MATRIX-001 Study-Specific Procedures (SSP) Manual
Section 4 – Informed Consent

TABLE OF CONTENTS

4 Introduction 1
4.1 Overview of Informed Consent Requirements and Procedures 1
4.2 Site-Specific Informed Consent Forms 2
4.3 SOP for Obtaining Informed Consent 2
4.4 Informed Consent for Screening and Enrollment 3
4.4.1 Informed Consent for Long-term Storage and Future Testing of Specimens and Related Health Information 3
4.4.2 Informed Consent for Rectal Sample Collection 4
4.4.3 Informed Consent for In-Depth Interview 4
4.4.4 Informed Consent for Off-Site Visits 4
4.4.5 Other Informed Consent Visual Aids 4
4.5 Comprehension Assessment 5
4.6 Documenting the Informed Consent Process 6
4.7 Ongoing Assessment of Participant Comprehension 7

4 Introduction

This section provides information on informed consent procedures for MATRIX-001. Informed consent is required for Screening, Enrollment, Rectal Fluid sample collection, Long-term Storage and Future Testing In-Depth Interview and, as applicable, consent for off-site visits. However, depending on IRB/IEC/DRA requirements, sites may choose to separate consent for any of these components. If this is done, each separate ICF must contain all required elements of informed consent.

4.1 Overview of Informed Consent Requirements and Procedures

Informed consent is a process by which an individual voluntarily expresses their willingness to participate in research, after having been informed of all aspects of the research that are relevant to their decision.

Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process, involving information exchange, comprehension, voluntariness, and documentation. Each of these aspects of the process is described in greater detail below. Please refer to the ICH E6 Sections 1.28 and 4.8 for further guidance on the informed consent process and documentation requirements.

US regulations (45 CFR 46.116) specify the elements of informed consent that must be conveyed to research participants through the informed consent process. It is the responsibility of the IoR, and all delegated study staff involved in the informed consent process to deliver all required information to potential study participants.

Based on the technical and regulatory reviews that are completed as part of MATRIX-001's protocol development and study activation processes, there is adequate assurance that once the MATRIX Prime has activated a site for study implementation, site-specific ICFs specify all information required by the regulations. However, responsibility for informed consent does not end with preparation of adequate ICFs.

It is the responsibility of the IoR and designated study staff to perform the following:

- Deliver all required information in a manner that is understandable to potential study participants
- Assure that informed consent is obtained in a setting free of coercion and undue influence
- Confirm that the participant comprehends the information
- Document each step of the process

4.2 Site-Specific Informed Consent Forms

A sample ICF is provided in the Protocol Appendix IV. Sites are responsible for adapting the sample ICFs as needed for local use. Local adaptation may include reformatting the consent forms in accordance with local IRB/IEC/DRA requirements. Sites are responsible for following the guidance in the Human Subjects Research Policy found on the MATRIX website when adapting site-specific ICF(s). The English site-specific consents ICF do not need reviewed and/or approved by the MATRIX Prime prior to IRB/IEC/DRA submission. After IRB/IEC/DRA approval is obtained, the approved ICF must be submitted to the MATRIX CTH Regulatory (matrixregulatory@lists.matrix4prevention.org) prior to initial use.

Each site is responsible for preparing bulk supplies of their approved ICF(s) and only using the currently approved versions during the study. Upon sites receiving final IRB/IEC/DRA and any other applicable regulatory approval(s) for an amendment to the ICF(s), the updated version should be implemented immediately and the approved ICF should be submitted to MATRIX CTH Regulatory (matrixregulatory@lists.matrix4prevention.org).

4.3 SOP for Obtaining Informed Consent

As a condition for study activation, each site must establish an SOP for obtaining informed consent from potential study participants by which the informed consent process will be conducted. This SOP should minimally contain the elements listed below.

- Information about applicable local laws, regulations and institutional policies pertaining to the informed consent process
- The minimum legal age to provide independent informed consent for research at the study site
- Procedures for determining participant identity and age (if not contained in a separate SOP)
- Procedures for determining participant literacy
- Procedures for providing all information required for informed consent to the participant
- Procedures for determining participant comprehension of the required information
- Procedures to ensure that informed consent is obtained in a setting free of coercion and undue influence
- Procedures for documenting the informed consent process
- Storage locations for blank ICFs
- Storage locations for completed ICFs
- Procedures (e.g., color-coding) to ensure that different versions of the study informed consent form are easily distinguished and used appropriately
- Procedures for implementing a change in the version of the ICF used
- Staff training requirements
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

4.4 Informed Consent for Screening and Enrollment

Informed consent must be obtained before performing any "on-study" procedures with the participant at the Screening Visit. For participants who do not consent to study participation, no procedures should be performed and no data that can be linked to the participant's name or other personal identifier(s) should be recorded.

Informed consent should be reviewed with the participant at the Enrollment Visit to ensure that the participant clearly understands all information and is still willing to participate in the study. Review of the informed consent must be documented in the participant's study files.

A single informed consent document for Screening and Enrollment will be used for MATRIX-001 unless otherwise determined/required by the IRB/IEC/DRA.

Additional details related to key steps in the process are provided in the remainder of this section.

4.4.1 Informed Consent for Long-term Storage and Future Testing of Specimens and Related Health Information

Study participants are asked to provide informed consent for long-term storage of biological specimens and related health data for possible future research testing. Related health data may include demographic information such as race, ethnicity, sex, and medical conditions. No personal identifying information will

be included. Participants may choose to not have their specimens or health data stored for possible future research testing or withdraw their consent for specimen storage at any time and still remain in the study.

For participants who do not consent to specimen and health data storage and possible future research testing, all specimens are still collected and stored on-site per protocol requirements. These specimens will be retained until the study is completed and all protocol-specified testing has been done. Thereafter, any remaining specimens already collected from these participants will be destroyed. Participants who provide consent to specimen and health data storage and possible future research testing will have their remaining (leftover) samples along with their demographic information retained at the end of the study.

4.4.2 Informed Consent for Rectal Sample Collection

Study participants are asked to provide informed consent for collection of rectal fluid samples at each visit starting with Visit 3 to test for the presence of study drug in the rectum. Participants may choose to not have this sample collection or withdraw their consent for rectal sample collection at any time and still remain in the study.

4.4.3 Informed Consent for In-Depth Interview

Study participants are asked to provide informed consent to participate in an in-depth interview (IDI) at the end of the study to collect feedback on the vaginal insert. A total of 24 participants across three sites are to be interviewed. Participants who agree to participate and are selected for the IDI will be compensated. Participants may choose not to participate in the in-depth interview or withdraw consent at any time and still be enrolled in the study.

4.4.4 Informed Consent for Off-Site Visits

Participants may be asked to provide informed consent to schedule off-site visits if unable to come into the clinic. Sites may require certain requirements for such visits including need for maintaining confidentiality, conditions of visit site and time required. Participants should be informed that off-site visits may affect the confidentially despite precautions taken by study staff. Visits 1-8 which require sample collections will need to be conducted on-site. Interim visits involving dispensing replacement inserts may be scheduled off-site with proper permission from participant. In-depth interview may also be scheduled for off-site if the participant does not have allotted time at Visit 8.

4.4.5 Other Informed Consent Visual Aids

Use of visual aids are encouraged throughout the informed consent process to facilitate participant comprehension. Each site should determine the most appropriate visual aids for its study population and ensure that a "kit" containing each of these aids is available in each room where informed consent discussions take place. In addition to the visual aids decided upon at the site, it may be helpful to point out such things as a locked file cabinet or a calendar on the wall. It may not be necessary to use each

visual aid with each participant. Study staff should use their best judgment of each participant's information needs and how best to address those needs. Suggested visual aids for the site to consider using are as follows:

- Calendar with study visit schedule
- Sample vaginal insert
- Urine specimen cup
- Blood collection tubes
- Speculum
- List of prohibited medications, activities/vaginal/anal practices and products

4.5 Comprehension Assessment

The participant must not sign the informed consent form until they fully understand the information contained therein, including visit procedures. Site SOPs should explain the procedures that study staff members are responsible for implementing to ensure that each participant understands the screening process and the study prior to signing the study ICF and undertaking any study procedures.

A comprehension assessment should be conducted and documented prior to a participant signing the ICF. This assessment should occur after the participant has completed the informed consent discussion described above, but before they sign the ICF. It is expected that study staff administering the informed consent and assessing comprehension will be sufficiently knowledgeable about MATRIX-001 to make good judgments about the potential participant's understanding of the required information. The site IoR or designee must be available to answer questions that might be raised by participants that cannot be answered by study staff. This discussion should be thoroughly documented on the IC Cover Sheet or chart notes.

A comprehension assessment tool is available on the MATRIX-001 webpage under Study Documents. Sites may use the tools as provided or may choose to adapt for their local use. All comprehension assessment tools should be submitted to local IRB/IECs for approval prior to use. Detailed instructions for use of all comprehension tools must be specified in the site SOP for obtaining informed consent.

True/False Assessment: This assessment tool is also structured around questions that correspond with the required elements of informed consent but uses true/false questions that may be administered either orally or written.

Regardless of the method used to assess comprehension, if the assessment results indicate misunderstanding of any aspect of the study, site staff should review those aspects again until the participant fully understands them. Site staff should ensure complete comprehension of all study aspects prior to the participant signing the ICF.

If, after all possible efforts are exhausted, the participant is not able to demonstrate adequate understanding of the study, do not ask them to sign the ICF to screen/enroll in the study. Similarly, if the participant has concerns about possible adverse impacts if they were to take part in the study or indicates

that the participant may have difficulty adhering to the study requirements, do not ask them to sign the ICF.

The comprehension assessment tool form is considered a study source document that should be completed, handled, and retained in the participant's study file like any other source document. After administering the assessment tool, study staff should carefully review the form to verify that all required points have been satisfactorily addressed by the participant and that this is adequately documented. Consideration should be given to having two study staff members complete this verification because failure to document comprehension of all required points will be considered an informed consent process protocol deviation.

Comments may be recorded in a designated area on the form (and on the back of the form if additional space is needed) or on an Informed Consent Coversheet (refer to section 4.6 below).

After the informed consent process is completed, the outcome of the process should be recorded directly on the assessment tool form (or in a chart note) and the staff member who completed the assessment tool form should ensure his/her signature is recorded in the space provided.

4.6 Documenting the Informed Consent Process

US FDA regulations and ICH E6 guidelines require that informed consent be documented by "the use of a written informed consent form approved by the IRB/IEC and signed and dated by the subject or the subject's legally authorized representative at the time of consent."

To fulfill this requirement, complete all signature and date lines on the ICF in dark ink. Legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a participant's full surname, and it is strongly recommended that initials not be used in place of a participant's full first name. However, if a participant commonly signs their name using an initial for their first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

In addition to completing signature requirements as described above, the participant must indicate on the ICF whether they agree to storage and future testing of biological specimens, rectal fluid sample collection, participation in in-depth interview and off-site visits. The participant may decline these options and still enroll in MATRIX-001.

Site staff are strongly encouraged to use an Informed Consent Coversheet (ICC) similar to the sample included on the MATRIX-001 webpage under Study Documents to clearly document the informed consent process. Sites choosing to use a coversheet should list the coversheet as a source document in their SOPs for Source Documentation and should use the coversheet consistently to document all informed consent processes with participants. The sample ICC indicates the items to be completed at the start of the informed consent session. The remainder should be completed at the end of the informed consent session. If a site chooses not to utilize the ICC, all elements of each informed consent process must be documented in detail in a signed and dated chart note.

It is essential that all informed consent documentation (e.g., comprehension assessment tool, ICF, coversheet) document that informed consent was obtained before any study procedures were conducted.

Regulations require that participants be given a signed copy of the ICF(s). If a participant opts not to receive a copy, document this on the coversheet or chart note and offer the participant an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full ICF.

4.7 Ongoing Assessment of Participant Comprehension

For enrolled participants, informed consent is an ongoing process that continues throughout the study follow-up period. Periodically, at study visits, staff should assess participants' comprehension using a discussion style similar to the initial assessment. The key elements of informed consent also should be reviewed at study follow-up visits. Elements of informed consent may be reviewed at every visit, or periodically, as per site SOPs. Reviewing key elements of informed consent during follow-up visits may focus on the remainder of study participation. These informal assessments will help to identify aspects of the enrollment informed consent process that are, and are not, optimally effective for study participants. This discussion should be noted in the Visit Checklist and/or participant's chart note for that visit date.