MATRIX-003 Study-Specific Procedures (SSP) Manual
Section 2 – Documentation Requirements

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2 Introduction

Site study staff members are responsible for the proper collection, management, storage, quality control, and quality assurance of all study-related documentation. This section contains information on the essential documents that each study site must maintain throughout the study. It also contains information related to establishing adequate and accurate participant research records for MATRIX-003.

2.1 Essential Documents

The E6 Good Clinical Practice: Consolidated Guidance specifies the essential documents that study sites must maintain. Although all required documentation must be available for inspection at any time, all documents need not be stored together in one location.

Section 2.3.2 below provides information on the required contents of these records. Study sites are not required to adopt this filing structure but are encouraged to consider it when developing their filing approach for the study. Further clarifications of the suggested filing structure are as follows:

- Essential documents may be stored in files and/or in binders, which may be subdivided, consolidated, and/or re-organized.
    - *NOTE: Sites that choose to file documents electronically must ensure computer systems are secure (i.e., username and password protected). See MATRIX's Good Documentation Practice (GDP) Policy (https://www.matrix4prevention.org/about/leadership-and-structure/matrix-prime/matrix-prime-documents) for further details on the requirements that must be met when using electronic systems/software.*
- It is recommended that a contents sheet be maintained and inserted as the first page(s) of each file/binder. Within each file/binder, it is recommended that documents be filed in ascending date order.
- Certain documents related to the investigational study products will be stored in site pharmacies. A listing of essential documents to be maintained in the pharmacies is provided in Section 2.4.
- To facilitate routine inspection by study monitors, certain laboratory-related essential documents should be stored in the study essential documents files/binders, for instance laboratory result ranges. Other lab-related essential documents (e.g., lab standard operating procedures [SOPs]) may be filed in site laboratories.
- A PTID-Name linkage log, and Screening and Enrollment Log should be maintained and updated throughout the duration of the trial. The suggested filing structure assumes that these logs will be stored in the study clinic or data management area throughout the screening and accrual process and not necessarily with the other essential documents.
- All significant communications between the study sponsor and/or management team and study sites should be printed and filed with other essential documents.

Note: When required documents are modified or updated, the original and all modified or updated versions must be retained. Communications that are Participant Identification (PTID)-specific should be printed and filed in the participant binder. Communications that are not PTID-specific can be printed and filed in regulatory documentation. All clinical site monitoring reports and correspondence should also be printed and filed.

2.2 Financial Disclosure Forms

Select clinical investigators listed on the MATRIX IoR Form (i.e., the Investigator of Record [IoR] and any sub-I[s] also listed in the Protocol Team Roster) must disclose any financial interests that may be affected by the outcome of the research or attest to the absence of relevant significant financial interests. Per 42 CFR 50 financial disclosure forms (FDF) must be completed prior to study start (i.e., first site activation). In addition, the applicable investigators must complete and sign a new FDF if there is a change in an investigator's financial interests during the study.

A blank 42 CFR 50 FDF is available on the MATRIX website (https://www.matrix4prevention.org/resources/regulatory-documents). All items can be entered electronically except for the signature and date unless part 11 compliant DocuSign is utilized.

At the beginning of the study and throughout study duration, whenever an FDF is completed, sites should email a signed copy to the MATRIX Prime/Clinical Trials Hub (CTH) Regulatory (matrixregulatory@lists.matrix4prevention.org).

2.3 Participant Research Records

MATRIX-003 study sites must maintain adequate and accurate participant research records containing all information pertinent to each study participant. Participant charts should be stored in a secure area/in locked file cabinets with access limited to authorized study staff. See Protocol section 13.6 for further information regarding confidentiality of participant information.

2.3.1 Concept of Source Data and Source Documentation

The *International Conference on Harmonization Consolidated Guidance for Good Clinical Practice* defines the terms source data and source documentation as follows:

The term **source data** refers to all information in original records and certified copies of original records related to clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the trial (including all screening and enrollment activities). Source data are contained in source documents, e.g., original records or certified copies (i.e., copies of source documents that have been verified via dated signature or initials to be exact copies having all the same attributes and information as the original records).

The term **source document** refers to original and/or certified copies of documents, data, and records (e.g., hospital records; clinical and office charts; laboratory records and notes; memoranda; participants' diaries and/or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies of transcriptions certified after verification for accuracy and completeness; microfiche; photographic negatives; microfilm or magnetic media; x-rays; participant files; and records kept at the pharmacy, laboratories, and medico-technical departments involved in the study).

Source documents are commonly referred to as the documents—paper-based or electronic —upon which source data are first recorded. All study sites must comply with the standards of source documentation specified in the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) requirements (ICH E6) and the MATRIX Good Documentation Practices (GDP) Policy found on the MATRIX website. Study sites must comply with all requirements and are encouraged, but not required, to comply with any recommendations.

2.3.2 Required Source Documentation

For MATRIX-003, participant research records should consist of the following source documents:

- Chart notes
- Documentation that the participant provided written informed consent to screen/enroll for and participate in the study prior to the conduct of any screening or study procedures
- Documentation that the participant met the study's eligibility criteria
- Prescription documentation
- A record of the participant's use of the investigational study product
- Pharmacy investigational product accountability, dispensing and chain of custody records (maintained in the study site pharmacy)
- A record of all contacts, and attempted contacts, with the participant
- A record of all procedures performed by study staff during the study (i.e., on visit checklists and/or other site-specific procedural flow sheets or chart notes)
- Local laboratory testing logs and result reports, or any other document defined as a source document for a test result

- Case Report Forms (CRFs) and other forms provided by the MATRIX Prime/CTH
- Study-related information on the participant's condition before, during, and after the study, including:
  - Data obtained directly from the participant (e.g., interview and/or other self-reported information)
  - Data obtained by study staff (e.g., exam and lab findings)
  - Data obtained from non-study sources (e.g., non-study medical records)
- Other source documents (e.g., site-specific worksheets, logs)

As a condition for study activation, **each study site must establish an SOP** that specifies the source document for study procedures. To establish consistency in source documentation across sites, a sample table for the required/recommended source for specific study procedures is available on the MATRIX-003 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents). Sites should include this table in (or use it as) the site SOP for source documentation and update it accordingly. Supplemental information on the use of chart notes, visit checklists, and forms provided by the MATRIX Prime/CTH is provided below. Detailed information on proper completion, maintenance, and storage of product dispensing documentation is provided in SSP Section 6.

2.3.3 Chart Notes

Study staff must document every contact with a study participant in a signed and dated chart note or contact log specifying the following information when necessary to document adherence to protocol requirements:

- Visit date at which a contact takes place or at which a particular procedure takes place
- Visit type (scheduled, interim, etc.)
- Purpose of the visit and location of the contact if other than the research clinic

Chart notes should also be used to document the following, as applicable:

- The screening and enrollment informed consent process (if an Informed Consent Coversheet is not used)
- Procedures performed that are not recorded on other source documents
- Additional information related to clinical exam findings to ensure appropriate follow-up
- Study-specific counseling sessions and any associated referrals that are not documented on other source documents
- Other pertinent data about the participant that are not recorded on other source documents and/or any clarifications or information needed to supplement data recorded on a CRF
- Reason(s) why protocol-specified procedures were not performed
- Explanation of why procedures in addition to those listed on a checklist were performed
- Contact attempts to follow up on participants who missed a scheduled study visit or require other follow-up, for instance abnormal results

2.3.4 Visit Checklists

Visit checklists are convenient tools which may serve as source documentation, if designed and completed appropriately. These checklists alone may not be sufficient for documenting all procedures but can be used to indicate that the procedure was completed. Chart notes may be required to supplement the information recorded within visit checklists. Sample Visit Checklists are available on

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

Tips for completing visit checklists in accordance with these requirements are as follows:

- Enter the PTID, visit date and, if applicable, visit code on the checklist; if source data are recorded on both the front and back of the checklist, enter the PTID and visit date on each page.
- Staff should only enter their initials beside the procedures that they perform. Initials should not be entered beside procedures performed by other staff members (i.e., do not enter another staff member's initials).
- Ideally, only one person should initial each line of the checklist. If the line includes multiple procedures and they are performed by different staff, indicate who performed which procedure in the comments. Checklists should generally be designed to avoid this practice.
- For items on the checklist that contain checkboxes, one set of initials is still sufficient, even if multiple boxes are checked.
- If all procedures listed on a checklist are performed on the same visit date, the date need not be entered beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date beside each procedure as each is performed.
- If a procedure listed on the checklist is not performed but is required, enter "ND" for "not done" beside the item. If a procedure listed on the checklist is not performed but is not required, enter "NA" for "not applicable" beside the item. Record the reason for "ND" or "NA" on the checklist (if not self-explanatory); initial and date the entry.

The sequence of procedures presented on the sample visit checklists is a suggested ordering unless specifically indicated. Site staff should modify the checklists to maximize the efficiency of site-specific study operations. Visit checklists, and visit flow, should be monitored and updated as needed to ensure that study visits are completed as quickly as possible, with minimal delays for participants and study staff.

Sites may alter the sequence of procedures to suit local staffing and logistical requirements unless otherwise stated on the sample visit checklist, and with the following exceptions:

- Written informed consent must be obtained before any study procedures are performed.
- On the day of enrollment, randomization must take place after confirmation of eligibility.
- The baseline behavioral questionnaire may be administered before or after randomization but prior to study product insertion.
- During follow-up, behavioral assessments should be administered prior to the HIV/STI risk reduction and protocol counseling as to not bias any responses provided when completing questionnaires. In-depth interviews (IDIs) will be conducted at the end of the applicable visit or on a different day based on participant and staff schedule.
- Any laboratory testing that is performed in the clinic, such as hCG and HIV testing, should be completed and results provided to the participant prior to study product administration. Additionally, clinicians should review the hCG and/or HIV test results prior to the clinical examinations and further specimen collection (i.e., blood collection) to ensure no procedures need to be modified in the case of a positive result.
- Pelvic exam procedures must be performed in the sequence shown on the Visit Checklist. For exams that are done if clinically indicated, procedures may be documented in chart notes and/or on the visit checklist.

2.3.5 Laboratory

Each lab test must have a defined source document, which is the first place the result is recorded or generated. Site laboratories will have a plan for the storage of these documents so that they are easily retrievable.

2.3.6 Case Report Forms (CRF)

See SSP Section 12 for further details regarding the use of CRFs with the Research Electronic Data Capture (REDCap) data management system. The REDCap system utilizes electronic CRFs, otherwise known as Instruments within REDCap. Electronic CRFs (eCRFs) have been designed to be used as source whenever possible. Prior to study activation, each study site will document the CRFs used as source as well as which CRFs are not used as source in a site SOP and/or the Source Documentation of Study Procedures as mentioned above. The specifications of the SOP must be followed consistently for all study participants. If study staff is not able to record data directly onto electronic forms designated as source documents, the following procedures should be undertaken:

- Record the data onto an alternative source document.
- File the alternative source document into the participant's study chart.
- Transcribe the data from the alternative source document onto the appropriate electronic form and enter a note on the form stating the alternate source document used.
- Write a chart note stating the relevant study visit date and the reason why an alternative source document was used.
- Perform quality control (QC) procedures as specified in the site-specific data management SOP to ensure accurate and correct data transcription.

The behavioral components of the study (i.e., behavioral surveys and IDIs) will be designed and managed by the Design to Delivery (D2D) Hub Pillar 2 team as detailed in SSP Section 11 Behavioral Measures. Behavioral CRFs have been designed as electronic CRFs in REDCap that will also be used as source when possible. If the behavioral data cannot be recorded directly onto electronic forms as source documents, the same procedures outlined here should be undertaken.

2.3.7 Protocol Deviations

Protocol deviations (PD) are required to be documented in participant records, along with efforts made to correct and prevent similar deviations in the future.

For MATRIX-003, the Protocol Deviation Log CRF will be used to document each reportable deviation identified. Exceptions:

1. Missed visits are considered protocol deviations; however, these will <u>not</u> be captured on the Protocol Deviation Log CRF. The Missed Visit CRF will capture this information instead.
2. Participant-reported behaviors that are protocol deviations and are reported to sociobehavioral research (SBR) study staff during administration of the SBR CRFs will not be captured on the Protocol Deviation Log CRF: please refer to **SSP section 11.3** for further details. According to site SOPs and as required by local IRBs, an SBR report from REDCap may be used for each Site IoR to review and sign off on compiled instances of PDs reported on SBR CRFs.

Corrective and preventive action plans are required components of protocol deviation documentation. It is important to ensure that chart notes or other source documents include any associated counseling that was done to address the protocol deviation (i.e., counseling on the importance of retention for

missed visit deviations). Note that the corrective and preventive actions must be documented but are not required to be completed prior to reporting the deviation to the MATRIX Prime/CTH.

Protocol deviations should be entered into the database within seven days of site awareness, even if all actions/plans are still in progress. If there is a question as to whether a deviation has occurred, or how it should be documented, the site should contact the MATRIX-003 Management Team (matrix003mgmtteam@lists.matrix4prevention.org) and/or the MATRIX Regulatory team (matrixregulatory@lists.matrix4prevention.org) for guidance. The site will be notified once a determination is made and, if determined to be a deviation, the seven-day reporting requirement will begin. Once the deviation is entered, MATRIX-003 Management Team/CTH Regulatory may follow up with the site if any clarifications or additional information is needed.

Sites are required to report to their Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) any PDs that pose a potential safety risk to a participant(s) and those that could affect the integrity of the study according to the local IRBs'/IECs' policies and guidelines. It is also recommended that a complete list of all PDs occurring at the site, including PDs not meeting immediate reporting standards noted above, be submitted to the local IRBs/IECs in accordance with their reporting policies. If a local IRB/IEC does not have a specific reporting policy, MATRIX recommends that this be done at the time of IRB renewal submission, annually or semi-annually, per local requirements. These listings will be provided to the sites on request. If needed, sites should request these PD listings from the MATRIX Data Management & Statistical Support Team at least two weeks prior to the planned date of submission to their local IRBs/IECs.

2.3.8 Document Organization and Participant Confidentiality

Study staff must make every effort to store all study records securely and confidentially. Case history records must be stored in the same manner for all participants, in areas with access limited to authorized study staff only. Study sites are responsible for purchasing file folders, binders, storage cabinets, and any other equipment or supplies needed to properly store all records.

Study-related documentation collected during the screening process should be stored in a file folder/binder for each potential participant. All screening documentation — for potential participants who eventually enroll in the study as well as for those who do not enroll or "screen out" — must be maintained and available for monitoring throughout the study. This documentation also must be available for reference should participants present to the site for re-screening. For participants who enroll in the study, screening documentation may be transferred to a separate file folder/binder that will serve as participants' study notebook for the duration of their participation in the study.

All documents contained in participant case history records must bear a participant identifier, which generally will consist of either the PTID or the participant name. The PTID should be used whenever possible to maximize participant confidentiality. Any documents transferred or transmitted to a non-study site location must be identified by PTID only. Care should also be taken to only refer to participants by PTID in email communication when people outside of the site are included.

Regardless of whether the identifier on a document is the participant name or PTID, the original identifier may not be obliterated or altered in any way, even if another identifier is added. When necessary to maintain confidentiality, identifiers may be obliterated on copies of original source documents. For example, if medical records obtained from a non-study health care provider bear the participant's name, the original documents bearing the name must be stored unaltered with other study documents bearing the name. However, a copy of the original documents could be made, the

PTID could be entered onto the copies, and then the participant name could be obliterated from the copies. Copies handled in this way could then be stored in participants' study notebooks.

All on-site databases must be secured with password protected access systems. Any lists, appointment books, or other documents that link PTIDs to other participant identifiers should be stored securely (i.e., locked cabinet/drawer if hard copy; password protected if electronic). When in use, documents that link PTIDs to other participant identifiers should not be left unattended or otherwise accessible to study participants, other study clinic participants, or any other unauthorized persons.

2.4 Study Product Accountability, Chain of Custody, and Dispensing Documentation in the Pharmacy

Pharmacy staff will document the receipt and dispensing of study product and the return/destruction of each unused (never dispensed) study product. Separate accountability records must be maintained for each lot of product as applicable, per instructions provided in the MATRIX-003 Pharmacy Manual available on the MATRIX-003 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents).

Study clinic staff will contribute to the documentation of product provision and chain of custody as described in SSP Section 6.

The specifications related to document security and participant confidentiality described in Section 2.3.8 also apply to records maintained in the study pharmacies. All records must be stored securely in the pharmacies with access limited to authorized study pharmacy staff only.

The following essential documents should be maintained in study site pharmacies:

- Current MATRIX-003 Protocol
- Current MATRIX IoR Form
- Current list of authorized prescribers and staff authorized to sign Prescriptions (names and signatures)
- MATRIX-003 Pharmacy Manual and applicable **site SOPs detailing investigational study product management and chain of custody**
- MATRIX-003 product shipping and receipt documentation, product storage temperature logs, and investigational product accountability records
- MATRIX-003 participant-specific records (including prescriptions, randomization assignment, record of receipt of participant study product and documentation of unused product returns)
- MATRIX-003 communications with the Product Development Team and/or product distributor*
- MATRIX-003 communications with site clinic staff, the MATRIX Prime/CTH, and/or the MATRIX Data Management & Statistical Support Team or other communications or locally required administrative, operational, and/or regulatory documentation*

*Relevant to significant decisions regarding study product management, accountability, and/or safety.

2.5 Record Retention Requirements

All records must be retained on-site throughout the entire period of study implementation, and for at least three years after completion or termination of the study. Study product records must be stored in

site pharmacies, with access limited to authorized study pharmacy staff only. Study records should not be re-located to an off-site location or destroyed without prior approval from the MATRIX Prime/CTH as detailed in MATRIX's GDP Policy (https://www.matrix4prevention.org).

2.6 Translation procedure

All study materials that are read verbatim or provided to the participant must be translated by the site into local language, as appropriate. Participant materials include the informed consent forms, informed consent comprehension assessment, behavioral questionnaires/surveys and IDI guides, and participant-facing material (i.e., fact sheets, instruction sheets, community education tools, etc.). Translated participant materials will not be reviewed by CTH prior to IRB/IEC submission; therefore, translated participant materials can be submitted for regulatory approval immediately upon completion. The site IoR/designee will attest in writing that any participant-facing materials requiring translation have been approved for use by their local IRBs/IECs prior to study activation.

Site teams are responsible for establishing a site-specific translation SOP as applicable. The Translation SOP should minimally contain the following elements:

- Description of the translation and back-translation process, including QC process.
- Who is responsible for conducting each step of this process (and whether it is occurring with on-site staff or through a contracted group).
- As applicable, a list of study materials that is not translated (i.e., staff administered questionnaires) if the interviewer(s) are proficient in both English and the local language and translation is not required to conduct the procedure.