MATRIX-002 Study-Specific Procedures (SSP) Manual
Section 7 – Clinical Considerations

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7 Introduction

This section presents information on clinical procedures performed in MATRIX-002. The Schedule of Study Visits and Evaluations in Appendix I of the protocol indicates when specific clinical and laboratory assessments are to take place. The IoR/designee should perform symptom-directed examinations at their discretion at any time during any visit if determined to be clinically necessary, particularly if there are any on-going conditions which may require follow-up.

Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in the Laboratory Considerations SSP Section. Instructions for completing data collection forms associated with clinical procedures are provided in the Data Collection SSP section and behavioral assessments in the Behavioral Measures SSP Section.

7.1 Baseline Medical Conditions (Pre-existing Conditions)

The participants' baseline medical history is initially collected and documented at the screening visit using the BASELINE MEDICAL HISTORY REVIEW GUIDE, available on the MATRIX-002 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-002/matrix-002-study-documents). Applicable items should be included in the PRE-EXISTING CONDITIONS LOG and actively reviewed and updated, as necessary, at the enrollment visit. The purpose of obtaining this information is to:

- Assess and document participant eligibility for the study
- Assess and document the participant's baseline medical conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up (i.e., adverse event identification)

In order to obtain a complete, accurate, and relevant participant self-reported medical history, it will be necessary to ask the participant about significant past medical conditions as well as any current conditions. Medical history information may also be obtained from reviewing the participant's medical records, as applicable and in accordance with IRB/IEC policies.

When collecting medical information from the participant, site clinicians should ask probing questions to obtain the most complete and accurate information possible. This is especially important regarding details about severity and frequency of baseline medical conditions.

Baseline medical conditions are a subset of a participant's medical history and consist of all ongoing and/or relevant medical conditions, problems, signs, symptoms and abnormal findings that are observed and/or reported before a potential participant is enrolled (randomized).

Relevant conditions include (but are not limited to): hospitalizations, relevant surgeries, allergies, conditions requiring prescription or chronic medication (lasting for more than 2 weeks), and any condition(s) currently experienced by the participant. The clinician should record as much information as possible about the severity and frequency of any baseline medical condition in the description field on the Pre-existing Conditions Log to best describe the condition at the time the participant enters the study. In addition to participant-reported conditions, the following should be recorded on the Pre-existing Conditions Log:

- Baseline medical Grade 1 and higher lab values
- Medically relevant physical exam abnormalities
- Pelvic exam abnormal findings
- Any identified STIs

Note: Generally, it is not expected that conditions less than Grade 1 would be included on the Pre-existing Conditions Log, unless determined to be relevant by the site clinician.

When reviewing a participant's medical history at screening, site staff should explore in detail any medical conditions or medications that are deemed exclusionary for this study. At the enrollment visit, a participant's history should be reviewed and updated as needed. Refer to protocol section 5.2 and 5.3 for a complete listing of study inclusion and exclusion criteria.

7.1.1 Pre-existing Conditions (Baseline Medical Conditions) at Screening and Enrollment

The Pre-existing Conditions Log is completed based on all screening source documents including, but not limited to, the Physical Exam CRF, Pelvic Exam CRF, and site-specific laboratory reports.

Information documented on the Pre-existing Conditions Log at the Screening Visit must be actively reviewed and updated at the Enrollment Visit, especially for those conditions that were ongoing at the Screening Visit. This includes a review and update of the condition's description and severity grade. Make sure the "*Is the condition ongoing?*" field is completed/updated for each entry prior to final eligibility confirmation.

If a baseline medical condition is resolved as of the date of enrollment/randomization, do not make any changes to the severity grade (similar to what is done when resolving adverse events). In this case, the response to the question, "*Is the condition ongoing?*" must be selected "*no*." If a baseline medical condition first identified at screening is ongoing at enrollment, assess the severity at the Enrollment Visit and update the severity grade (up or down) as applicable to reflect the severity at the time of enrollment/randomization.

After reviewing/updating each Pre-existing Condition at Enrollment, mark the item "complete" in REDCap.

Recurrent Chronic Conditions: Recurrent chronic conditions should be marked as "yes" for the question "Is the condition ongoing?" at the Enrollment Visit, even if the participant is not currently experiencing an acute event (e.g., intermittent headaches, seasonal or acute allergies). For severity grading, the highest severity experienced for the condition should be used. In the 'Description of medical history condition/event' item, note the typical severity for outbreaks/acute episodes of the condition, and whether the condition is currently being experienced by the participant, or historical. When assessing chronic conditions, it is important to note what, if any, medications a participant may take for a reported chronic condition.

Anaphylactic Reactions: During screening, if a participant reports having a history of anaphylactic reactions (such as acute anaphylaxis after eating peanuts), even if it has happened only once before in their lifetime, it is still important for the site clinician to document these events on the Pre-existing Conditions CRF. Per the "acute allergic reaction" row of the DAIDS Toxicity Table, an acute anaphylactic event is considered a severity grade 4 as it is, by definition, a life-threatening reaction. Record the condition/event as "allergic reaction to peanuts" and note types of symptoms (e.g., "throat swelling" or "shortness of breath") indicate the severity grade 4 in the "Description of medical condition/event" field. At the Enrollment Visit, check "yes" to the question, "Is the condition ongoing?" and check "no" for the question "Is condition/event gradable?", as the participant was not experiencing an anaphylaxis event at the time of enrollment/randomization. An AE submission for an anaphylactic reaction is required if this same event occurs after enrollment or during study follow-up. Any acute allergic reaction less than a grade 4 should be documented as a chronic condition.

7.1.2 Follow-up Medical History Review

An updated participant self-reported medical history is required at protocol specified scheduled visits/contacts. This is done by asking if the participant has any changes in medical history from the previous visit. A medical history review should also be performed at interim visits when a participant complains of symptoms or when the purpose of the visit is to re-assess previously-identified AEs.

One purpose of the participant-reported follow-up history is to determine whether previously- documented conditions have changed in severity or frequency. A second purpose is to determine whether new symptoms, illnesses, conditions, etc., have occurred since the medical history was last assessed. The applicable CRF question, chart notes, or a site-specific tool, if desired, may serve as the source document. All newly-identified participant-reported symptoms and conditions will be considered AEs and documented in the participant chart.

For purposes of this study, a "newly-identified" condition is defined as one of the following:

- not present at baseline (enrollment);
- ongoing at baseline but has increased in severity or frequency during follow-up (includes ongoing baseline conditions or AEs that increase in severity or frequency during follow-up);
- ongoing at baseline, resolves during follow-up, and then re-occurs (excludes chronic condition which should be reported in accordance SSP Section 7.1.1 above)

Any symptoms reported by the participant should be further probed and evaluated. Clinicians should be sure to ask about ongoing baseline symptoms as well as any symptoms listed as "recovering/resolving" on an AE Log CRF.

If, during follow-up, a baseline medical condition resolves or increases in severity or frequency from baseline, this is not updated on the Pre-existing Conditions Log CRF. If the condition increases in severity or frequency from baseline complete an AE Log CRF to document the new AE (i.e., the baseline condition at an increased severity and/or frequency). The question "Was this AE a worsening of a baseline medical condition?" should be answered "yes".

The Pre-existing Conditions Log CRF can be updated with new or corrected information during follow-up, but only when new information related to the participant's baseline medical history is uncovered after enrollment/randomization. If information is added to the Pre-existing Conditions Log CRF after the Enrollment Visit, a chart note explaining the update is required.

7.2 Concomitant Medications

The Concomitant Medications Log CRF is used to document all concomitant medications used by a given participant during study participation.

Protocol section 6.6 requires site staff to document all medications taken by study participants beginning at screening and continuing throughout the duration of the study. Medications include the following:

- Prescription and "over-the counter" medications and preparations
- Vaccinations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- PEP or PrEP
    - Use of PEP or PrEP is exclusionary as outlined in eligibility but use during the study should be recorded and study product discontinued per protocol section 9.3
- Intravaginal medications/agents (tablets, creams, gels, suppositories, rings, etc.)
    - Antibacterials or antifungals, such as metronidazole, miconazole, etc.
    - Hormonal agents, such as oestradiol
    - Miscellaneous, such as povidone iodine, hydroxyquinoline, copper, etc.
    - Spermicides, such as nonoxyl-9

- Contraceptive medications, if applicable
  - Injectable contraceptive (Depo, NET-EN, Cyclofem, etc)
  - Oral Contraceptive birth control pills
  - Implants/IUD

Use of sexual lubricants should be recorded on the Concomitant Medications Log CRF as well.

Note: Alcohol consumption and recreational drug use should not be reported as concomitant medications on the Concomitant Medications Log. Instead, excessive alcohol consumption (defined as binge drinking, heavy drinking, and any drinking by pregnant women or people younger than age 21 (as per the CDC: https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm) and recreational drug use may be considered baseline medical conditions, per site clinician judgment, in which case they should be recorded on the Pre-Existing Conditions Log.

It is helpful to ascertain the baseline medication information in the context of the baseline medical history. Site staff should ask open-ended questions to elicit participant report of current medications, and use the information obtained in the medical history to probe for additional medications that the participant may otherwise forget to report.

At each follow-up visit, review the participant's concomitant medications. Ask the participant if she has started taking any new medications, and record on the Concomitant Medications Log any new medications she reports having started since her last medications assessment.

In addition, review all previous entries that do not have a "Date Stopped" entered and ask the participant whether she is still taking the medication (and at the same dose and frequency). If the participant has stopped taking a medication, enter the last date the participant used the medication in the "Date Stopped" field. If the participant is taking the same medication but at a different dose or frequency, enter the date the participant last used the medication at the original dose or frequency in the "Date Stopped" field, and complete a new Concomitant Medications Log entry for the new dose or frequency. Ensure that concomitant medications mentioned in previous parts of the visit are documented correctly and consistently on the Concomitant Medications Log, so that study records are not discrepant.

7.3 Prohibited Medications, Products and Practices

Certain medications, products and practices are prohibited for the first month following the initial film insertion at V2: Enrollment as detailed in the protocol. Participants will be counseled to avoid using protocol prohibited medications and practices during this time using the MATRIX-002 PROTOCOL COUNSELING GUIDE AND WORKSHEET, available on the MATRIX-002 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-002/matrix-002-study-documents).

If a participant reports any of the above during the first month of product use the site staff will counsel the participant about the importance of adhering to the protocol. There are no restrictions on sexual activity, intravaginal practices or products during the second month of participation (after the second film insertion). Use of a prohibited vaginal practice or product during month one will be captured as a protocol deviation.

Site IoRs should use their discretion when determining whether or not to enroll participants using medications not explicitly identified in the protocol, but which may impact study results or participant safety.

7.4 Physical Exam

Protocol Section 7.8 outlines all required physical exam assessments which are done as part of a full physical examination. A full physical exam is required at Screening. During the physical exam, site staff should assess for any other medical condition that would make participation in the study unsafe or interfere with interpreting the study data or achieving the study objectives. Physical exams may identify additional baseline medical information that participants inadvertently do not report in their baseline medical history. In such situations, the clinician should add the information to the Pre-existing Conditions CRF as well.

A targeted physical examination will be done, if clinically indicated after the Screening Visit. Site clinicians may use their discretion to determine whether or not to conduct a more comprehensive physical exam in response to reported symptoms or illnesses present at the time of the visit.

Physical exam assessments should be documented on the appropriate CRF.

7.4.1 Weight

Participant weight is measured at the Screening Visit. Weight may be measured in kilograms or pounds with the appropriate unit of measure indicated on the CRF.

7.4.2 Height

Participant height may be measured in centimeters or inches with the appropriate unit of measure indicated on the CRF at the Screening Visit.

7.4.3 Blood Pressure

Blood pressure is a component of the Full Physical Examination at the Screening Visit; devices are expected to be calibrated regularly per manufacturer's directions.

7.5 Pelvic Exam

7.5.1 Pelvic Exam Instructions

Pelvic exams are conducted at all clinic study visits. Ideally all in-person visits should be scheduled when bleeding is not expected.

See below in the event a participant is experiencing menses or any vaginal bleeding at the time of an exam.

- During enrollment, if the participant is experiencing or reports menses-like bleeding beyond mild spotting, reschedule the visit and complete within the 45-day screening window.
    - If the Enrollment visit cannot be completed with the 45-day screening window, the participant will be considered a screen failure and will be permitted to be re-screened once if interested.

- At Week 4 Visit, if the participant is experiencing or reports menses-like bleeding beyond mild spotting, reschedule the exam within the window period, if possible. Window periods are outlined in SSP Section 05 Study Procedures.
    - If it is not possible to schedule the visit within the designated window period, contact the PSRT for guidance.
- If a participant presents for an interim visit complaining of ongoing genital symptoms, perform a pelvic exam to evaluate symptoms. If the participant is not comfortable with completing an exam, they should be scheduled to return for a pelvic exam as soon as possible after vaginal bleeding stops.

General Technique:

- Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to ensure participant comfort and accurate documentation of exam findings. If not standard of care, consider having an additional person (medical assistant or nurse) present during the examination to ensure participant comfort.
- Use clean hand/dirty hand technique, and/or assistants, to avoid contamination. Keep extra gloves available as two hands may be needed at different time points during the exam.
- Use a speculum of appropriate type and size to permit adequate visualization of the vagina and cervix. When appropriate, a Graves speculum is preferred to enable visualization of all anatomic areas and tissues. Prior to insertion, ensure that the speculum functions properly and has no rough edges.

Position the Participant:

- Drape the participant and establish a comfortable examination position that allows for appropriate examination of the genitalia such as dorsal lithotomy with or without use of stirrups; position should allow for the perineum and vulva to be inspected. Make all necessary adjustments to equipment and room to ensure participants comfort: i.e. adjust stirrups and back elevation as needed.

Examine the External Genitalia:

- For pelvic exams, a visual exam (i.e. a naked eye examination) should be performed of the external genitalia including the perineum, and perianal area. Do not insert the speculum before examining the external genitalia.

Examine the Internal Genitalia (Cervix and Vagina):

- The speculum may be lubricated with warm water only, if needed. No other lubricant may be used. Gently insert the speculum and open it once past the pelvic floor muscles, using gentle downward pressure, so as to avoid trauma while enabling visualization of the cervical face and upper vagina. If the cervix is poorly visualized, to avoid iatrogenic injury, remove the speculum and use a gloved finger (lubricated with warm water if needed) to establish the position of the cervix. Then re-insert the speculum. Perform naked eye exam of the cervix and vagina, noting any abnormal findings.
- To complete the naked eye examination of the vagina, slowly withdraw the speculum with the blades moderately open, re-focusing as needed. Alternatively, the speculum may be rotated ninety degrees to allow visualization of the anterior and posterior vaginal walls; retract the speculum away from the cervix and close the blades to rotate.
- Removal of Visual Obstruction: After collection of vaginal and endocervical specimens, any obstruction (e.g., mucus, cellular debris) may be removed using a large saline-moistened swab (scopette) in a gentle dabbing fashion to remove the obstruction. Avoid twisting or rolling the swab over the surface of epithelium. Do not use a dry swab to remove any obstruction at any time, as this may cause trauma to the epithelium. If saline is not available, a swab moistened with water will also suffice.

A bimanual exam is not required following the Screening Visit, unless clinically indicated (i.e. to assess for PID).

7.5.1.1 Pelvic Specimen Collection

Clinicians should collect pelvic specimens, as detailed in SSP Section 09 (Laboratory Considerations), during the pelvic examination *while the speculum is in place*.

Performed if indicated and/or per local standard of care according to site SOPs:
- Pap test
- Saline/KOH wet mount for candidiasis and/or BV

7.5.1.2 Documenting Pelvic Exam Findings

All abnormal pelvic exams findings should be noted. If an exam is conducted at baseline, abnormal findings will be documented on the Pelvic Exam CRF and the Pre-Existing Conditions Log. When an exam is conducted during follow up, all abnormal findings identified will be documented on the Pelvic Exam CRF and AE Log, as appropriate. Supplemental information may also be recorded in chart notes or on other designated source documents as needed.

Note: All pelvic exam findings consistent with the "grade 0" column of the FGGT are considered normal. The following also are considered normal:

- anatomic variants
- gland openings
- Nabothian cysts
- mucus retention cysts
- Gartner's duct cysts
- blood vessel changes other than disruption
- skin tags
- scars
- cervical ectopy

IUD strings may be visible upon exam and are also considered a normal finding. If present, they should be documented in the chart notes or source document. Sites may determine whether they choose to consistently document the presence of IUD strings (best practice) or not. It is recommended that if a participant has an IUD, but the strings are not visible upon exam, this should be documented and followed up on as per site's standards.

7.6 STI/RTI/UTI Evaluation, Management and Treatment

Clinical and laboratory evaluations are performed in MATRIX-002 to diagnose the following STIs and RTIs:

- Chlamydia infection
- Gonorrhea infection
- Trichomonas
- Urinary tract infection (UTI), as clinically indicated

- Syphilis infection
- HIV

All participants diagnosed with an active sexually transmitted or reproductive tract infection (STI/RTI) or UTI based on the presence of symptoms should be provided treatment and or referral for treatment per site standard of care and applicable site standard operating procedures (SOPs). STIs/RTIs will be treated in accordance with current CDC guidelines which can be accessed at: http://www.cdc.gov/std/treatment or current WHO guidelines can be accessed at: http://www.who.int/reproductivehealth/topics/rtis/evidence/en/index.html

Asymptomatic bacterial vaginosis (BV) does not require treatment per current WHO guidelines. Asymptomatic vaginal candidiasis also should not be treated. During screening, these asymptomatic infections are not exclusionary and during follow-up these asymptomatic infections are not considered AEs.

Syndromic Management: Syndromic management of STIs is acceptable per site SOP and local standard of care; however, a thorough laboratory evaluation is expected in the context of this research study so that a specific diagnosis might be uncovered. STI/RTI tests of cure are not required.

Potential participants presenting with an active (symptomatic or per laboratory or clinical diagnosis) infection requiring treatment at Enrollment will be excluded from study participation. Per current CDC guidelines, the following symptomatic infections require treatment and are exclusionary: gonorrhea, chlamydia, syphilis, active herpes simplex virus (HSV) lesions, anogenital sores or ulcers, or symptomatic genital warts, chancroid, pelvic inflammatory disease (PID), other vaginitis, and trichomoniasis.

Participants who are otherwise eligible but are diagnosed with BV and/or candida at screening may be treated within the screening/enrollment window period and enrolled if all symptoms have resolved and no other exclusion criteria apply (i.e. recent antibiotic use).

Infections should be considered "symptomatic" when a participant self-reports or complains of symptoms associated with the infection.

Participants' partners should be offered treatment, or referrals, **as per sites' SOPs**.

Urinary tract infections (UTIs)

Participants who are otherwise eligible but have symptoms consistent with a UTI at screening may be treated and enrolled if all symptoms have resolved and no other exclusion criteria apply (i.e. recent antibiotic use). The following symptoms are considered indicative of a possible UTI:

- Frequent urge to urinate
- Pain and burning during urination
- Lower abdominal pain and/or uncomfortable pressure above the pubic bone

A urine culture is not required at screening.

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 blood, protein or glucose on dipstick, even if noted incidentally while testing for leukocyte esterase and nitrates, should be reported as a laboratory abnormality AE as they are listed on the DAIDS toxicity table.

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.

Urine dipstick and/or culture may be performed per site SOP when a UTI is suspected during follow-up. The results do not need to be returned before presumptive treatment, but the results will influence how the AE is captured. When the participant initially reports symptoms suggestive of a urinary tract infection, capture each symptom as a separate AE. If urine dipstick and/or culture results are positive, update the AE Log CRFs to reflect a single AE for grade 2 Urinary Tract Infection per UTI criteria defined in the FGGT. If the urine dipstick and/or culture is negative, the AE(s) will remain reported as symptoms only. Results of any urine cultures and dipsticks performed must be documented in chart notes and/or other site-specific source documents.

Note that urine dipstick is only performed if clinically indicated. At the screening visit, positive dipstick results do not directly impact eligibility, but abnormal hematuria, protein and glucose parameters should prompt further evaluation or consideration pending IoR review. Abnormal hematuria, protein and glucose uncovered at the screening visit should be captured on the Pre-existing Conditions Log. In follow-up, findings of hematuria, abnormal protein and glucose on the dipstick should be reported on the AE Log CRF as indicated. Note that findings of leukocytes/nitrites are not gradable per the DAIDS toxicity table, and like other non-gradable labs should not be reported as baseline conditions or AEs.
When clinically appropriate, investigators should use oral or parenteral medications when at all possible to avoid intravaginally administered medication use. Observed single dose treatment should be provided whenever possible, per clinician discretion.

HIV Testing

At Screening and/or Enrollment (prior to randomization), all participants will undergo HIV testing. Participants who have a rapid HIV test that is positive or indeterminate at V1 Screening and/or V2 Enrollment are not eligible for enrollment. During follow-up visits, refer to Protocol Appendix II: Algorithm for HIV Testing.

Participants who have a reactive HIV test result during follow-up visits will be discontinued. In addition, if a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition, testing will be performed immediately. Any participant who has a positive HIV test after enrollment, will have product use and study participation permanently discontinued. All participants with confirmed HIV infection will be counseled and referred to available resources for medical and psychosocial care and support. Site staff should follow-up on all referrals as per site standards to determine if the participant actually sought the care to which they were referred, the outcome of the referral, and whether additional referrals are needed. All referrals, outcomes, and follow-up plans and actions should be fully documented in participant study records.

Protocol-specified examinations and laboratory tests will provide information upon which appropriate clinical care decisions can be made. Study staff must refer participants to non-study HIV care providers. Study staff will provide and explain all study examination findings and test results to participants. They also will provide copies of laboratory test result reports to participants and their non-study providers (if the participant grants approval).

7.7 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for product discontinuation (Section 9.3), guidance on product discontinuation in response to observed AEs (Section 9.4), HIV (Section 9.6), pregnancy (Section 9.5) and early study termination (Section 9.8).

All clinical and product use management must be fully documented in participant study records. When the PSRT is consulted in relation to clinical and product use management, completed PSRT query forms (including a response from the PSRT) must be printed and filed in participant study records. Unless otherwise specified in protocol section 9, the IoR/designee should immediately consult the PSRT for any product discontinuations.

In the event that the film needs to be removed due to an immediate/allergic reaction or adverse event, remove the film by:

- Inserting appropriate size speculum to visualize vagina/cervix
- Remove any visible film with a scopette/swab/forcep
- Insert 10cc of sterile normal saline solution into the vagina
- Use a pipette to perform lavage (flush the saline around the vagina and cervix for about a minute
- Remove lavaged fluid with a pipette; dispose of saline
- Repeat with an additional 10cc of sterile normal saline solution if necessary (i.e. if additional film is visible)
- Remove speculum

7.8 Permanent Discontinuation Criteria

Protocol section 9.3., includes a list of the reasons a participant would be permanently discontinued from product use.

If there are any other issues or clinical concerns with the participant using the second dose, the site IoR/Designee may temporarily hold study product and contact the PSRT for guidance using the PSRT QUERY FORM, available on the MATRIX-002 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-002/matrix-002-study-documents).

Participants who experience a known or potential HIV exposure during study participation or have a recognized risk of exposure and thus need PEP will have study product permanently discontinued and will be referred for PEP or PrEP initiation. Those who need PEP will be encouraged to start it as quickly as possible and within 72 hours of potential exposure.