MATRIX-001 Study-Specific Procedures (SSP) Manual
Section 8 – Adverse Event Reporting and Safety Monitoring

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8 Introduction

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MATRIX-001.

8.1 Adverse Event Reporting and Safety Monitoring

This section should be used together with Section 8 of the MATRIX-001 protocol and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 (DAIDS Toxicity Table)
- Addendum 1: Female Genital Grading Table for Use in Microbicide Studies dated November 2007 (FGGT)

8.1.1 Adverse Events (AE)

For MATRIX-001 the ICH-E6 definition for an adverse event is applicable beginning at the time of enrollment through study termination. Adverse events for study-related procedures will be captured from Visit 2 and study product relatedness will be assessed following randomization at Visit 3.

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

Relevant medical conditions, signs, symptoms, and clinically significant problems/findings identified prior to enrollment are considered pre-existing conditions. Such conditions should be documented on the Pre-Existing Medical Conditions Form case report form (CRF). If any condition is ongoing at the time of enrollment, it is a pre-existing condition regardless of its medical significance. If this condition worsens (increases in severity or frequency per the DAIDS Toxicity Table or FGGT) after enrollment, the worsened condition is considered an AE. Reversion of this AE to baseline severity grade is considered resolution of the AE. However, if a pre-existing condition resolves after enrollment, but then recurs at a later date, the recurrence is considered an AE.

Each site's standard operating procedures (SOP) for source documentation should define the extent to which the AE CRF will be used as a source document. The site-specific Delegation of Duties Log should designate study staff authorized by the Investigator of Record (IoR) to complete AE CRFs.

Regardless of who initially completes these forms, a clinician listed on the site's FDA Form 1572 should review the AE(s) to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

8.1.2 Serious Adverse Events (SAE)

Serious adverse events (SAE) are a subset of all AEs. For each AE identified in MATRIX-001, an authorized study clinician (as detailed on the Delegation of Duties Log) must determine whether the AE meets the definition of SAE. The AE CRF includes a specific question to record this determination.

SAEs are defined as AEs occurring at any dose that:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Per ICH SAE definition, hospitalization itself is not an AE, but is an outcome of the event. Thus, hospitalization in the absence of an AE is not regarded as an AE and is not subject to expedited reporting. The following are examples of hospitalization that are not considered to be AEs:
  - Protocol-specified admission (e.g., for procedure required by study protocol)
  - Admission for treatment of target disease of the study, or for pre-existing condition (unless it is worsening or increases in frequency of hospital admissions as judged by the clinical investigator)
  - Diagnostic admission (e.g., for a work-up of an existing condition such as persistent pretreatment lab abnormality)
  - Administrative admission (e.g., for annual physical)
  - Social admission (e.g., placement for lack of place to sleep)
  - Elective admission (e.g., for elective surgery)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

In addition to entering an SAE into the database (Adverse Events Form CRF), a Serious Adverse Event form must be downloaded from the MATRIX website (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-001/matrix-001-study-documents), completed and emailed to CONRAD (at ConradSafety@evms.edu) and cc the Protocol Safety Physician (bungeke@upmc.edu) within 24 hours of site awareness. If there is any question whether the event meets the criteria for "serious" it should be reported anyway. The site must also report the SAE per local regulatory requirements.

8.2 AE Terminology

Study staff must assign a term or description to all AEs identified in MATRIX-001. The guidance below should be followed when assigning AE terms/descriptions:

- Whenever possible, a unifying diagnosis should be assigned to describe a cluster of signs and/or symptoms.
- Document associated signs and/or symptoms related to a diagnosis in the comments section of the AE CRF.
- When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, each individual sign and symptom must be identified and documented as an individual AE.
- Whenever possible, use specific terms to indicate the anatomical location of the AE (e.g., "rectal ulcer," "vaginal" instead of "genital" or "uterine cervix" instead of "cervical").
- Use medical terms and correct spelling of such terms.

- Do not use abbreviations, unless the abbreviations are for accepted laboratory findings (e.g., "AST increased", "SGOT decreased").
- Do not include information on severity grade, relatedness to study product or timing of study product use in the AE term/description. Limit the AE text to the medical description and anatomical location, when needed.
- Any untoward effect that the study product has on a participant – for example, "vaginal irritation" or "vaginal discomfort" – should be reported as an AE on an AE CRF.
- "Genital ulcer disease" is not a codable event. Rather, an STI diagnosis should be reported in the AE term/description. If there is no STI diagnosis, the AE should be reported as "ulcers" with the anatomical location (e.g., "anal" or "rectal") specified.
- Seasonal allergies should be graded according to the "estimating severity grade" row of the DAIDS Toxicity Table (not the "acute systemic allergic reaction" row).
- Any event that occurs as a result of a study-related procedure should be recorded as an AE. Specify in AE text description if the AE is related to a procedure (iatrogenic).

AEs not listed in any of the above-mentioned grading tables should be graded according to the "estimating severity grade" row of the DAIDS Toxicity Table.

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

- If the severity of an AE falls into more than one grading category on the DAIDS Toxicity Table, assign the higher of the two grades to the AE.
- Urinary Tract Infections (UTIs) should be diagnosed based on the presence of symptoms and lab results indicative of a UTI (i.e., dipstick, microscopy and/or urine culture) as per site standard of care
    - Isolated findings of protein or glucose or hematuria on dipstick, even if noted incidentally while testing for leukocyte esterase and nitrates, should be reported as a laboratory abnormality AE.
    - Urinary Tract Infection: Report "urinary tract infection" for all instances of lower urinary tract infections diagnosed by symptoms and positive lab results (i.e., urine microscopy, culture or dipstick). Do not report "bacterial urinary tract infection" or "cystitis". The term "urinary tract infection" is sufficient. Do not report UTIs based on participant report of symptoms alone.
- Procedures per se should not be reported as AEs; rather the underlying condition which leads to a procedure may be considered an AE. Any associated procedures may be considered treatments for the AE. For example, while "appendectomy" would not be considered an AE, "appendicitis" would, with "appendectomy" documented as a treatment provided for the adverse event. Also, planned procedures or surgeries are not AEs. Rather, the underlying diagnosis or condition that warrants the procedure or surgery may be a reportable AE. Any adverse experiences resulting from a planned procedure or surgery are AEs and should be reported on an AE Log form. The AE term/description should specify the procedure as the cause of the AE. For example, a throat infection that resulted from the tonsillectomy should be reported as an AE of "throat infection due to tonsillectomy".
- COVID-19: If a participant is suspected or confirmed to have COVID-19, "COVID-19" should be reported as the AE term. Grade based on the "estimating severity grade" row of the DAIDS Toxicity Table. It is not necessary to include details on whether the reported AE is suspected or confirmed in the comments.

- 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 dental pain or dentalgia related to an underlying dental caries diagnosis, include the dental caries diagnosis in the AE term or description.

8.2.1 Product Leakage

Participants may experience leakage/discharge/expulsion which they identify as study product related. For the purposes of MATRIX-001, if a participant reports product related discharge/leakage, this will be captured on the eCRFs and should not be reported as an AE. If a participant reports abnormal discharge and does not specifically identify study product, an AE for vaginal discharge should be captured.

8.2.2 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.

Vaginal bleeding: Genital bleeding that is different from baseline (per participant assessment) and not attributable to contraceptive use or her menstrual cycle (per clinician assessment) should be captured as an AE.

If the newly identified bleeding episode is determined to be different from baseline (i.e. longer, heavier, more/less frequent) and not related to the current contraceptive method, record the episode on an AE CRF. Grade and term the episode per the applicable "Abnormal Uterine Bleeding Unrelated to Pregnancy" or the "Unexplained Infrequent Bleeding" row of the DAIDS FGGT (menorrhagia, metrorrhagia, or postcoital bleeding). Note that shorter than baseline menses is not included in the FGGT and should not be considered an AE.

Once a bleeding AE has been reported, each subsequent bleeding episode should be assessed to determine whether the episode is consistent with previously reported bleeding AEs, or if it is the first of its kind. Physical and pelvic examinations will be conducted per IoR discretion to assess the bleeding. Clinician discretion should be used to determine if a new AE needs to be documented or if a previously reported AE is ongoing. If the AE increases in severity per the DAIDS FGGT, a new AE CRF should be completed to document this change in severity and the clinician may deem a pelvic exam is necessary.

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

- If both Menorrhagia and Metrorrhagia are present, a single adverse event should be reported as "Menometrorrhagia" and graded per the Menorrhagia row of the FGGT.
- Bleeding associated with speculum insertion and/or specimen collection, including biopsies, judged to be within the range of normal according to the clinical judgment of the IoR or designee is not considered to be an AE. If the bleeding exceeds the amount considered normal by the clinician, it should be considered an AE and should be documented and reported if applicable using the term cervical friability. The severity of cervical friability should be graded per the cervical edema and friability row of the DAIDS FGGT.

- Bleeding that is associated with an observed abnormal pelvic exam finding should be considered an AE and should be documented and reported, if applicable, using the term associated with the exam finding, with the anatomical location noted. The fact that blood or bleeding was present should be documented in the chart notes and on the Pelvic Exam CRF and may also be noted in the comments section within the AE CRF, but the term metrorrhagia should not be used to document the AE.
- The term metrorrhagia should be used to refer to bleeding that meets AE reporting criteria that is not menses related and is not associated with an observed pelvic exam finding. For example, the term could be used to report bleeding of variable amounts occurring between regular menstrual periods such as spotting between menses, ovulation bleeding, and breakthrough bleeding. This term should also be used to report blood-tinged discharge and blood observed in the vagina with no identified source. Note that bleeding determined to be related to a participant's contraceptive method is not reportable as an AE but should be documented on the Pelvic Exam Form CRF.
- If a participant reports genital bleeding after sexual intercourse, this event should be recorded as "postcoital bleeding" and graded per the "Postcoital Bleeding" row of the DAIDS FGGT.

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

Sexually transmitted infections (STIs)/Reproductive tract infections (RTIs)
The following terminology should be used only if STI diagnosis is based on clinical evaluation and confirmed, when appropriate/possible, by laboratory result(s).

- Chlamydia: Report genital infections using the term "genitourinary chlamydia infection." Report rectal infections using the term "rectal chlamydia".
- Gonorrhea: Report genital infections using the term "genitourinary gonorrhea infection." Report rectal infections using the term "rectal gonorrhea".
- Trichomoniasis: Report 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.
- Genital herpes: Such testing is not required in the protocol and should only be done if clinically indicated and per site standards/capability. Note that laboratory testing is required in order to use the term "genital herpes" for AE reporting. Any new lesion/ulcer observed during the study should be reported as an AE even if it is thought to be due to prior herpes diagnosis/infection. The criterion for diagnosing genital herpes should be per the FGGT. 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., vaginal ulcer, vulvar ulcer).
- Genital warts: Report all outbreaks of genital warts as AEs, regardless of whether infection with HPV was known to be pre-existing before enrollment/randomization. Report the AE using the term "external" or "internal" and include the anatomical location of the warts (e.g., cervical, vaginal, perianal), for example "external anal condyloma".
- Syphilis: A Grade 2 Syphilis AE is defined as a positive treponemal test along with a positive non-treponemal test and no previous treatment OR a four- fold rise in titer on the non-treponemal test after previous treatment regardless of symptoms OR non-oral lesions positive by darkfield exam for treponemes. Additionally, a confirmed positive treponemal test with a negative non-treponemal

test without a prior history of treatment also constitutes a grade 2 syphilis AE. Report all syphilis events using the term "syphilis infection" (no anatomical location is required when reporting syphilis infections). Contact the MATRIX-001 Protocol Safety Review Team (PSRT) in the event a participant has a positive treponemal test and a negative non-treponemal test as this could represent late latent syphilis.

- Bacterial Vaginosis (BV): Such testing is not required per protocol and should only be done if clinically indicated. Only report symptomatic infections that are confirmed with saline wet mount testing and that fulfill Amsels criteria as AEs, using the term "symptomatic bacterial vaginosis". Asymptomatic BV should not be recorded as an AE. If a clinician notes abnormal vaginal discharge and ultimately diagnoses the participant with asymptomatic BV by wet mount, this clinical event should be captured as "vaginal discharge- clinician observed".
- Candidiasis: Such testing is not required per protocol and should only be done if clinically indicated. Only report symptomatic infections that are confirmed with KOH wet prep and/or culture as AEs, using the term "vulvovaginal candidiasis."

In the absence of laboratory confirmation of an STI or RTI diagnosis, use the term "vulvovaginitis" when 2 or more of the genital/vaginal signs or symptoms listed below are present, per the DAIDS Toxicity Table. Comment on the individual signs/symptoms in the "Comments" field of the AE 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, per the DAIDS Toxicity Table, in the absence of a laboratory-confirmed STI/RTI. Comment on the individual signs/symptoms in the "Comments" field of the AE 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, anorectal, 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 to describe the AE on the AE CRF.

If the pain is assessed as genitourinary and a specific anatomic location is known, the term reported on the AE CRF should be described as such (i.e., "bladder pain" or "adnexal tenderness").

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

If the pain cannot be localized to a specific organ but is believed to be gynecologic in origin it should be described on the AE CRF using terms that identify a reproductive or genitourinary anatomical location (e.g. "pelvic 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 (on Pre-Existing Medical Conditions Form CRF) or adverse events (on the Adverse Event Form CRF) unless requested by the IoR or designee. These laboratory results can be identified as "NCS" (Not Clinically Significant) in the source documentation, if determined by a study clinician.

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

If an adverse event falls between two grades on the toxicity table, record the higher grade.

The IoR or designee should carefully review all protocol specified laboratory tests to identify any AEs or health problems. Documentation of this review is required by initialing and dating each page of lab results. Abnormal laboratory values should be marked as "Clinically Significant" or "Not Clinically Significant". The severity of all lab abnormalities will be graded and recorded in the source documentation.

8.2.5 HIV and AE Reporting

HIV infection is not included in the DAIDS Toxicity Table but for the purposes of MATRIX-001, HIV infection will be considered an AE and reported as "HIV seroconversion." If a participant seroconverts and develops one or more signs or symptoms of acute HIV-infection, it is appropriate to report these sign(s)/symptom(s) as a single AE using ONLY the term "HIV seroconversion" for the AE term on the AE CRF. Use the comments section of the AE CRF to describe each HIV-related sign/symptom (e.g., fatigue, pharyngitis). Should HIV seroconversion be asymptomatic, please note that in the comments section. Asymptomatic HIV seroconversion should be graded as Grade 2; symptomatic seroconversions should be graded at least as

Grade 2. Should any individual symptom reach Grade 3 or higher status, the event of "HIV seroconversion" should be graded at the highest level of any individual symptom.

Notify the MATRIX-001 PSRT in the event of an HIV diagnosis.

8.2.6 Reporting Sexual Assault

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

In the event that a participant reports a sexual assault which did not result in physical and/or psychological sequelae, sites should report the event as a "Sexual Assault Survivor" as the AE text. Note that for the purposes of AE reporting site staff should accept participant report of sexual assault rather than probing regarding this issue.

Participants who disclose any form of violence by an intimate partner (or other family member) or sexual assault by any perpetrator should be offered immediate support, care, and referrals according to site-specific SOPs/standards regarding intimate partner violence (IPV) and sexual assault response. Generally, response to reports of sexual assault should include first line support (i.e., listening and offering comfort, help, and information/referrals to connect the participant to services and social support) offering the participant an opportunity to provide a complete history of events, and receive relevant physical evaluations, and treatment and/or referral for any injuries.

Emergency contraceptive and STI prophylaxis/treatment should be offered, if indicated per local standard of care. Plans for continued follow-up and care should be outlined to check in on the participant's well-being and uptake of referrals, as appropriate. Depending on the time between the assault and presentation to the clinic (i.e. if within 72 hours), the use of HIV post-exposure prophylaxis (PEP) should also be considered and the participant directed to appropriate services. If PEP is initiated, study product should be permanently discontinued as per section 9.3 of the protocol.

8.3 AE Severity Grading

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in MATRIX-001 must be graded on a five-point scale:

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

Severity is not the same as seriousness, which is based on the outcome or action associated with an event. The severity of all AEs identified and/or reported will be graded using the following grading tables:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 (DAIDS Toxicity Table)
- Addendum 1, Female Genital Grading Table for Use in Microbicide Studies dated November 2007 (FGGT)

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

8.4 AE Relatedness Assessment

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

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

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

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

Similarly, one of the following procedure relationship categories must be assigned to each AE. When recording an AE that is the result of a study-related procedure, the "Relationship to study procedure" should be selected as "Related" and an explanation provided in the "Comments" section that the event is a 'result of a study-related procedure'. If the AE is only related to a study procedure, then "Relationship to study product" should be marked as "Not related".

8.5 AE Outcomes and Follow-up Information: During Study Participation

All AEs identified in MATRIX-001 must be followed clinically at each scheduled visit until they resolve or return to the condition or severity grade that was present at baseline (i.e. at the time of randomization) or stabilize. "Stabilization" is defined as continuing at the same severity grade for at least 2 weeks or as determined by the investigator.

At each follow-up contact, a staff member (preferably a clinician) should review all previously identified ongoing AEs and evaluate and document their current status.

- Outcomes must also be reported on the AE CRF.

- In many cases, the final outcome of an AE will not be available when the AE CRF is first completed. In such cases, the status/outcome should be selected "continuing" until the final outcome becomes available or the participant terminates the study (whichever is earlier) at which point the "Outcome" on the form should be updated.

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. More frequent evaluations may be performed at any time if required to properly monitor and/or manage participant safety, at the discretion of the IoR or designee. It is acceptable for AE follow-up/evaluation to be conducted over the phone, as clinically appropriate.

If an AE increases in severity per the DAIDS Toxicity Table after it has been reported initially on the AE Log, it must be reported as a new AE at the increased severity on a new AE CRF (i.e., a new instance in the study database). In this case, the outcome of the first AE will be documented as "severity frequency increased". The outcome date of the first AE and the onset date of the new (worsened) AE will both be the date upon which the severity increased per the DAIDS Toxicity Table or FGGT (see instructions for these items within the CRF Completion Guidelines for additional guidance).

Resolution dates for AEs should be based on the date when all associated symptoms resolve or when treatment is completed (whichever occurs later) or when severity increases, in which case a new AE CRF would be completed. For asymptomatic STIs, the resolution date is the date the participant completes treatment.

8.6 AE Outcomes and Follow-up Information: After Study Termination

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

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

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

- AEs that are new or found to have increased in severity at the SEV
- SAEs ongoing at the SEV

Refer to protocol Section 8.3.1 for further guidance on frequency of evaluations.

8.7 Reporting Recurrent AEs

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 (new instance 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 their baseline condition, it would not be considered an AE. For example, if a participant reports that

they have three (3) migraines a month before the study, and they continue at the same frequency and severity during the study, these migraines should not be reported as AEs.

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

8.8 Social Harms

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

In the event a social harm occurs, study staff should fully document the issue(s) or problem(s) and make every effort to facilitate resolution. Social harms should be documented on the Social Harm Form CRF. The IoR will report any social harm, in their judgment, to be serious or unexpected to the MATRIX-001 PSRT and IRB/IEC according to local requirements. Social harms that result in SAEs should be considered 'serious or unexpected'. The appropriate AE reporting is expected in this situation. Social harms that are not SAEs but may be considered serious or unexpected include serious threats of physical harm, significant psychological duress, or discontinued provision of food, housing or financial support. Determination of whether a social harm is serious or unexpected is at the discretion of the IoR or designee; the MATRIX-001 PSRT can always be consulted as needed.

Sites should follow site standards in responding to social harms. 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 their thoughts on what can/should be done to address the problem, including what they 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 help address the problem and collaborate with the participant to develop a plan to try to address the problem. Document the plan in signed and dated chart notes.
- Take all possible action to try to address the problem, per the plan agreed upon with the participant. Document all action taken, and outcomes thereof, in signed and dated chart notes.
- As with medical AEs, follow all problems to resolution or return to baseline.
- Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.
- If the reported social harm is associated with an AE, report the AE on an AE CRF. Also report the issue or problem to all IRBs/IECs responsible for oversight of MATRIX-001, if required per IRB/IEC guidelines.

- Consult the MATRIX-001 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.

8.8.1 Gender-Based Violence (GBV)/Intimate Partner Violence (IPV)

Gender-based violence (GBV) is any harmful act perpetrated against a person's will based on socially ascribed gender differences. GBV is used to maintain and reinforce power differences based on gender, including sexual assault, IPV, and stalking.

Participants who disclose any form of GBV, regardless of relatedness to study participation, should be offered immediate support, care, and referrals according to site standards and as informed by site social harms response plans and resources. Generally, response to reports of GBV should include first line support (i.e., listening and offering comfort, help, and information/referrals to connect the individual to services and social support), as well as offering the participant an opportunity to provide a complete history of events, and receive relevant physical evaluations, and treatment and/or referral for any injuries. Emergency contraceptive and STI prophylaxis/treatment should be offered, if indicated. Depending on the form of the GBV incident and the time between the incident and presentation to the clinic (i.e., if within 72 hours), the use of PEP should also be considered. If PEP is initiated, study product should be permanently discontinued as per section 9.3 of the protocol. Plans for continued follow-up and care should be outlined to check in on the participant's well-being and uptake of referrals, as appropriate.

The following resources may be helpful.

From the WHO:

- Responding to intimate partner violence and sexual violence against women (https://www.who.int/reproductivehealth/publications/violence/9789241548595/en/)
- Caring for women subjected to violence curriculum https://www.who.int/publications/i/item/9789240039803)
- Strengthening health systems to respond to women subjected to intimate partner violence or sexual violence (https://www.who.int/reproductivehealth/publications/violence/vaw-health-systems-manual/en/)
- Ethical and safety recommendations for intervention research on violence against women (https://apps.who.int/iris/bitstream/handle/10665/251759/9789241510189-eng.pdf)

From other sources:

- Sexual Violence Research Institute Guidelines for the prevention and management of trauma among researchers of sexual and intimate partner violence (https://www.svri.org/sites/default/files/attachments/2016-06-02/SVRIVTguidelines.pdf)
- CHARISMA SOP Guidance and Job Aid for Addressing Partner Relationships and Intimate Partner Violence in Pre-Exposure Prophylaxis (PrEP) Services (https://www.prepwatch.org/resources/sop-job-aid-ipv-prep-services/)

8.9 Safety Distributions from Product Developers and/or MATRIX Prime

Study sites may receive product- and safety-related information throughout the period of study implementation. This information will be distributed by the Product Developer.

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

8.10 Safety Monitoring, Review and Oversight

Please refer to Section 8 of the protocol for a complete description of the participant safety monitoring procedures in place for MATRIX-001. Participant safety is of the utmost importance in MATRIX-001. 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 entering data into OpenClinica (i.e. AE CRFs). Sites are expected to enter any AEs that meet criteria for being an SAE within 24 hours of site awareness of the event to ensure that this information is passed to the PSRT in a timely fashion.

The MATRIX-001 PSRT will routinely review safety data reports prepared by FHI Data Management Center. The PSRT will meet approximately monthly via conference call to discuss cumulative study safety data and any potential safety concerns.

The Independent Safety Physician (ISP) will review participant safety data approximately every 3 months (see protocol Section 10.6.1), since no Data and Safety Monitoring Board (DSMB) oversight is planned for MATRIX-001. The ISP will be an independent physician with no interest (financial or otherwise) in the outcomes of this study.

If at any time a decision is made to discontinue enrollment and/or study product use in all participants, CONRAD will notify USAID, the FDA, Gilead and any investigators conducting studies under the same IND and (as necessary); site IoRs/designee will notify the responsible IRB/IEC expeditiously per local guidelines.

Appendix 8-1: MATRIX-001 Protocol Safety Review Team Plan

MATRIX-001 Protocol Safety Review Team (PSRT) Plan

Roles and Responsibilities of the MATRIX-001 Protocol Safety Review Team (PSRT)
The roles and responsibilities of the MATRIX-001 PSRT are to:

1. Conduct regular reviews of standardized study safety data reports. Once the Clinical Data Manager 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 MATRIX-001 Management Team as appropriate.

2. Respond to queries regarding product use management including permanent discontinuation of study product.

The protocol specifies a number of situations in which study product use should be permanently discontinued; designated site staff may implement these discontinuations 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 and/or participant evaluability.

PSRT Composition
The following comprise core members of the MATRIX-001 PSRT:

- Protocol Co-Chairs
- MATRIX-001 Safety Physician
- Clinical Research Managers (CRM)
- Product Developer (CONRAD) Representative(s)

Ideally, all members of the PSRT will participate in routine conference calls. At a minimum, a Protocol Co-Chair and the MATRIX-001 Safety Physician must take part in the call 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.

Site consultation with the MATRIX-001 PSRT will be facilitated using the MATRIX-001 PSRT Query Form, which is available on the MATRIX-001 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-001/matrix-001-study-documents) Site staff will email the completed query form to the Protocol Safety Physician (i.e., Dr. Katherine Bunge,

email: bungeke@upmc.edu) who will work with the PSRT to prepare a consensus response to the query, and then email the final response to the site. A group email address (matrix001psrt@lists.matrix4prevention.org) will be used to facilitate communication with the MATRIX-001 PSRT. All PSRT communications will be facilitated using this email address. The PSRT review process is expected to occur within three business days. When necessary, site requests for responses within one business day can usually be accommodated. All members of the PSRT are encouraged to review the information provided by the site in the query form and to contribute to the response; however, final determination rests with the Protocol Co-Chairs.