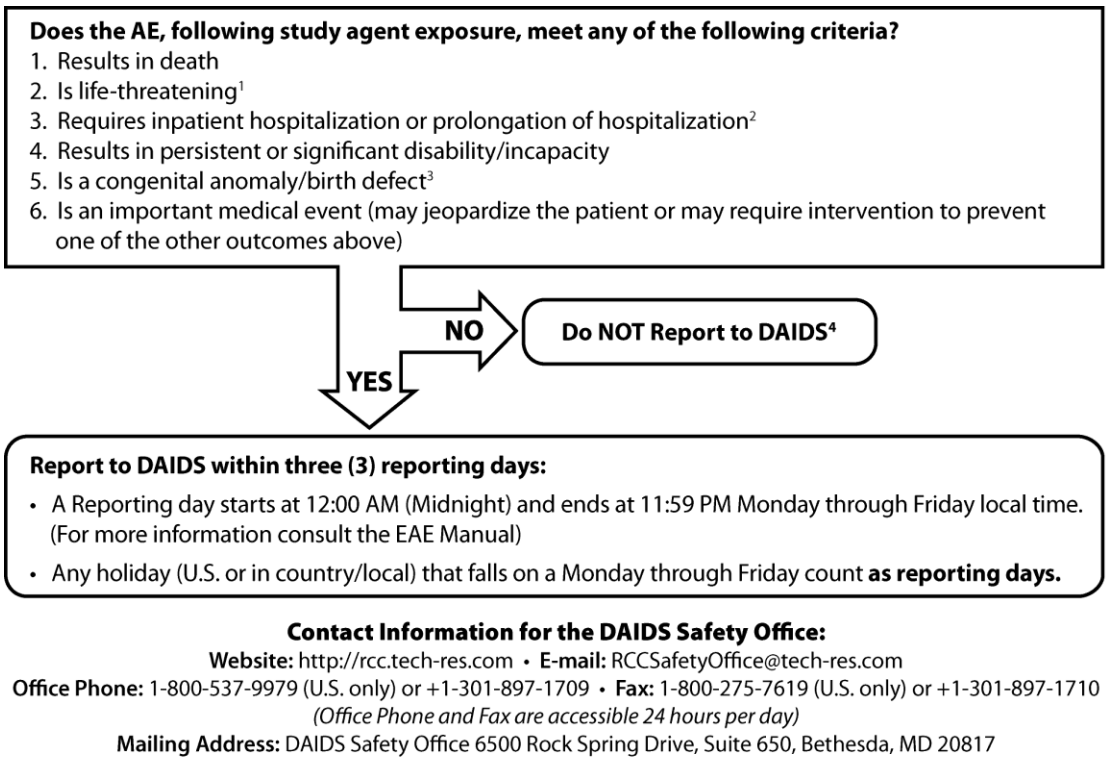
For each EAE reported to DAIDS, sites are required to submit an updated report to DAIDS as soon as significant additional information becomes available. Note that updates made to EAE reports should also be made to the corresponding AE Log CRF documenting the AE, as applicable. Similarly, any updates 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, the increase in severity must be reported as a new AE to the SDMC (as described previously).

Figure 8-1
Expedited Adverse Event Reporting Requirements for MTN-024/IPM 031



Contact Information for the DAIDS Safety Office:
Website: http://rcc.tech-res.com • **E-mail:** RCCSafetyOffice@tech-res.com
Office Phone: 1-800-537-9979 (U.S. only) or +1-301-897-1709 • **Fax:** 1-800-275-7619 (U.S. only) or +1-301-897-1710
(Office Phone and Fax are accessible 24 hours per day)
Mailing Address: DAIDS Safety Office 6500 Rock Spring Drive, Suite 650, Bethesda, MD 20817

[1] "Life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does NOT refer to an event that hypothetically might have caused death if it were more severe.

[2] Per the ICH SAE definition, hospitalization is NOT an adverse event (AE), but is an outcome of the event. **DO NOT REPORT**: Any admission unrelated to an AE (e.g., for standard labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep); protocol-specified admission (e.g., for a procedure required by protocol); admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) **and** has not increased in severity or frequency as judged by the clinical investigator. (**NOTE**: A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and **would be** reportable.)

[3] Clinically insignificant physical findings at birth, including those regarded as normal variants, do NOT meet reporting criteria. If a clinically significant anomaly is reported, all findings (including those of no individual significance) should be included in the same report. For example, do NOT report an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant. But if either finding occurred with a major cardiac defect, report all findings in the SAE Report.

[4] Please ensure that any other protocol-specific reporting requirements are met.

8.2 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in MTN-024/IPM 031. 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 AE text description (item 1) if the AE is related to a procedure (iatrogenic). For example, if a participant experiences cervical bleeding as a result of the cervical biopsy, then "cervical bleeding due to cervical biopsy" should be submitted as an AE. "Cervical bleeding" maps to "Reproductive system and breast disorders" System/Organ Class (SOC) whereas "Cervical bleeding due to biopsy" maps to "Injury, Poisoning, and Procedural Complication" SOC.

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 will appear in safety reports.

When reporting AEs 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 item 1. 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 clearly identify in item 1 AEs that are **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 the AE is **<u>not</u> due to the act** of study ring insertion or removal, do not include mention of the ring in item 1.

- If text is present in the "Comments" field that the AE is due to the act of ring insertion or removal, this same text needs to be in item 1. If not, this may result in a Clinical Query asking that this information be added to item 1 so that the AE is described completely and accurately.

It is fine to include text in the "Comments" field explaining why the AE has been judged "related", but such text is not required.

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 clinician observed versus participant reported.

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 present both by history and on examination, only report the one with the most severe grade. (Grade 3 and 4 vaginal discharge is listed as "NA" in the FGGT and is not pictured here.) If they are the same grade, report 'vaginal discharge by participant report' as the AE term.

- Vaginal bleeding: All guidance on vaginal bleeding is provided in SSP Section 7.

STI/RTI

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-024/IPM 031, each suspected genital herpes outbreak should be reported using the term marked on the Pelvic Exam CRF describing the lesion together with the anatomical location (e.g., vulvar ulceration, 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 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 "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, rapid 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

8.2.2 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 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 on item #1 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 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”).

8.2.3 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 on the PRE-1 CRFs 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 Laboratory Result DataFax CRF. 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.

8.2.4 Postmenopausal Considerations

AEs that are related to menopause, worsened by menopause, or require changes in clinical management of the participant must be reported using the appropriate menopausal related terms or indicating the AE is associated with menopause by adding 'menopausal' to the description on item 1 on the AE Log CRF. For example, vaginal dryness which is known to be related to menopause should be reported as 'menopausal vaginal dryness.' If the AE is not related to the participant's menopause, do not relate the event to the menopause on item 1 or in the comments section. Please refer to the listed example for reporting terms on line 1 (after clinical judgment):

When recording the rationale or alternative etiology for AEs which are "not related" to study product, but are associated with menopause do not record "due to menopause" as this will have implications on MedDRA coding. Instead, simply record "menopausal symptoms" as the alternative etiology.

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-024/IPM 031 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-024/IPM 031 will be graded using:

- DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT)
- If not identified there, the DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table), dated December 2004 (Clarification dated August 2009) will be utilized.

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

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:

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" row of the Toxicity Table (not the "acute systemic allergic reaction" row).
- When grading using the "general infection" row of the Toxicity Table, note that if the condition requires treatment, it must automatically be graded at Grade 2 or higher.
- Urinary tract infection (UTI), which is expected to be diagnosed on the basis of symptoms should be graded according to the "infection (other than HIV infection)" 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.
- 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 that represent an increase in severity should be reported as AEs and 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.

If a biopsy is performed at a later date, update the AE-1 CRF to indicate the results of the biopsy (item 1 - AE Diagnosis) and update the severity grade (item 3), as appropriate, per the "Intraepithelial Neoplasia by biopsy" row of the FGGT.

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.

Study staff should 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 products, an alternative etiology, diagnosis or explanation should be provided in the "Comments" line on the AE Log CRF. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required. When recording an AE that is the result of a study-related procedure, mark the "Relationship to study product" as "Not Related" and provide an explanation in the "Comments" section that the event is a 'result of a study-related procedure'.

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

All AEs identified in MTN-024/IPM 031 must be followed clinically until they resolve (return to baseline) or stabilize (persist at a certain severity grade (above baseline) for two consecutive monthly evaluations.

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 case report form. In many cases, the final outcome of an AE will not be available when the AE Log CRF is first completed and faxed to DataFax. In such cases, the form should be updated when the final outcome becomes available and re-faxed to DataFax at that time.

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 two consecutive monthly evaluations. 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 stabilization has been documented. 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. In this case, the outcome of the first AE will be documented as "severity/frequency increased." The outcome date of the first AE and the onset date of the new (worsened) AE will both be the date upon which the severity or frequency increased.

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 "continuing at end of study participation" and the AE Log CRF should be re-faxed to DataFax.

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

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 (mtn024safetymd@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-024/IPM 031 PSRT also 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 case report forms based on the re-assessments.

8.6.1 Reporting Recurrent Adverse Events

If an AE previously reported on an AE CRF resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new AE CRF.

Regular occurrences of the same adverse event that are expected in follow-up are not typically considered separate adverse events.

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 occur, study staff should fully 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, in his/her judgment, to be 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.
- 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-024/IPM 031, if required per IRB/EC guidelines.
- Consult the Protocol Safety Review Team (PSRT) for further input and guidance as needed. As is the case with medical AEs, data collected on social harms will be monitored by the PSRT.

8.8 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 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. 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-024/IPM 031 protocol for a complete description of the participant safety monitoring procedures in place for MTN-024/IPM 031. Section 13 of this manual is a reference for a description of the reports prepared by the MTN SDMC in support of MTN-024/IPM 031 safety monitoring procedures.

Participant safety is of the utmost importance in MTN-024/IPM 031. 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 to the DAIDS and IPM, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- Clinical Affairs staff at the MTN SDMC will review clinic and laboratory data received at the SDMC and apply clinical data quality control notes (queries) to data requiring confirmation, clarification, or further follow-up by site staff. These queries will be issued to site staff for resolution on an ongoing basis throughout the period of study implementation. 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 Officers will review all EAE Forms received for MTN-024/IPM 031 and follow up on these reports with site staff, the MTN-024/IPM 031 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 monthly conference call 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.

Section Appendix 8-1
MTN-024/IPM 031 Protocol Safety Review Team Plan

Roles and Responsibilities of the PSRT

The roles and responsibilities of the MTN-024/IPM 031 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 temporary hold or permanent discontinuation of study product.

   The protocol specifies a number of situations in which study product use should be temporarily held, permanently discontinued and/or resumed; designated site staff may implement these holds, discontinuations, and/or resumptions in the absence of consultation with the PSRT. In other situations, however, product use management must be undertaken in consultation with the PSRT. (Protocol Section 9.3 and 9.4)

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, participant evaluability, and/or re-joining of study participant's which previously withdrew consent (Protocol Section 9.8)

PSRT Composition

The following individuals comprise the MTN-024/IPM 031 PSRT:

- Beatrice Chen, Protocol Chair
- Katie Bunge, MTN Protocol Safety Physician
- Devika Singh, MTN Protocol Safety Physician
- Ken Ho, MTN Protocol Safety Physician
- Lydia Soto-Torres, DAIDS Medical Officer (MO)
- Annalene Nel, IPM Medical Officer
- Jill Zeller, SDMC Clinical Affairs Safety Associate (CASA)

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, 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. MTN CORE (FHI 360) Clinical Research Managers, SDMC Project Managers, Statistical Research Associates, and Site Investigators and study coordinators may attend PSRT calls as observers and/or discussants.

PSRT Communications

A group email address (mtn024psrt@mtnstopshiv.org) will be used to facilitate communication with the PSRT. All PSRT communications will be sent to this email address.

Site consultation with the PSRT will be facilitated using the MTN-024/IPM 031 PSRT Query Form, which is available in the Study Implementation Materials section of the MTN-024/IPM 031 web page. Site staff will email completed query forms to the Protocol Safety Physicians (mtn024safetymd@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 (1-412-641-8947) 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 PSRT query process described above.

To document calls made to the emergency safety telephone number, near the time of the call (either before or after) site staff will complete the site section of the MTN-024/IPM 031 Emergency Phone Contact form (available in the Study Implementation Materials section of the MTN-024/IPM 031 web page) and email the form to the Protocol Safety Physicians. Within 24 hours after the call, the responding Protocol Safety Physician will complete the remainder of the form and email the completed version to site staff, copied to the study management team.