MATRIX-003 Study-Specific Procedures (SSP) Manual
Section 5 – Study Procedures

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5 Introduction

This SSP section provides information on requirements for MATRIX-003 study procedures, including screening, enrollment and participant follow-up visits and will focus on use of Visit Checklists and the associated paper case report forms (CRFs)/documents used at study visits/contacts. Details regarding MATRIX-003 REDCap case report forms (CRFs), behavioral assessments and laboratory procedures can be found in the applicable SSP sections. The Visit Checklists and paper CRFs are available on the MATRIX-003 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents).

The provided Visit Checklists templates should be carefully reviewed and updated by sites to ensure all protocol procedures are listed. Sites can modify the Visit Checklists to include site specific information. Sites are responsible for the content of their final versions of Checklists. MATRIX Clinical Trials Hub (CTH) does not need to review site specific Visit Checklists.

A list of MATRIX-003 paper case report forms (CRFs)/Tools can be found in Appendix 1 along with guidance for using the form.

While this section provides guidance for study procedures, the most current version of the MATRIX-003 protocol is the primary reference for all study procedures. The protocol supersedes this SSP section, or any other MATRIX-003 document, should there be inconsistencies.

Note: The study products used in this study are placebo intravaginal rings. For ease and consistency of reference, throughout this Manual, and in select implementation materials, the study product will be referred to as either the "ring" or "intravaginal ring" or "IVR".

5.1 Visit Locations

Given the nature of study procedures required for MATRIX-003, all study procedures for V1 (Screening), V2 (Enrollment), V4 & V8 (Day 14 Clinic Visits), V5 (Day 28 Clinic Visit/1st Ring Removal), V6 (2nd Ring Insertion) and V9 (Day 28/2nd Ring Removal/Site End Visit) should ideally occur at the study clinic. These visits may be conducted at an off-site location as applicable and IRB/IEC approved, and if the participant consented to off-site visits. Due to the potential extended length of a visit, and for participant convenience, in-depth interviews may be scheduled on a different date than the clinic visit as per protocol.

For all study visits/procedures (after obtaining written informed consent), sites may utilize telephone or online applications to conduct appropriate visit procedures in a remote fashion (as IRB/IEC approved) to limit time spent in the clinic. This may include, but is not limited to, remotely conducting interviews, providing protocol counseling, and administering behavioral surveys, when applicable. Any modifications to study visits will be documented accordingly. The remaining study visits (V3, V7) are telephone contacts but may be conducted through SMS if IRB/IEC approved, or in-person if preferred by the participant.

5.2 Eligibility Determination SOP

It is the responsibility of the site Investigator of Record (IoR) and other designated staff to ensure that only participants who meet the study eligibility criteria be enrolled in the study**. Each study site**

must establish a standard operating procedure (SOP) that describes how study staff will fulfill this responsibility. The SOP should contain, at a minimum, the following elements related to eligibility determination procedures, including:

- During-visit eligibility assessment procedures
- Post-screening visit eligibility assessment and confirmation of procedures (i.e. review of laboratory results)
- Final confirmation and sign-off of procedures prior to enrollment/randomization
- Documentation of each eligibility criterion (met or not met)
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures (if not specified elsewhere)
- Determining literacy and when a witness is required
- Determining participants speak/understand a language being used in the study

Sites may reference the ELIGIBILITY CRITERIA (paper) CRF available on the MATRIX-003 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents) when developing their site eligibility SOP.

5.3 Screening Visit

The term "screening" refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MATRIX-003. The study eligibility criteria are listed in Protocol Sections 5.2 and 5.3; and required screening procedures are listed in Protocol Section 7.2.

5.3.1 Screening and Enrollment Timeframe

All protocol-specified screening procedures must take place up to 45-days prior to enrollment/randomization. The 45-day window begins the day written informed consent is obtained (signed), even if no other procedures were done on that day.

Screening procedures (as part of the same screening attempt) may be conducted over multiple days, if needed, to complete all required procedures as long as the screening procedures happen within the 45-day screening window. In cases where the screening visit is conducted over multiple days, all procedures are considered part of the same screening visit/screening attempt.

The term "screening attempt" is used to describe each time a participant screens for the study (i.e., each time they provide written informed consent for participation in the study). As per protocol section 7.2, potential participants may undergo one additional screening attempt, per the discretion of the IoR/designee.

If the participant cannot be enrolled within 45 days of the screening visit/obtaining written informed consent, the participant must repeat the entire screening process, beginning with the informed consent process. This will be counted as the participant's re-screen attempt. When re-screening participants, all screening procedures, with the possible exception of a Pap test, need to be repeated. A new participant identification number (PTID) is assigned to the participant. In the event of a re-screen, the participant's original PTID will be linked to their newly assigned re-screen PTID.

5.3.2 Screening Visit Procedures

Required screening procedures are specified in protocol section 7.2 and reflected in the SCREENING VISIT CHECKLIST template available on the MATRIX-003 webpage (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents). Sites should utilize the available checklist to guide screening visit procedures as outlined in the protocol. Sites can modify the checklist (i.e., add specific information regarding order of blood tube collection, include site specific forms, add amount of participant reimbursement), as needed. The order of items on the Screening Checklist may be done per site preference, except for obtaining written informed consent, which must be obtained prior to performing any study related procedures, while adhering to the process detailed in SSP Section 04 (Informed Consent).

After obtaining written informed consent, staff should immediately assign the participant a PTID by completing MATRIX-003 PTID ASSIGNMENT LOG. The log will contain a list of pre-populated PTIDs, unique to each site, and will be provided by the MATRIX CTH Data Management & Statistical Support team as further described in SSP Section 12 (Data Collection). Participants will then undergo a series of eligibility questions, clinical evaluations, laboratory tests and counseling to determine eligibility. Locator and demographic information will also be obtained. Participants will be reimbursed for the visit and may be scheduled for enrollment, if found presumptively eligible.

Eligibility is assessed by the IoR/designee listed on the DOD Log. Remaining screening procedures should be conducted and marked as done by entering initials on applicable rows of the Screening Visit Checklist. All applicable items to be performed during the visit should be reviewed and marked complete prior to the participant leaving the clinic.

Any questions or concerns related to a participant's eligibility should be sent to the protocol safety physician by completing a PSRT QUERY FORM available on the MATRIX-003 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents).

5.3.2.1 Additional Screening Details

Pap smear

Documentation of a Pap smear performed in the last 3 years must be available for the result to be considered for eligibility (i.e., provided by participant or obtained through electronic medical record/EMR if applicable)

- The Pap result must be normal, Grade 0 for the participant to be eligible
- The result should be filed in the participant's chart as source documentation

Otherwise, a Pap should be collected at the Screening Visit

- The Screening Visit Pap result must be available prior to determining final eligibility and must be Grade 0 or Grade 1 with no treatment required to be eligible
- The result should be filed in the participant's chart as source documentation
- Abnormal results from a Pap collected at screening should be handled (i.e., referrals and follow up) and documented per site standard

MATRIX-003 PARTICIPANT VISIT CALENDAR TOOL

The calendar tool is available on the MATRIX-003 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents)

and can be used to automatically calculate upcoming visit date(s). At V1, enter the Screening Visit date to calculate the last possible day for enrollment (45 days from screening).

5.3.3 Screening and Enrollment Log

The E6 Good Clinical Practice: Consolidated Guidance requires study sites to document screening and enrollment activity on screening and/or enrollment logs.

Study sites are expected to track screening and enrollment activity on screening and/or enrollment logs. A paper screening and enrollment log may be created and kept by sites per site standards. A sample MATRIX-003 SCREENING AND ENROLLMENT LOG is available on the MATRIX-003 Study webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents). Sites can also generate a real time site screening and enrollment report as needed through REDCap, listed under "Reports" on the lefthand side of the MATRIX-003 REDCap dashboard.

5.3.4 Participants Found to be Ineligible (Screen Failures)

Screening procedures should be discontinued when the participant is determined to be ineligible. For all participants who screen fail, the following should be in place:

- Completed applicable ICF(s) and associated consent documents (i.e., ICCA and coversheet)
- Reason(s) for ineligibility, with date of determination, documented in chart notes and/or on the MATRIX-003 Eligibility Checklist
- Clinically significant abnormalities (i.e. labs) should be provided and explained to the participant within a reasonable timeframe (even if not exclusionary and/or referral not necessary). Document on Visit Checklist and/or in chart notes as applicable.
- If a participant screens out due to a clinical condition or lab abnormality that requires follow-up, appropriate referrals should be provided and documentation of the referral should be included in the participant chart.
- All source documentation completed up until the time ineligibility was determined
- Chart notes completed up until the time ineligibility was determined
- Indication of what visit procedures were conducted up until the point of ineligibility determination on the Visit Checklist
- Complete Participation Disposition form in REDCap
- Update Screening and Enrollment Log, by completing row on the log, updating with date of discontinuation of screening and reason for screen failure, as applicable

5.4 Enrollment Visit

The Enrollment Visit must take place withing 45 days of the Screening Visit (informed consent date). If an IRB/IEC determined a site is required to use separate informed consents, written (Enrollment) Informed Consent must be obtained (and associated IC documents completed) prior to performing any enrollment study visit procedures. The Enrollment Visit serves as the baseline visit for MATRIX-003. All procedures for this visit must be conducted on the same day and cannot be split across multiple days.

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR/designee should contact the MATRIX-003 Protocol Safety Review Team (PSRT) and the MATRIX-003 Management Team immediately for guidance on subsequent action to be taken.

5.4.1 Enrollment Visit Procedures

Study enrollment procedures are specified in protocol section 7.3.1 and reflected in the ENROLLMENT VISIT CHECKLIST template available on the MATRIX-003 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents).

The participant's final eligibility status should be determined by reviewing/evaluating each item on the MATRIX-003 ELIGIBILITY CHECKLIST. The IoR/designee, as specified on the site DOD Log, must review and sign the eligibility checklist at enrollment to determine final eligibility of a participant.

All procedures listed as pre-randomization procedures on the Enrollment Visit Checklist must be completed prior to randomizing a participant. The randomization process is outlined in SSP Section 12 (Data Collection). A participant is considered enrolled in the study once they have been randomized to the order/sequence of ring use, A then B or B then A. The process for obtaining an intravaginal ring from the pharmacy is detailed in SSP Section 06 (Study Product Considerations).

5.4.1.1 Additional Enrollment Details

Evaluation of Bleeding at Enrollment

Per protocol, participants should ideally be scheduled for enrollment when they are not expecting menses-like bleeding. Assessment of vaginal bleeding may be somewhat subjective, therefore the intention is to clarify that menses-like bleeding is meant to mean moderate to heavy vaginal, and does not include light bleeding or spotting.

If a participant presents for enrollment and reports menses-like bleeding, ideally they should be rescheduled to enroll following the cessation of heavy bleeding and within the 45-day screening/enrollment window if possible. Heavy bleeding may interfere with microbiota testing.

Examples of spotting or bleeding at Enrollment that would NOT be problematic:

- A participant has an IUD and typically experiences a few days of spotting each month
- A patient who uses Depo Provera and reports minimal bleeding when they are close to/due for their next injection
- A participant is having light spotting or brown discharge at the end of a menstrual period

Examples of bleeding that would ideally warrant re-scheduling the enrollment visit:

- A participant who is experiencing moderate bleeding (menses-like or equivalent to the flow of a menstrual period), regardless of whether the bleeding is related to their menses or contraceptive method
- A participant who recently started using Nexplanon or Depo and is experiencing heavy bleeding (i.e. needs to change pads frequently)

Bleeding that is noted on exam should be documented on the Pelvic Exam form with details included in the visit chart note.

Ring Insertion and Evaluation of Placement

Per protocol, the participant has two attempts to self-insert the assigned intravaginal ring. If after two attempts the participant is unsuccessful at self-insertion, the ring is inserted by a clinician. The process is described below. Insertion instructions may be provided and reviewed with the participant before or after obtaining the ring from the pharmacy.

- Review IRB/IEC approved intravaginal ring insertion instructions with the participant
  - Participant MATRIX-003 INTRAVAGINAL RING USE INSTRUCTIONS are available on MATRIX webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents)
- Obtain intravaginal ring from pharmacy as detailed in SSP Section 06 (Study Product Considerations)
- Provide assigned intravaginal ring to the participant
- Have participant open the package with clinician present; clinician to visually inspect appearance of ring (both sides). Documentation of inspection should be documented on CLINICAN OBSERVATION FOR INSERTION COI form
- Have participant attempt 1st Intravaginal Ring Self-Insertion
  - Note: self-insertion is not directly observed by the clinician, but the clinician should be immediately available for questions (i.e. behind an exam curtain, outside the door)
  - Following the first self-insertion attempt, clinician to immediately evaluate placement by performing a digital genital exam to ensure the ring is inserted and proximal to the introitus.
    - If correct ring placement is confirmed on digital exam, ask the participant to walk around the exam room
      - If the participant is comfortable, proceed with remaining visit procedures on Visit Checklist.
      - If the participant is uncomfortable, instruct the participant to push the ring further up into the vagina and then walk around again
      - If the participant is uncomfortable after trying to adjust the ring, the clinician may repeat a digital exam
    - If ring is not palpable at all carefully inspect the surrounding area (i.e., floor/exam table) to locate ring.

- Have participant attempt 2nd Intravaginal Self-Insertion
  - The same ring is used for the second insertion. Although not required, the ring may be rinsed with clean water if needed prior to second insertion attempt if requested by participant.
  - The ring insertion and assessment of placement should proceed as described above. If the second ring is unable to be placed correctly and/or found to be uncomfortable for the participant, proceed with clinician insertion.
- Proceed with Clinician Insertion
  - Wash hands thoroughly and apply gloves
  - Open ring package
  - Remove ring with gloved hand and fold the ring in half
  - Part the labia with the other hand
  - Insert the ring into the vagina and swiftly guide/push the ring into correct position proximal to the introitus
  - Confirm placement by digital genital examination
  - Ask participant to walk around the examination room to determine whether the ring is comfortable. Advise adjustment as necessary. Repeat digital genital exam if needed.
  - Proceed with remaining procedures per protocol and as listed on Visit Checklist

Once the ring is inserted (self-insertion or clinician insertion), the participant should be instructed to attempt removal and reinsertion.

- Have the participant review the removal instructions (included in the MATRIX-003 INTRAVAGINAL RING USE INSTRUCTIONS)
- Have the participant attempt removal
  - The clinician should be nearby (i.e. behind a curtain or outside of door) to answer questions and/or provide assistance as needed
- If after two attempts the participant is unable to remove the ring, the clinician should remove the ring
- The participant should then attempt re-insertion using the steps described above

The time of final ring insertion should be documented in the Visit Checklist. Details regarding ring insertion should be detailed in a narrative chart note. Any (observed or voiced) challenges with insertion should be included in the clinician's narrative note and/or CLINICIAN OBSERVATION FOR INSERTION CRF.

If during the ring insertion process, the ring is dropped but not contaminated it may be rinsed with clean water and re-used. If it is contaminated (i.e. falls in the toilet) or the participant is uncomfortable using it, a new ring should be obtained from the pharmacy by completing a new prescription.

5.5 Follow-Up Visits

Throughout the study follow-up period, two types of follow-up visits may be conducted (scheduled and interim visits).

Scheduled visits are those visits required per protocol. Each participant will complete a total of seven clinic follow-up visits/contacts, including a final contact/study exit visit (SEV) as detailed in the table in Section 5.5.1 below.

Interim visits are those visits that take place between scheduled visits. These visits may be performed at any time during the study, and any visit procedures may be conducted as indicated. All interim visits will be properly documented in study files and on applicable CRFs. Procedures performed during an interim visit will depend on the reason for the visit.

- For example, if a participant presents to the site to report an AE, all clinically relevant procedures to assess the AE and required documentation would be performed for that interim visit.

See SSP Section 12 (Data Collection) for more details on recording interim visits.

In the event an inserted intravaginal ring needs to be removed, for instance due to an allergic reaction, see SSP section 07 Clinical Considerations for guidance on ring removal.

In the event the participant returns to have the intravaginal ring reinserted (i.e. ring is removed/expelled at home and participant is unable to reinsert the ring), refer to the Ring Insertion and Evaluation of Placement instructions in section 5.4.1.1. If a new ring is needed (i.e. original ring is contaminated), refer to the process for obtaining an intravaginal ring from the pharmacy as detailed in SSP Section 06 (Study Product Considerations).

Refer to SSP Section 07 (Clinical Considerations) for additional guidance as needed.

5.5.1 Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the study allows for visit window periods as outlined below.

Table 1: Visit Windows

Visit#	Visit Name	Target Visit Date	Window Period*
V3	Day 7 Phone Visit	Day 7	Day 7 +/- 2 days
V4	Day 14 Mid-point Clinic Visit	Day 14	+/- 2 days
V5^	Day 28 Clinic Visit (1st Ring Removal)	Day 28	+/- 2 days
V6	Day 0 Clinic Visit (2nd Ring Insertion)	V5 + 7 days	V5 + 7-21 days
V7	Day 7 Phone Visit	V6 + 7 days	+/- 2 days
V8	Day 14 Mid-point Clinic Visit	V6 + 14 days	+/- 2 days
V9	Day 28 Clinic Visit (2nd Ring Removal) (Early Termination Visit if applicable)	V6 + 28 days	+/- 2 days
^Per section 10.7.2, all participants randomized into the study who complete Visit 5 will be included in the primary analysis.			
*Any visit outside of the window period will be considered a protocol deviation			

Sites are encouraged to complete required study visits on the target day, if possible. If this is not possible, the visit may be completed within the visit window (for visits with a window). Visits completed within the visit window will be considered completed ("retained") visits.

Although the visit windows allow for some flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at specific intervals.

To assist sites with scheduling participant visits, a MATRIX-003 VISIT CALENDAR TOOL is available on the MATRIX webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents).

5.5.1.1 Missed Procedures

All procedures specified by the protocol to be performed at a follow-up visit, ideally, will be completed at a single visit on a single day. If all required procedures cannot be completed on a single day (i.e., because the participant must leave the study site before all required procedures are performed or participant needs to return for a blood draw), the remaining procedures may be completed on subsequent day(s) within the allowable visit window. As described in SSP Section 12 (Data Collection), all CRFs completed for a visit that takes place over more than one day are under the same visit (even though the dates recorded on the CRFs may be different).

If study visits must be done over more than one day, please ensure that:

- HIV pre-test counseling and HIV testing occur on one day (note: if HIV testing is done using a rapid test, post-test counseling should ideally occur on the same day).

Any procedures that are not conducted within the visit window will be considered missed and a deviation should be completed.

5.5.1.2 Missed Visits

In an effort to prevent missed visits, participants should be scheduled early enough in the visit window to allow for rescheduling within the window, if needed.

If a visit/contact is missed (i.e. out of window) following an intravaginal ring insertion visit, sites must make every effort to make up the missed visit and required study procedures. Provided the missed visit is conducted prior to the start of the next window period, the out of window visit study procedures/details will be conducted under the visit that was missed and a deviation will need to be completed for an out of window visit.

In any of these missed visit scenarios, sites should contact the MATRIX-003 Management Team for additional guidance as needed.

5.5.2 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol section 7.3. Additional procedural clarifications/specifications are provided in this section. While sites should aim to perform procedures in the order indicated on their site-specific visit checklists, this might not always be possible. Further operational guidance on completing protocol-specific procedures, is incorporated into the sample Visit Checklists and in SSP Section 02 (Documentation Requirements).

As a general guide, during follow-up:

- Locator information must be obtained/reviewed at every visit
- Explain procedures performed at each visit and confirm willingness to continue participation

- Protocol counseling will be provided at all in-clinic visits and at specified contacts per protocol
- Medical and menstrual history review, AE assessment and documentation, assessment of concomitant medications and provision of any available lab results will be done at all in-clinic follow up visits
- Pelvic examination is conducted at every in-clinic visit
- 1st intravaginal ring removal occurs at V5 (in clinic)
- 2nd intravaginal ring insertion occurs at V6 (in clinic)
- 2nd intravaginal ring removal occurs at V9 (in clinic)
- Behavioral questionnaires are conducted at visits/contacts as detailed in the protocol and specified in SSP Section 11 (Behavioral Measures)
- Participants will be reimbursed at each visit and scheduled for their next visit as applicable
- Condoms will be offered at V4, V5, V8, and V9*
- A pregnancy test and an HIV test and associated counseling are done at V1, V2, V6, V9 and if indicated at other in-person clinic visits
- Chart notes should be written for each visit/contact and should include details of any prn tests/procedures that are performed

*Site will be required to purchase/have non-spermicidal condoms available to offer to participants.

5.5.3 Follow-Up Visit Procedures

5.5.3.1 V3 & V7 (Day 7 Phone Visit)

Per protocol, this is a phone call but may be an SMS or in-person visit per participant preference and IRB/IEC approval. See protocol and V3 & V7 Visit Checklists for specific procedures.

5.5.3.2 V4, V8 (Day 14 Clinic Visit)

Per protocol, this is a clinic visit. See protocol and V4 & V8 Visit Checklists for specific procedures.

5.5.3.3 V5 (Day 28 Clinic Visit/1st Ring Removal)

- At V5 (Day 28 Visit), participant is provided with removal instructions (included in the MATRIX-003 INTRAVAGINAL USE INSTRUCTIONS) and removes 1st Ring. If participant is unable to remove the ring after 2 attempts, it will be removed by a study clinician.

- Intravaginal Ring Removal by Clinician
  - Wash hands thoroughly and apply gloves
  - Perform digital genital examination to locate the ring
  - Remove the ring by hooking it with gloved finger and pulling it out.
  - Inspect the ring and cassettes to determine if they are intact
  - If ring is not located, proceed to speculum examination.
  - May turn speculum 90 degrees to visualize entire cervix and proximal vagina. If ring is visualized, grasp and remove with fingers or forceps as the speculum is removed
  - Proceed with remaining procedures per protocol and as listed on Visit Checklist

The time of ring removal should be documented in the Visit Checklist.

Once removed, the used ring should be inspected for appearance (both sides). If there are any concerns with the ring (i.e. missing cartridge, discoloration, deformity), place the ring in a biohazard bag, label it with the PTID, ring type (A or B), insertion and removal date, and contact the Management Team for further guidance.

Otherwise, once the ring is removed and visualized by the clinician for appearance and accountability, the ring should be disposed of in a biohazard container (i.e. Sharps or equivalent) and/or to be destroyed locally, in accordance with Site SOPs and local regulations. Further disposal instructions are included in the MATRIX-003 Pharmacy Manual.

Ring removal inspection details should be documented in the CLINICIAN OBSERVATION FOR REMOVAL COR form.

5.5.3.4 V6 (2nd Ring Insertion)

This visit should ideally occur when the participant is not having menses-like bleeding, as detailed in V2 above. Obtain ring as outlined in SSP Section 06 (Study Product Considerations). At V6 during the pelvic exam, sample collection will be conducted prior to ring placement.

5.5.3.4.1 Additional V6 Details

Adhere to ring insertion and placement evaluation instructions as described in Section 5.4.1.1. Confirmation of checking for ring placement should be documented on the Clinical Observations for Insertion (COI) CRF and in chart notes, as applicable. The time of ring insertion should be documented in the Visit Checklist. Participant ring removal and reinsertion as described in section 5.4.1.1 at Enrollment (V2) is NOT required at this visit.

5.5.3.5 V9 (Day 28/2nd Ring Removal/IDI/Study Exit Visit)

This is the last scheduled visit.

5.5.3.5.1 Additional V9 Details

Removal of Ring

The participant should be provided with removal instructions (included in the MATRIX-003 INTRAVAGINAL USE INSTRUCTIONS), and will have two attempts at self-removal. If the participant is unable to remove the ring, follow clinician removal instructions as described in 5.5.3.3. Note the time of ring removal on V9 checklist. Inspect and discard the ring as described above.

Participant IDI Subset

Details regarding the participant IDI can be found in SSP Section 11 (Behavioral Measures).

Sexual Partner IDI Subset

At V9, review and confirm permission to contact the sexual partner. If the participant agrees, the partner's contact information will be collected per the site's standard and the partner's preference. Alternately, the site will give the participant the site's phone number for the sexual partner to initiate contact with the

study staff. If selected, study staff will contact the sexual partner (or provide the site's contact information) as approved by the IRB/IEC and as outlined in the site's SOP.

If the sexual partner is interested in participating in the IDI, a visit will be scheduled to review and obtain written informed consent and to perform the visit procedures, per protocol. Multiple visits may be conducted to complete the IDI visit for the sexual partner subset but per protocol must be conducted within one month of participant V9.

5.5.4 Final Contact/Termination Considerations

The Final Contact/Termination visit will be V9 and conducted in clinic. Per protocol Section 7.3.4, V9 constitutes the Early Termination Visit; utilize V9 Visit Checklist and complete applicable procedures.

Additional contacts after study exit may be required for:

- Participants who are pregnant during the study to obtain pregnancy outcome
- Participants with certain types of AEs, per protocol that are ongoing at study exit to ensure stability or resolution

For each participant, any additional contact(s) should be scheduled based on the participant's overall clinical picture at study exit, as well as the time required to obtain all final study test results. It is recommended that follow-up contact plans be documented in chart notes. All additional contacts must be documented in participant study records, but no CRFs are completed for these contacts.

5.5.5 Participants Who Become Infected with HIV

Participants who test positive for HIV at Screening or Enrollment are not eligible to participate.

If a participant becomes infected with HIV after the Enrollment Visit, refer to the HIV algorithm in the protocol. The participant will return to have the ring removed and will be referred to local care and treatment services. They may return to the clinic for additional counseling and other support services, as needed and as available per site SOP (see protocol section 7.4.1 & 9.6).

Study follow-up visits and procedures will be discontinued after removing the ring, and the participant will be considered terminated from the study. A visit to remove the ring will be scheduled and a full Early Termination Visit will be conducted, if the participant is willing (see protocol section 7.3.6)

5.5.6 Participants Who Become Pregnant

If a participant becomes pregnant, the ring will be removed and follow-up visits and procedures will be discontinued, and the participant will be considered terminated from the study (see protocol sections 7.4.2 & 9.7). An early Termination Visit will be conducted, if the participant is willing (see protocol section 9.8). Participants will be referred to local health care services and may return to the clinic for additional counseling, as needed per site SOP.

Sites should develop a plan with such participants to attain the pregnancy outcome and include applicable details, if necessary, in the site-specific informed consent and/or IRB/IEC submission. One

contact method to obtain this information is sufficient. For example, the participant could call or e-mail the site to inform the site of the outcome.

5.5.7 Participants Who Permanently Discontinue Study Product for Other Reasons

Per protocol section 9.5, study product use need not be held in the event of an STI/RTI requiring treatment, unless other permanent discontinuation guidelines apply in which case consultation with the PSRT is required.

5.5.8 Early Termination Visit

Staff should schedule a visit for ring removal and make every reasonable effort to complete a final evaluation prior to terminating the participant.

Protocol Sections 7.4 and 9.8 detail early termination or withdraw of a participant and when the PSRT must be notified.

Per protocol, V9 will constitute the Early Termination Visit. The V9 Visit Checklist should be used as a guide for early termination procedures, if the participant is willing to complete one last visit. If the participant is terminating early from the study for any reason, staff should complete the following:

- Schedule a visit for ring removal and/or retrieval.
- Record the reason(s) for the withdrawal in participants' study records.
- Consult the PSRT regarding early terminations per protocol and/or IoR decision. Print and file outcome correspondence in the participant chart.
- Note PSRT consultation is not required for voluntary withdrawals.
- Update participant locator form, and document how the participant would like to receive any follow up test results (as needed).

5.5.9 Replacing Participants

Per protocol section 10.3, replacement participants will be considered in consultation with study leadership if loss to follow-up (LTFU) is higher than expected.

Appendix 1: MATRIX-003 Paper Case Report Forms (CRFs)/Tools

Appendix 1 lists the MATRIX-003 paper CRFs/Tools along with guidance for use of the forms. The forms are specifically listed on each applicable Visit Checklist. Templates can be found on the MATRIX-003 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents).

MATRIX-003 T/F ICCA (True/False Informed Consent Comprehension Assessment)

This form:

- Or an equivalent form should be used to assess and document comprehension of informed consent
- May be modified to meet site standards or details included in the site Informed Consent SOP
- Should be reviewed and approved by the site's IRB/IEC prior to use
- Should be completed by the participant prior to signing consent

MATRIX-003 INFORMED CONSENT COVERSHEET

This form:

- Or an equivalent form should be used to document the informed consent process
- May be modified to meet site standards and local/country/federal requirements
- Should be completed during the Screening Visit to ensure accuracy and completeness of the informed consent document(s)
- Documentation should clearly state that informed consent was obtained prior to performing any study procedures

MATRIX-003 ELIGIBILITY CHECKLIST

This form:

- Is used to assess eligibility starting at V1
- Documents review of each criterion, utilizing the source indicated on the form
- May be modified to indicate the specific source used by site, if the source differs from that listed
- Documents if each criterion is met, by initialing YES or NO in the appropriate visit column
- Includes initials and date of late entries that occur after the Screening Visit (i.e., updates made after receiving lab results)
- Is signed by the IoR/designee who reviewed the completed screening entries once all screening criteria are completed. The designee(s) should be listed on the DOD Log.
- Should be moved into the Enrollment Visit tab as applicable following the Screening Visit, as the same form is used to review/assess final eligibility at Enrollment.
- Is used to carefully review each criterion at the Enrollment Visit and to initial YES or NO under the enrollment column
- Is completed on the day of enrollment; all inclusion criteria must be YES and all exclusion criteria must be NO to be eligible
- Determines and documents final eligibility, the form must be reviewed in entirety and signed/dated by the IoR/designee at the Enrollment Visit
- If a participant is found to be ineligible during the Screening or Enrollment Visit and the checklist has been partially completed, there is no need to continue filling out the checklist past the point when ineligibility is determined

BASELINE MEDICAL HISTORY REVIEW GUIDE

This guide:

- Is designed to review body systems (ROS) at the Screening Visit, with an emphasis on the genital system. Alternately, site may use their own ROS form as long as the components on this form are included

- Will serve as source and should be used to populate details onto PRE-EXISTING CONDITIONS LOG and CONCOMITANT MEDICATIONS LOG, as applicable
- Should be signed and dated by the IoR/designee who completed it
- May include additional handwritten details/notes that are signed/dated. If notes are written on the back of the form, include PTID, date and sign/date entries

MATRIX-003 PROTOCOL COUNSELING GUIDE AND WORKSHEET

This document:

- Includes the counseling required per protocol: protocol adherence, study product, HIV pre- and post-test counseling, HIV/STI risk reduction counseling, and contraceptive counseling
- Is a general guide/reference for the details to be covered during counseling sessions
- Includes a list of the counseling required at each visit (subsequent pages)
- Should be used starting at V1 to perform the counseling required at the Screening Visit
- Is used to document the counseling performed (using the guidance) by initialing each counseling component after it is completed
- Includes an additional notes section to guide subsequent counseling as needed
- Should be moved into the Enrollment Visit tab (and then to subsequent visits) as the form is designed to be used throughout the duration of subject participation

MATRIX-003 PARTICIPANT VISIT CALENDAR TOOL

This tool:

- Can be used to assist with scheduling participant visits by calculating target visit dates and window periods
- Can be marked as a favorite or saved on a desktop or iPad for ease of use
- Can be saved under the participant's PTID to populate the document as the participant moves through study visits:
  - At V1, the tool will calculate the last possible day for enrollment. Use the date of informed consent date as the Screening Visit date
  - At V2, enter the enrollment date to calculate the target dates and window periods for V3 – V5
  - At V5, enter the V5 date to calculate the target date and window periods for V6.
  - At V6, enter the V6 date to calculate the target dates and window periods for V7 - V9
- Can be saved under the participant's PTID and populated/saved after entering visit dates as described above. At the last visit, after entering the actual date of V9, the completed tool with the participant's PTID, actual visit dates, and calculated target dates and window periods can be printed and filed in the participants record

PARTICIPANT RANDOMIZATION FORM

This form:

- Is used to obtain the randomization sequence for the participant (A then B or B then A)
- Is in a sealed envelope; a set of sequentially numbered envelopes are provided to the site by the MATRIX CTH Data Management & Statistical Support team
  - Please see SSP Section 12 (Data Collection) for the randomization process and instructions on how to complete and use this form
- Is copied and then the copy is taken to the pharmacy for PoR review and to dispense the appropriate ring as outlined in SSP Section 06 (Study Product Considerations)