MATRIX-003 Study-Specific Procedures (SSP) Manual
Section 4 – Informed Consent

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4 Introduction

This section provides information on informed consent procedures for MATRIX-003. Informed consent includes Screening, Enrollment, Long-term Storage and Future Testing, Participation in an In-depth Interview, Permission to Contact Sexual Partner, and if applicable Off-site Visits. MATRIX-003 uses one consolidated Informed Consent Form (ICF) for all participant procedures, and a separate ICF for the sexual partner subset. Sites should follow their Institutional Review Board/Independent Ethics Committee (IRB/IEC) and national drug regulatory authority (DRA) recommendations/guidelines regarding the site-specific informed consent(s). For instance, if an IRB/IEC/DRA requires additional individual consents, sites may use the consolidated ICF to prepare and utilize separate consents. 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 an ongoing process throughout the study 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's protocol development and study activation processes, there is adequate assurance that once the MATRIX Prime/Clinical Trials Hub (CTH) 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 Investigator of Record (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 III. A separate sample ICF for the sexual partner 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 site-specific consents do not need to be reviewed and/or approved by the MATRIX Prime/CTH prior to IRB/IEC/DRA submission. After IRB/IEC/DRA approval is obtained, the IRB/IEC/DRA approval letter, listing the approved consent with version and date, must be submitted to MATRIX CTH Regulatory (matrixregulatory@lists.matrix4prevention.org) prior to initial use.

Each site is responsible for 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 IRB/IEC/DRA approval letter, listing the approved consent with version and date should be submitted to MATRIX CTH Regulatory (matrixregulatory@lists.matrix4prevention.org).

4.3 Standard Operating Procedures (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
- Process for consenting persons deemed illiterate
- 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 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)
- Quality control (QC)/quality assurance (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.

A single informed consent document for Screening and Enrollment will be used for MATRIX-003, unless otherwise determined/required by the IRB/IEC/DRA. 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. This will be documented on the Enrollment Visit Checklist, with additional details in chart notes as applicable.

A separate informed consent document will be used for sexual partners who agree to participate in the sexual partner subset.

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

4.4.1 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. 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 for 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. At the end of the study, the CTH Data Manager will provide sites and the CTH lab, as applicable, with a comprehensive list of participants and their consent decision to determine if samples should be retained or destroyed.

4.4.2 Consent to Participate in an In-depth Interview

Study participants will be asked to provide informed consent for participation in a conversation-style interview (in-depth interview or IDI) with trained staff. Participants are asked questions such as: experiences using the product; product design, packaging and delivery preferences; and other topics related to product use. Participants may choose not to participate and still join the study. Participants may also change their mind about the IDI at any time during the study. Sites should follow local guidelines should this occur (i.e. re-consent, update original choice) and/or include in a narrative chart note. The Informed Consent Summary instrument in REDCap should also be updated, as applicable.

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

4.4.3 Permission to Contact Sexual Partner

Study participants will be asked permission to include their sexual partner and/or contact their sexual partner to participate in an IDI at the end of the study to gather more feedback about the intravaginal ring. Sites should follow IRB/IEC guidance for including the sexual partner and how contact with the sexual partner should occur. The consent should be modified as needed based on IRB/IEC guidance. If both the participant and her partner agree, and the partner is selected to participate in the IDI, trained study staff will ask the partner about their views on the intravaginal ring and its characteristics and their partner's experience with using the ring. Participants may choose not to provide consent for sites to include/contact their sexual partner but still join the study. Participants may also change their mind about permitting sites to include/contact their sexual partner at any time. Sites should follow local guidelines should this occur (i.e. re-consent, update original choice) and/or include in a narrative chart note. The Informed Consent Summary instrument in REDCap should also be updated, as applicable.

4.4.4 Consent for Off-site Visits

Participants will be asked to provide permission to schedule off-site visits at the participant's home or another location as part of the study, as applicable and approved by the IRB/IEC. Participants should understand that off-site visits may affect their confidentiality even if the study staff take precautions not to disclose the purpose of the visits. Participants may choose not to participate in off-site visits and still join the study.

4.4.5 Informed Consent Visual Aids

Use of IRB/IEC approved visual aids are encouraged throughout the informed consent process to facilitate participant comprehension. Each site should determine and prepare 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, as applicable. 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 intravaginal ring
- Urine specimen cup
- Blood collection tubes
- Speculum
- List of prohibited activities/vaginal practices and products for the duration of the study including abstinence from penetrative vaginal sex during the first 14 days each ring is used (V2 – V4, V6 – V8)

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-003 to make good judgments about the potential participant's understanding of the required information. The site IoR/designee must be available to answer questions that might be raised by participants that cannot be answered by study staff conducting the consenting process. This discussion should be thoroughly documented on the IC Cover Sheet or chart notes.

A sample screening/enrollment informed consent comprehension assessment (ICCA) is available on the MATRIX-003 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents). The ICCA was designed for use with a single MATRIX-003 consent, including consent addenda (i.e., IDI, long-term storage, permission to contact sexual partner, offsite visits). Sites may use the ICCA as provided or may choose to adapt it for their local use. If the consent is divided in any way, sites may use separate comprehension assessments if deemed necessary. The ICCA should be submitted to local IRB/IECs for approval prior to use. Instructions for use of the ICCA should be specified in the site SOP for obtaining informed consent.

True/False Assessment: The ICCA is structured around questions that correspond with the required elements of informed consent and uses true/false questions that may be administered either orally or written.

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 (that cannot be adequately addressed) about possible adverse impacts if they were to take part in the study or indicates that they may have difficulty adhering to the study requirements, do not ask them to sign the ICF.

The ICCA 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 ICCA, 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.

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

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, participation in an in-depth interview, permission to contact sexual partner, and as applicable for off-site visits. The participant may decline these options and still enroll in MATRIX-003.

Site staff are strongly encouraged to use an Informed Consent Coversheet (ICC) similar to the sample included on the MATRIX-003 under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents) to clearly document the informed consent process. This ICC was designed for use with a single MATRIX-003 consent, including consent addenda (i.e., IDI, long-term storage, permission to contact sexual partner, offsite visits). If the consent is divided in any way, sites should use separate ICC as deemed necessary. Sites choosing to use a coversheet should list the coversheet as a source document in their source documentation SOP 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. The sample ICC also includes documentation of a second verifier to ensure accuracy and completeness of the consent document while the participant is still in the clinic.

It is essential that informed consent documentation (i.e., on the coversheet) document that informed consent was obtained before any study procedures were conducted.

Regulations require that participants be offered 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 signed ICF.

4.7 Ongoing Assessment of Participant Comprehension

Informed consent is a dynamic process that should continue throughout the duration of study to ensure participant understanding of protocol requirements. Site staff should review protocol requirements and processes at study visits/contacts as applicable and as deemed necessary. Study participants are free to withdraw consent at any time during participation.