MATRIX-007 Study-Specific Procedures (SSP) Manual Section 3 – Informed Consent

TABLE OF CONTENTS

3. Introduction

This section provides information on informed consent for MATRIX-007, including detailed guidance for the standardized approach to the informed consent process that must be followed by all countries and sites, and where country-specific processes are permitted. The study involves one informed consent: *Pregnant Participant and Infant Informed Consent for Enrollment, Off-site Visits, and Infant Photography/Video.*

The version numbers of the all sample ICF issued are available in SSP section 1.1 (current protocol specifications). Note that actual consent types needed will vary by country depending on country-specific eligibility criteria, IRB/IEC policies, and relevant study components to be implemented. It is recommended that a list of country specific ICFs be included in Informed Consent SOPs.

3.1. 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 relevant to their decision. It is not merely a form or a signature, but a process involving information exchange, comprehension, voluntariness, and documentation. Please also refer to Section 4.8 of the International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP) for further guidance on the informed consent process and documentation requirements.

United States (US) regulations (45 Code of Federal Regulations [CFR] 46) specify the elements of informed consent that must be conveyed to research participants through the informed consent process. It is the responsibility of the country PI, and by delegation of all study staff involved in the informed consent process, to deliver all required information to potential study participants.

It also is the responsibility of the country Principal Investigator (PI) and designated study staff to:

- Deliver all required information in a manner that is understandable to the potential study participant and in participants' native language or a language they understand.
- Assure that informed consent is obtained in a setting free of coercion and undue influence
- Confirm that the participant comprehends the information
- Document the consent process

Per protocol, an illiterate participant can be consented and enrolled in MATRIX-007 providing they are otherwise willing and eligible—and if independent consent is ensured. If a participant is illiterate, an impartial witness should also be present for the informed consent process.

Written informed consent will be obtained at the enrollment visit from pregnant study participants for themselves to enroll and prospectively for their infants to enroll once born. This will be done prior site IRB/EC requirements prior to any procedures done at the Enrollment visit.

3.1.1. Informed Consent SOPs

As a condition of study activation, each study site must outline procedures for obtaining informed consent in standard operating procedures (SOPs). It is recommended that the following elements be covered:

- Procedures for determining participant identity and age
- 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
- Should the mother no longer be living, procedures for confirming guardianship of an infant, and reconsenting of the guardian before continued infant participation
- Storage locations for blank ICFs
- Storage locations for completed ICFs
- Procedures (e.g., color coding) to ensure the appropriate version and type of ICF are easily distinguished and used appropriately, if applicable
- QA/QC procedures related to the above (if not specified elsewhere)

A **sample Informed Consent Job Aid** and **IC coversheet** is available on the MATRIX-007 website as a resource for staff members conducting informed consent to ensure all required procedures are completed. This tool can be adapted to align with country-specific informed consent procedures.

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

3.1.2. Informed Consent for Off-site Visits and Infant Photographs/Video

Included in the ICF is a consent for off-site visits in which enrolled study participants are asked to provide informed consent for visits that may take place outside of the study site. Participants may choose not to be visited off-site or withdraw their consent for off-site visits at any time and still

remain in the study. See SSP Section 5 Study Procedures for more information on conducting off-site visits.

The ICF also will also have an option for declining or accepting photographs/video of infants with identified or suspected congenital anomalies. Mothers should understand that declining infant photographs/video will not exclude them or their infant's ability to participate in the study. Refer to SSP section 6 Clinical and Safety Considerations for a description of the congenital anomaly assessment and photography process.

Some sites may choose to separate consent for off-site visits and/or infant photographs/video into standalone ICFs from the main ICF, per IRB/EC requirements or site preference. Regardless of whether the off-site visits ICF and infant photography/video is a stand-alone form or included as part of the main ICF, these components should be conducted at the same visit as the main ICF.

Consent for off-site visits and infant photography/video is documented on the **Eligibility CRF** when documenting overall consent for the study.

3.2. Site-Specific Informed Consents

A sample ICF is provided along in the MATRIX-007 protocol. Country teams are responsible for adapting the sample as needed for local use. Local adaptation may include reformatting the ICF in accordance with local IRB/EC requirements, as well as translating the forms into applicable participant languages. Countries are responsible for following the procedures and policies of their IRBs when adapting and translating site-specific ICFs. Unless waived by the IRB, all adapted ICFs must still contain the required elements of informed consent as defined in 45 CFR 46.116. All ICFs (English and translated,) must be approved by Clinical Research Manager (CRM) prior to IRB/EC submission. After ethics approval, final stamped ICFs must be submitted to the CRM for record keeping. Country teams should maintain approved versions of all ICFs in their country team MATRIX-007 SharePoint folder.

Each country team/site is responsible for preparing bulk supplies of their approved ICF and for only using the currently approved versions of the ICF during the study. A strong system for tracking version control and approvals of ICFs is also recommended and should include, at a minimum, the version number and date of the ICF as well as the implementation dates (start and end) when that version was in use. If additional guidance on version control tracking is needed, sites are encouraged to ask their CRM for assistance.

Upon receiving final IRB/EC and any other applicable regulatory approval(s) for an amendment to the ICFs, sites should implement the updated ICFs immediately. See section 3.8 below regarding considerations for whether reconsent of current participants applies. Previous versions of *blank* ICF forms should be destroyed to avoid staff using an old/outdated form.

3.3. Informed Consent Support Materials

A sample fact sheet has been developed for CARE PrEP and is available on the MATRIX-007 website for use with participants, partners, and community members, as study staff deem appropriate. Materials used for participant education in the consent process should be translated into local languages as appropriate and IRB/EC approved before use. These materials can be used during the informed consent process, or any other time throughout the study once they are approved for use.

Use of visual aids, in addition to the fact sheet, is 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 each site, it may be helpful to point out such things as a locked file cabinet, a referral clinic across the way, or clinical equipment such as a blood pressure cuff or hand-held doppler. 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.

3.4. Comprehension Assessment

Research staff are responsible for determining whether each potential participant understands all information provided to them to ensure they can make an informed decision about study participation. The participant must not be asked to agree to take part in the study or sign the ICF until comprehension is assessed.

It is expected that research staff administering the ICF will be sufficiently knowledgeable about MATRIX-007 to make good judgments about potential participants' comprehension of the required information. Procedures for assessment of comprehension should be outlined in SOPs. Sites should adapt the sample **Informed Consent Job Aid** which includes open-ended questions and required points of comprehension. This tool is designed to be laminated and used as a staff guide (not a worksheet that is completed for each participant). Teams can choose to adapt these questions or use an alternative approach to assessment of participant understanding. Any comprehension assessment form or tool must be IRB approved.

3.5. Documenting the Informed Consent Process

US regulations require that informed consent be documented by "the use of a written informed consent form approved by the IRB/EC and signed (including in an electronic format) by the subject or the subject's legally authorized representative. A written copy shall be given to the person signing the informed consent form."

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 her first name, the initial may be used, provided this practice is acceptable per the policies of the study implementing partner and/or IRB

In addition to completing signature requirements as described above, the participant must indicate on the ICF whether they agree to off-site visits and infant photographs/video (unless the site has chosen to create stand-alone ICF(s) for these topics, in which case each form should be completed separately). The participant may decline these study components and still enroll in the study.

If the participant is not literate, the witness who was present during the informed consent discussion must sign and date the ICF to attest that the information in the ICF and any other written information was accurately explained to and apparently understood by the participant, in the participant's language of fluency, and informed consent was freely given by the participant. The participant's printed name, signature, and signature date lines on the ICF should be completed as described below and illustrated in Figure 3-1. Following these procedures fulfills the protocol requirement for obtaining written informed consent from all study participants.

- Unless other conventions that have been endorsed by IRB/ECs, the witness should write the participant's printed name and date in the participant agreement section of the consent. The participant should add their fingerprint or make their mark on the "participant's signature" line, and the witness should write the following statement: "This is the mark of [Name of participant]," and sign and date the statement.
- The witness will print, sign, and date their name in the section designated for "Witness."

Figure 3-1: Informed Consent Form Signature Lines for Illiterate Participants

If **all boxes** are checked, ask the participant to sign/mark here:

Mary Phiri
Printed Name of Participant

_____ 11 APR 2023
Signature / Mark of Participant Date

This is the mark of Mary Phiri. 11 APR 2023

If a mark is used, the witness should write the following statement: "This is the mark of [Name of participant]," and sign and place a date below the statement.

WITNESS - if participant cannot read/write themselves

I have witnessed a verbal explanation of the research study; its procedures and risks and I believe that the participant has understood that explanation.

Debra Ross
Printed Name of Witness

_____ 11 APR 2023
Signature of Witness Date

PERSON CONDUCTING CONSENT

I certify that the nature and purpose, the potential benefits, and possible risks associated with participating in this research have been explained to the above individual. All questions were answered and the participant demonstrated an understanding of the information provided.

Martha Moore
Printed Name of Person Who Obtained Consent

_____ 11 APR 2023
Signature of Person Who Obtained Consent Date

Site staff should use an **Informed Consent (IC) Coversheet** to document required elements of informed consent, including verification of emancipated/mature minor status for those under 18 years of age. Sites should list the coversheet as a source document in their SOPs and should use the coversheet consistently to document informed consent processes with all participants. A sample IC coversheet template is available on the MATRIX-007 web page. An IC coversheet should be

completed for each enrollment ICF completed. The first section of the coversheet should be completed at the start of the informed consent session. The remainder should be completed at the end of the informed consent session.

It is essential that informed consent from the participant be obtained before any study procedures are conducted. This will be documented through completion of the Eligibility CRF, through timestamps on completed fields. Study staff must indicate on the CRF that consent was obtained prior to establishing that the participant is eligible to enroll.

Regulations require that participants be given a signed copy of the ICF. 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 informed consent form.

Signed ICFs and respective IC Coversheets should be kept together in a secure, stored location on site for all participants for at least the duration of the study. These documents should be filed separate from any documents identified by PID. It is strongly recommended that the PID NOT be written on the top of the consents or IC Coversheets.. These will serve as the primary source document of consent for a participant. IC cover sheets or consents for participants who do not enroll should also be retained. These can all be filed together in a screening file, kept separate from any documents for enrolled participants. See SSP section 1 (introduction, site activation, and document requirements) for guidance on document organization and retention.

3.6. Reconsenting

There may be times when site staff have to reconsent participants, due to minor modifications or protocol amendments. Updated ICFs should be implemented in a "timely manner" as "without delay" upon receipt of the IRB/EC/RE-approved revised ICF(s) per the ICH E6 (R2). Based on this definition, participants should be re-consented using the most recent IRB/EC/RE-approved site-specific ICF(s) without delay, usually by or at the participant's next study visit.

Reconsenting must also be done for infants if the mother is no longer the legal guardian, due to death or relinquishment as caretaker, at any point during the infant's study follow-up as required by site IRBs/ECs and per site SOPs.

Reconsent procedures may be abbreviated when done due to changes in the ICF. The staff member conducting the informed consent session should review the changes made to the ICF with the participant but does not need to read or review the entire ICF again, unless this is required by the local IRB. Note that any time reconsenting procedures are being conducted using an ICF that contains signature blocks for specimen storage, ALL items should be reviewed and re-signed based on the participant's current preferences. The signature lines at the end of the consent for participant, staff, and witness must also be completed in full.

Participant understanding of the consent information should be assessed and all questions should be answered prior to signing the new ICF(s). Once comprehension has been evaluated and ensured, signatures should be obtained. The participant should be offered an updated, signed copy of the ICF to take home.

Similar procedures should be conducted for participants who change their mind about participating in the optional components of MATRIX-007 study, namely off-site visits and infant photography/video. Using the most current version of the appropriate ICF, review the information pertinent to the participant's decision. If the current ICF differs in any way from the version the participant originally signed, these changes should be reviewed as well. Note that any time

reconsenting procedures are being conducted using an ICF that contains signature blocks for these options sections, ALL items should be reviewed and re-signed based on the participant's current preferences. The signature lines at the end of the consent for participant, staff, and witness must also be completed in full.

3.7. Consenting for Re-enrollment for Subsequent Pregnancies

If a participant has completed their study participation, exiting the study, but then becomes pregnant again still presumptively meeting the PrEP exposure inclusion criteria, they may be eligible to enroll again in MATRIX-007 for the subsequent pregnancy. In this case, the informed consent process must be completed again in its entirety, with the participant consenting for both themselves and the infant(s) from this new pregnancy.

Should a participant in current MATRIX-007 post-partum follow-up become pregnant again and desire to screen for MATRIX-007 for this new pregnancy, the participant should have a new ICF completed to consent to study procedures for themselves and the baby from this new pregnancy at the visit in which they will 'enroll' for the new pregnancy. The participant may still continue to complete study procedures for the previous pregnancy as well. If the participant becomes pregnant again during current study participation but declines to consent for the new pregnancy, only procedures related to the previous pregnancy may be conducted.

See SSP section 5 Study Procedures for more details on re-enrollment for subsequent pregnancies.

3.8. Informed Consent Process for Participants Who Resume Participation After Terminating Early

In the event a participant is terminated from the study early or withdraws consent and decides to rejoin the study, they must undergo a re-consenting process which includes a complete review of the ICF to restart participation in the study regardless of any previously documented written informed consent.

For participants resuming study participation, written informed consent from the participant, must be obtained prior to any study procedures (see SSP section 5). Participants rejoining the study should also undergo informed consent procedures for off-site visits and infant photography/video, however they may decline participation in these optional components and still re-join the study.

The documentation requirements for the new written informed consent documents are the same as the requirements for participants joining the study for the first time (See SSP section 4 Study Procedures).