Section 4. Informed Consent

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This section provides information on informed consent procedures for MTN-033. This study utilizes one study informed consent (Screening, Enrollment, and Long-term Storage), which consists of:

- Informed consent for screening and enrollment
- Informed consent for the following optional activity: long term specimen storage and possible future research testing

Depending on IRB/EC requirements, the site may choose to use a separate informed consent form specifically for the consent of long term specimen storage and possible future research testing; however, if this is done, all required elements of the informed consent must be contained on the form.

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 Section 4.8 of the International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP) and the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials 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 Investigator of Record (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 the MTN protocol development and study activation processes, there is adequate assurance that once the MTN LOC (FHI 360) has activated a site for study implementation, site-specific informed consent forms specify all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate informed consent form.

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

DAIDS has determined that the task/responsibility of obtaining informed consent may be delegated to staff "qualified" by education, training, experience, and knowledge of the trial, as long as this practice is permitted per local laws, regulations, and institutional policies. The staff roster/delegation of duties log should include a responsibility code for the task/responsibility of obtaining informed consent and applicable staff authorized and "qualified by education, experience, training, and knowledge of the trial", as determined by the IoR, to obtain IC must be delegated this responsibility appropriately. Study staff delegated the role of obtaining IC must be listed as sub-investigators on the Form FDA 1572.

4.2 Site-Specific Informed Consent Forms

A sample informed consent form (ICF) is provided in the MTN-033 study protocol. The site responsible for adapting the sample as needed for local use. Local adaptation may include reformatting the consent form in accordance with local IRB/EC requirements. The site must follow all procedures in the MTN Manual of Operations (MOP) and the DAIDS Protocol Registration Manual when adapting site-specific ICF. The ICF must be reviewed and approved by MTN LOC (FHI 360) prior to IRB/EC submission. After regulatory approval is obtained, the approved ICF must be submitted to the DAIDS Protocol Registration Office (DAIDS PRO) prior to its initial use.

The site is responsible for preparing bulk supplies of its approved ICF(s) and only using the currently approved version of the ICF(s) at all times during the study. A system for tracking version control and approvals of the currently approved ICF is recommended. It is also recommended that the site consider the use of color-coding or other techniques to ensure that the various study informed consent forms are easily distinguished and used appropriately. Upon receiving final IRB/EC and any other applicable regulatory approval(s) for an amendment to the informed consent form, the site should implement the consent form immediately and submit the updated version to DAIDS PRO per the timelines outlined in the protocol registration manual.

4.3 SOP for Obtaining Informed Consent

As a condition for study activation, the 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.

- The minimum legal age to provide independent informed consent for research at the study site
- Procedures for determining participant identity and age
- Procedures for determining participant literacy and provision of informed consent for those who are illiterate.
- Local laws, regulations, and institutional policies pertaining to the informed consent process
- 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 informed consent forms
- Storage locations for completed informed consent forms
- Procedures (e.g., color-coding) to ensure that different versions of the study informed consent forms are easily distinguished and used appropriately
- Procedures for implementing a change in the version of the informed consent form used
- Staff training requirements
- Staff responsibilities for all 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 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 should be documented in the participant's study files.

An overview of the standardized approach to the informed consent process is provided in Figure 4-1. Additional details related to key steps in the process are provided in the remainder of this section.

4.4.1 Informed Consent for Specimen Storage and Possible Future Research Testing

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 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 are allowing for the remaining (leftover) samples along with their demographic information to be kept and not destroyed at the end of the study.

Figure 4-1
Overview of MTN-033 Informed Consent Process

Briefly **describe the steps** in the informed consent process and the time required to complete.

ASK — Does s/he have time to complete this today?

- If yes, proceed.
- If no, schedule return appointment.

ASK — Is s/he ready to read the **informed consent form** or have it read to her/him?

- If yes, proceed.
- If not, determine what s/he needs and provide information or schedule return appointment.

Read consent form, section by section, asking if s/he has questions and discussing as you go along.

ASK — Does s/he feel comfortable that s/he understands all aspects of the study?

- If yes, proceed.
- If not, determine what s/he needs and provide more information or schedule return appointment.

Administer **comprehension assessment.**

ASK — All items on the form should be asked or completed by the participant.

- If participant demonstrates understanding of all required points, proceed.
- If not, discuss misunderstandings and probe problem areas with open-ended questions. Provide information and review consent form, and any other materials as needed to resolve misunderstandings. If after further discussion s/he demonstrates understanding, proceed. If s/he does not understand all points, s/he is ineligible for enrollment.
- If participant is fatigued or requests more time, or if staff judge that participant needs more time, schedule return appointment and repeat steps in the process as needed.

If the participant demonstrates understanding, and chooses to take part in the study, complete all name, signature, and date lines on the informed consent form. Offer participant a copy of the form. Document the process per DAIDS policy and site SOPs.

- If the participant chooses to take part in the study, proceed with enrollment.

4.5 Informed Consent Support Materials

4.5.1 Other Informed Consent Visual Aids

Use of visual aids is encouraged throughout the informed consent process to facilitate participant comprehension. The 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. Sample study products and supplemental gel use instructions will be provided to the site to use as visual aids. 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, a referral clinic across the way, 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 gel applicator and gel use/applicator insertion instructions
- Urine specimen cup
- Blood collection tubes
- Coital Simulation Device
- Study Information Booklet
- Other randomization explanation visual aids (e.g., sack or box containing two items of different colors)

4.6 Comprehension Assessment

The participant should not be asked to agree to take part in the study, or to sign the informed consent form, until s/he fully understands the information contained in the informed consent, 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 informed consent form, respectively, and undertaking any study procedures.

One method is to use a written assessment tool that participants must complete prior to signing the informed consent form. Another approach is the use of open-ended questions to ascertain participant understanding during the informed consent discussion.

4.6.1 Comprehension Assessment Tools and Scoring System

Templates of two open-ended assessment and one True/False assessment tools are available as separate electronic files on the Study Implementation Materials section of the MTN-033 webpage. The site may use the tools as provided or may choose to adapt for their local use.

The assessment tools are also structured around questions that correspond with the required elements of informed consent for research.

- Open-Ended Assessment Tool: Each question should be read to the potential participant, giving his/her time to respond to each one. Each question should be satisfactorily answered by the participant before moving to the next question. For each question, the checklist specifies particular points that must eventually be included in the participant's response. These are identified on the tool as "Required Points of Comprehension."

- True/False Assessment Tool: A scoring system should be incorporated into this assessment; site staff should re-review the contents of the informed consent until the potential participant can answer all questions correctly. For example, if a participant answers less than 80% correctly, the participant should be re-counseled and the entire assessment should be repeated. This process should be repeated until it is determined the participant is unable to demonstrate adequate understanding. For participants that answer over 80% correctly, the questions not understood should be reviewed with the participant to ensure understanding of the information. The review and proper understanding of the information should be documented on the assessment tool, in the participant's chart notes or other site-specific source document.

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 100% understanding of the IC prior to the participant providing written informed consent. 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 informed consent form or 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 they may have difficulty adhering to the study requirements, do not ask them to sign the informed consent form to screen/enroll in the study.

4.6.2 Administration of Comprehension Assessment

The comprehension assessment tool will be administered to each potential participant after they have completed the informed consent discussion described above and before they are asked to sign the informed consent form. It is expected that study staff administering the informed consent and assessing comprehension will be sufficiently knowledgeable about MTN-033 to make good judgments about the potential participants' understanding of the required information.

The comprehension assessment tool 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 4.7 below). All required points must be satisfactorily addressed by the participant, before proceeding to the final informed consent decision and signing of the informed consent form (s).

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

All comprehension assessment tools should be submitted to local IRB/ECs for approval prior to use. Detailed instructions for use of all comprehension tools must be specified in the site SOP for obtaining informed consent.

4.7 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/EC 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 informed consent form 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).

On the study informed consent form, in addition to completing signature requirements as described above, the participant must indicate on the form whether they agree to storage and future testing of biological specimens. The participant may decline this option and still enroll in MTN-033.

The DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials lists detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS policy must be met. In order to also meet some of the suggestions listed in the DAIDS policy, site staff are strongly encouraged to use an Informed Consent Coversheet similar to the sample included on the MTN-033 webpage under Study Implementation Materials. Sites choosing to use a coversheet should list the coversheet as a source document in their SOPs for source documentation for MTN-033 and should use the coversheet consistently to document all informed consent processes with all participants. The first half of the coversheet (items up to and including "Start time of informed consent discussion") should be completed at the start of the IC session. The remainder should be completed at the end of the informed consent session. If a site chooses not to utilize the Informed Consent Coversheet, all elements of the informed consent process must be documented in a comprehensive signed and dated chart note and/or the process must be outlined, in detail, in a SOP. Should the site choose to utilize this option, they should ensure that the person obtaining the informed consent documents in the patient's chart that the informed consent was obtained per SOP.

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

Regulations require that participants be given a signed copy of the informed consent forms. If a participant opts not to receive a copy, document this on the cover sheet 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.

4.8 Ongoing Assessment of Participant Comprehension

For enrolled participants, informed consent must also be understood as 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 enrollment assessment. The key elements of informed consent also should be reviewed at study follow-up visits. The site may choose to review key elements of informed consent with individual participants, or in group sessions. Elements of informed consent can 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. The assessments also may identify rumors or misperceptions about the study that require a response by the Protocol Team. This discussion should be noted in the participant's chart note for that visit date.