MATRIX-001 Study-Specific Procedures (SSP) Manual
Section 5 – Study Procedures

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5 Introduction

This section provides information on requirements for study procedures in MATRIX-001, including screening, enrollment and participant follow-up visits. While this section provides guidance for study procedures, the most current version of the MATRIX-001 protocol is the primary reference for all study procedures.

Note: The study product used in this study is an insert containing Tenofovir Alafenamide (TAF)/ Elvitegravir (EVG) which will be administered vaginally. For ease and consistency of reference, throughout this Manual, and in select implementation materials, the study product as well as the placebo will be referred to as either the "vaginal insert" or "study insert."

5.1 Visit Locations

Given the nature of study procedures required to be performed during MATRIX-001, all study procedures for all study visits are expected to occur at the research site / study clinic; however, certain procedures may be conducted off-site per site guidelines. In certain instances, the IDI may be conducted off site per the discretion of the Investigator of Record (IoR) or designee and if the participant has provided the proper consent for off site visits.

5.2 Eligibility Determination SOP

It is the responsibility of the site 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 procedures (i.e. review of laboratory results)
- Final confirmation and sign-off 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)
- Quality control (QC)/quality assurance (QA) procedures (if not specified elsewhere)
- Eligibility checklist
- Reference to Eligibility Criteria CRF

NOTE: For MATRIX-001 Eligibility inclusion/exclusion criteria, each criterion is "prior to Enrollment " unless otherwise specified.

5.3 Screening (Visit 1)

The term "screening" refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MATRIX-001. The study eligibility criteria are listed in Protocol Sections 5.2 and 5.3; and required screening procedures are listed in Protocol Section 7.1.

5.3.1 Screening and Enrollment Timeframe

All protocol-specified screening procedures must take place within 8 weeks prior to enrollment. The 8-week window begins the day written informed consent is obtained (signed), even if no other procedures were done on that day.

Per protocol Section 7.1, unscheduled visits (as part of the same screening attempt) may be conducted if needed, to complete all required procedures. 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). Potential participants may undergo one additional screening attempt, per the discretion of the IoR or designee.

If all screening and enrollment procedures are not completed within 8 weeks of 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 rescreen attempt. When rescreening participants, all screening procedures need to be repeated. Note, however, a new participant identification number (PTID) is not assigned to the participant in this case. Rather, the original PTID assigned at the first screening attempt is used for any repeat screening attempts, as well as future study visits should the participant successfully enroll in the study.

5.3.2 Screening Visit Procedures

Required screening procedures are specified in protocol section 7.1 and reflected in the applicable visit checklist available on the MATRIX-001 webpage.

After provision of written informed consent, participants will be assigned a PTID and undergo a series of clinical evaluations, laboratory tests and a behavioral eligibility assessment. Locator and demographic information will also be obtained. Participants will be reimbursed for their time and can be tentatively scheduled for enrollment, if found presumptively eligible.

Further details on PTID assignment, structure, and related information are included in SSP Section 12 (Data Collection).

Clinical screening visit procedures required for all participants are described in Protocol section 7.1, Laboratory specific procedures are described in detail in SSP Section 9 (Laboratory Considerations).

Participants will be counseled about HIV and receive appropriate pre- and post-test counseling as well as risk reduction counseling including the provision of male condoms. Protocol contraceptive requirements are only applicable to participants of child-bearing potential. For this reason, counseling on effective contraceptive use will be provided as applicable. Sites should use the MATRIX-001 Protocol Counseling Guide and Worksheet available on the MATRIX-001 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-001).

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. A sample Screening and Enrollment Log suitable for use in MATRIX-001 is available on the MATRIX-001 webpage under Study Documents. Study sites are encouraged to reference the eligibility codes listed at the bottom of the sample log when recording the reason(s) for screening failure/discontinuation.

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 informed consent form(s) (ICF)
- Reason(s) for ineligibility, with date of determination, documented on the Eligibility Criteria case report form (CRF) and in chart notes (if required)
- If a participant screens out due to a clinical condition requiring follow-up, appropriate referrals should be provided to ensure well-being of the participant and documentation of all referrals should be included in the participant chart.
- Documentation that any clinically significant abnormalities (laboratory results, etc.) were provided and explained to the participant within a reasonable timeframe (even if referral is not necessary), regardless of eligibility determination.
- All source documentation, chart notes, and CRFs completed up until the time that ineligibility was determined
- Completion of the Final Disposition CRF
- Indication of what visit procedures were conducted on the visit checklist
- Complete row on the Screening and Enrollment Log, updated with date of discontinuation of screening and reason for screen failure.

5.4 Enrollment (Visit 2)

The participant's final eligibility status should be determined by evaluating and then marking off all items on the MATRIX-001 Eligibility Checklist. The Eligibility Checklist should be completed on the day of enrollment and the site IoR (or designee) and a second delegated staff member should sign and date the Eligibility Checklist to confirm and verify eligibility status prior to randomizing the participant. If a participant is found to be ineligible during the 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. Any incomplete portions of the checklist would be marked as not applicable and the visit would be stopped.

The Enrollment visit should be scheduled within 8 weeks of the Screening visit, after menstrual flow ceases, ideally in the luteal phase of the menstrual cycle. A participant is considered enrolled in the study only after providing written informed consent and eligibility has been confirmed.

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR or designee should contact the MATRIX-001 Protocol Safety Review Team (PSRT) and the MATRIX-001

Management Team for guidance on subsequent action to be taken. Report to institutional review board (IRB)/independent ethics committee (IEC) as applicable.

5.4.1 Enrollment Visit Procedures

All procedures for the Enrollment Visit should be conducted on the same day.

Study enrollment procedures are specified in Protocol section 7.2.1 and reflected in the Enrollment Visit Checklist available on the MATRIX-001 webpage. The procedures detailed will be completed as part of eligibility confirmation prior to the randomization visit.

5.5 Randomization (Visit 3)

Visit 3 should be scheduled 10-14 days after Visit 2, not less than 10 days after biopsy collection. Visit 3 should be scheduled so that the participant would not be menstruating during the 3 days of product use. Per Protocol section 7.2.2, once results from pregnancy and HIV test results are reviewed and participant remains eligible, the participant may be randomized (1:1) to receive TAF/EVG versus placebo vaginal insert. Participants will also be randomized (1:1:1) into three time points for pharmacokinetic (PK) tissue sampling after the last dose (24, 48, or 72 hours post last dose). See SSP Section 12 (Data Collection) for information on completing the randomization process.

5.5.1 Randomization Visit Procedures

All procedures at the randomization visit must be conducted on the same day and cannot be split across multiple days. HIV and Pregnancy testing must be performed prior to randomization and the results must be negative to proceed with randomizing. Participants who test positive for pregnancy or HIV at this visit will have study participation stopped prior to randomization. Study randomization procedures are specified in Protocol Section 7.2.2 and reflected in the Randomization Visit Checklist (available on the MATRIX-001 webpage under Study Documents).

- Sites will conduct point-of-care (POC) pregnancy and HIV testing. A negative result for both must be confirmed prior to participant continuation of randomization visit and procedures.
- All participants will have samples collected prior to the first self-insertion of the study product. Verify that the biopsy site has healed prior to proceeding. Vaginal (and if applicable, rectal) fluid for PK, pharmacodynamics (PD), and microbiome, and cervicovaginal lavage (CVL) for secreted soluble marker will be collected.
- The vaginal insert(s) will be self-inserted deep (approximately 4-5 cm) in the vagina. Study staff will verbally explain the procedure using the ***Vaginal Insert Guide*** as a visual and written reference. Refer to SSP Section 10 (Counseling) for product specific counseling.
- Doses two and three will be dispensed for self-insertion for the next 2 consecutive days following Visit 3. The ***Insert Adherence Tool*** should be provided to participants to help with dose insertion questions and tracking.
- A discrete pill carrier case will be provided to all participants.

5.6 Pharmacokinetics, Pharmacodynamics, and Sample Collection

Refer to Table 9 in Protocol Section 7.11 for the schedule of PK and PD specimen collection. Refer to SSP Section 9 (Laboratory Considerations) and the applicable Visit checklist for sampling time-point procedures post dosing for specimen collection technique and order of collection. See Table 1 below for guidance on collection time-point ranges. **The study site should carefully record the date and time of all sample collections. An out of window sampling time will be considered a protocol deviation based on the time the first sample is taken, when multiple sample types are being collected.**

Table 1: Sample Collection Time-Points After Product Administration

Sampling Time-point	+/-	Acceptable Range
24 hours	4 hours	20h – 28h
48 hours	8 hours	40h – 56h
72 hours	8 hours	64h – 80h
10 days	+4 days	10 days – 14 days

5.7 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 6 clinic follow-up visits post enrollment. For cycling participants, visits should be scheduled around menstrual cycles to ensure specimen collections and product use do not occur during a menstrual cycle.

Interim visits are those visits that take place between scheduled visits. All interim contacts (e.g., phone calls and/or unscheduled clinic visits) will be properly documented in study files and on applicable CRFs. Procedures required 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-related procedures to assess the AE and required documentation would be the required procedures for that interim visit. See SSP Section 12 (Data Collection) for more details on recording interim visits.

5.7.1 Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the MATRIX-001 protocol allows for certain visits to be completed within a visit window, if possible. A complete listing of visit windows is available in Table 2 below. To assist with visit scheduling, sites can refer to the MATRIX-001 Scheduling Tool.

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. Product use and visits should be scheduled around menses where possible. Visits scheduled after a biopsy should be at least 10 days after the biopsy was taken.

Table 2: Scheduled Visit Windows

Study Visit	Visit Description	Visit Window
Visit 1	Screening	
Visit 2	Enrollment	within 8 weeks of Screening
Visit 3	Randomization; Phase 1 - 1st dose	10-14 days post Enrollment
Visit 4	24-hrs post 3rd dose	3 days after Randomization
Visit 5	Start of Phase 2 - 4th dose	10-14 days post Visit 4*
Visit 6	5th dose	2 days post Visit 5
Visit 7	24/48/72-hrs** post final dose	4-8 hours of scheduled time
Visit 8	Study Exit Visit	10 days post Visit 7 + 1 week

**Visit 5 should ideally be scheduled 10-14 days after Visit 4 and after menses. If unable to schedule in the 10-14 days after Visit 4, please document reasons for extending (i.e. menses).*

***Participants only attend Visit 7 at 1 timepoint as determined by Randomization.*

5.7.2 Follow-Up Visit Procedures

Required follow-up visit procedures are listed in Protocol Section 7.3. Several additional clarifications of the procedural specifications are provided in the remainder of 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, including procedure order during follow-up, is incorporated into the sample visit checklists and in SSP Section 2 (Documentation Requirements).

As a general guide, during follow-up, the following will occur in addition to the PK/PD/Tissue sample collection schedule noted in section 5.6 above:

- Locator information must be obtained/reviewed at every visit.
- Protocol counseling will be provided at all visits, except for the final contact. This may be customized to individual participant needs and abbreviated as applicable.
- A pregnancy test is done if clinically indicated at Visits 4-6. Per protocol, a pregnancy test will be conducted at Visits 3, 7 and 8.
- HIV testing and counseling is required at Visits 3, 7 and 8, and when clinically indicated.
- Chemistries (AST, ALT, creatinine) and complete blood count (CBC) with differentials and platelets are performed at Visit 7 and when clinically indicated.
- Medical and medication histories interim review, AE assessment and documentation (including social harms [SH]), assessment of concomitant medications and provision of any available lab results will be done at all visits. Local lab results will be provided to participants except study lab results that will be analyzed at the conclusion of the study, including Nugent and HSV2.

- Pelvic exams are done to assess vaginal mucosa at every visit including both visual inspection and sample collections (i.e. pH, wet mount). Verify that the biopsy site has healed prior to starting Phase 2 at Visit 5.
- In-clinic self-insert administration (doses 1, 4 and 5) occurs at Visits 3, 5 and 6. At home self-insertion will be done for doses 2, 3 and 6-10.
- Behavioral assessment questionnaires are administered at Visit 7. Product use questionnaires will be administered at Visits 3, 4 and 7 and the IDI can be conducted at visit 8. In the event the IDI cannot be conducted at SEV, the IDI should be done within 7 days of SEV.
- Participants will be reimbursed for their time at each visit and scheduled for their next visit as applicable.
- Condoms will be available to participants at the clinic throughout the study.
- The site team may invite participants (selected purposively) for an IDI during Visit 7, or soon thereafter. The interview must be scheduled and completed during the Visit 8 window, before study exit. Refer to SSP Section 11 (Behavioral Measures) for additional details.

5.7.3 Visits Conducted Over Multiple Days

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 (e.g., because the participant is menstruating), the remaining procedures may be completed on subsequent day(s) within the allowable visit window, if that visit has a window. Details should be clearly documented in the narrative notes. As described in SSP Section 12 (Data Collection), all CRFs completed for a visit that takes place over more than one day are assigned the same visit code (even though the dates recorded on the CRFs may be different).

If study visits must be split, please ensure that:

- HIV pre-test counseling and HIV testing occur on one day (note: if HIV testing is done using a rapid test, pre- and post-test counseling should also occur on the same day, if possible).
- PK/PD/Biomarker specimens are collected on the same day to avoid complicating interpretability of the data.

Any procedures that are not conducted within the visit window will be documented as a protocol deviation. See section 5.7.3 below for guidance on which missed procedures should be made up at an interim visit.

5.7.4 Missed Procedures

For participants who do not complete any part of a scheduled visit within the allowable visit window, the procedures should be marked as missed (see the CRF completion guidelines).

If a Post-Dosing visit is missed after the participant receives their dose, sites must make every effort to make up the missed visit and required study procedures (as soon as possible) and retain the participant for their remaining scheduled study follow-up visits.

In any of these missed procedure scenarios, sites should contact the MATRIX-001 Management Team for additional guidance as needed.

5.7.5 Final Contact/Termination Considerations

Since participants' SEV include laboratory testing, additional contacts after the Visit 8 SEV may be required to provide them additional study test results, referrals, and post-test counseling, if needed. Follow-up contact may also be conducted for any new adverse events reported at Visit 8. Record this information on the Participant Contact Log found on the MATRIX-001 webpage. In addition, for participants who become pregnant during study participation, additional contacts may be required to ascertain the participant's pregnancy and infant outcome (see Protocol Section 7.4.2 for details). Study sites may complete these contacts at the study clinic or at community-based locations, depending on site capacities and site and participant preferences, with IRB/IEC approval. All final contacts will be documented in participant study records. The date of termination should be marked as the date of last contact with the participant and recorded in the Final Disposition CRF (FINAL).

After completing their SEV, participants will no longer have routine access to services provided through the study, such as HIV counseling and testing. Participants should be counseled about this — ideally before and during their SEV — and provided information on where they can access such services after study exit per site policy.

5.7.6 Participants Who Become Infected with HIV

Study product should be temporarily held upon first reactive/positive HIV test. Study product use must be discontinued immediately for participants who are confirmed to be positive for HIV (see protocol section 7.4.1). If possible, an exit visit should be conducted with safety labs (no genital collections) and HIV resistance testing, as well as additional local standard of care tests.

A participant who is confirmed to have HIV after the Enrollment Visit will be discontinued, and the participant will be considered terminated from the study. The participant will be referred to local care and treatment services and may return to the clinic for additional counseling and other support services, as needed per site SOP.

An AE form should be completed and the PSRT notified.

5.7.7 Participants Who Become Pregnant

If a participant becomes pregnant, follow-up visits and procedures will be discontinued, and the participant will be considered terminated from the study (see protocol section 7.4.2). Pregnancy Report and History CRF should be completed and the PSRT notified. A final SEV, with relevant safety procedures, should be conducted if the participant is willing. Participant will be referred to local health care services and may return to the clinic for additional counseling, as needed per site SOP. Any pregnancy that occurs while a participant is taking study drug product must be recorded in the Antiretroviral Pregnancy Registry (APR) online at http://www.apregistry.com/. The Investigator must register the pregnancy within fifteen (15) calendar days of first becoming aware of the pregnancy and maintained through to pregnancy outcome. A copy of the report will be provided to the sponsor and reported to the IRB/IEC, as needed, in accordance with local requirements.

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.

5.7.8 Participants Who Permanently Discontinue Study Product for Other Reasons

For participants who permanently discontinue study product use for any clinician-initiated reason (other than HIV seroconversion or pregnancy) or for any participant-initiated reason (e.g., participant declines study product use or decides to withdraw from the study), the site IoR/designee may opt to discontinue study follow-up visits and procedures, after consulting the MATRIX-001 PSRT and Management Team. If a participant permanently discontinues study product use due to an AE, the site must continue to follow the participant until resolution (return to baseline) or stabilization of the AE is documented.

If study participation is discontinued, participants will be asked to complete all procedures scheduled for Visit 8 SEV, if willing.

If follow-up continues, participants will continue to come in for protocol-specified follow up visits through their scheduled termination/final contact.

5.7.9 Criteria for Early Termination of Study Participants

As outlined in Protocol Section 9.6, participants may voluntarily withdraw from the study for any reason at any time. The IoR/designee also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the PSRT. Participants also may be withdrawn if CONRAD, USAID, MATRIX, government or regulatory authorities, including the FDA and Office for Human Research Protections (OHRP) or a site IRB/IEC terminate the study prior to its planned end date.

The Visit 8 / Early Termination Checklist should be used as a guide for early termination procedures per Protocol section 9.6, 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:

- Record the reason(s) for the withdrawal in participants' study records.
- Complete the Final Disposition CRF
- Consult the PSRT regarding early terminations per IoR decision and print and file outcome correspondence in the participant chart. 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) and be informed of study results.

5.7.10 Replacing Participants

Additional participants may enroll in the study, per Protocol section 10.4, to replace enrolled participants who have permanent product discontinuation or are lost to follow-up. The site may contact the MATRIX-001 Protocol Management Team for questions or concerns about replacement participants.