Section 4. Informed Consent

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This section provides information on informed consent procedures for MTN-017. MTN-017 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 activities: long term specimen storage and possible future research testing, in-depth phone interview (IDPI) and Extra Samples Group (only applicable at participating sites)

Sites may choose to use a separate informed consent form specifically for the consent of long term specimen storage and possible future research testing; phone IDPI; and, extra samples group (where applicable).

4.1 Overview of Informed Consent Requirements and Procedures

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

4.2 Site-Specific Informed Consent Forms

A sample informed consent form (ICF) is provided in the MTN-017 study protocol. Sites are responsible for adapting the sample as needed for local use. Local adaptation may include reformatting the consent forms in accordance with local IRB/EC requirements, as well as translating the forms into applicable participant languages. Sites are responsible for following the procedures in the MTN Manual of Operations (MOP) Section 11.2 and the DAIDS Protocol Registration Manual when adapting and translating site-specific ICFs. All ICFs (English, translated, and back-translations) must be reviewed and approved by MTN LOC (FHI 360) prior to IRB/EC submission. After ethics approval, ICFs (English, translations, and back-translations) must be submitted to the DAIDS Protocol Registration Office (DAIDS PRO) prior to their initial use.

Each site is responsible for preparing bulk supplies of their approved ICFs and only using the currently approved versions of the ICFs at all times during the study. It is recommended that all sites 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 forms, sites should implement the consent forms immediately.

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. At each site, the informed consent process will be conducted according to site SOPs.
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. **If the participant is not literate, s/he cannot enroll in this study**
- 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 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. 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.

The 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.

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.

4.4.2 Informed Consent for In-Depth Phone Interview

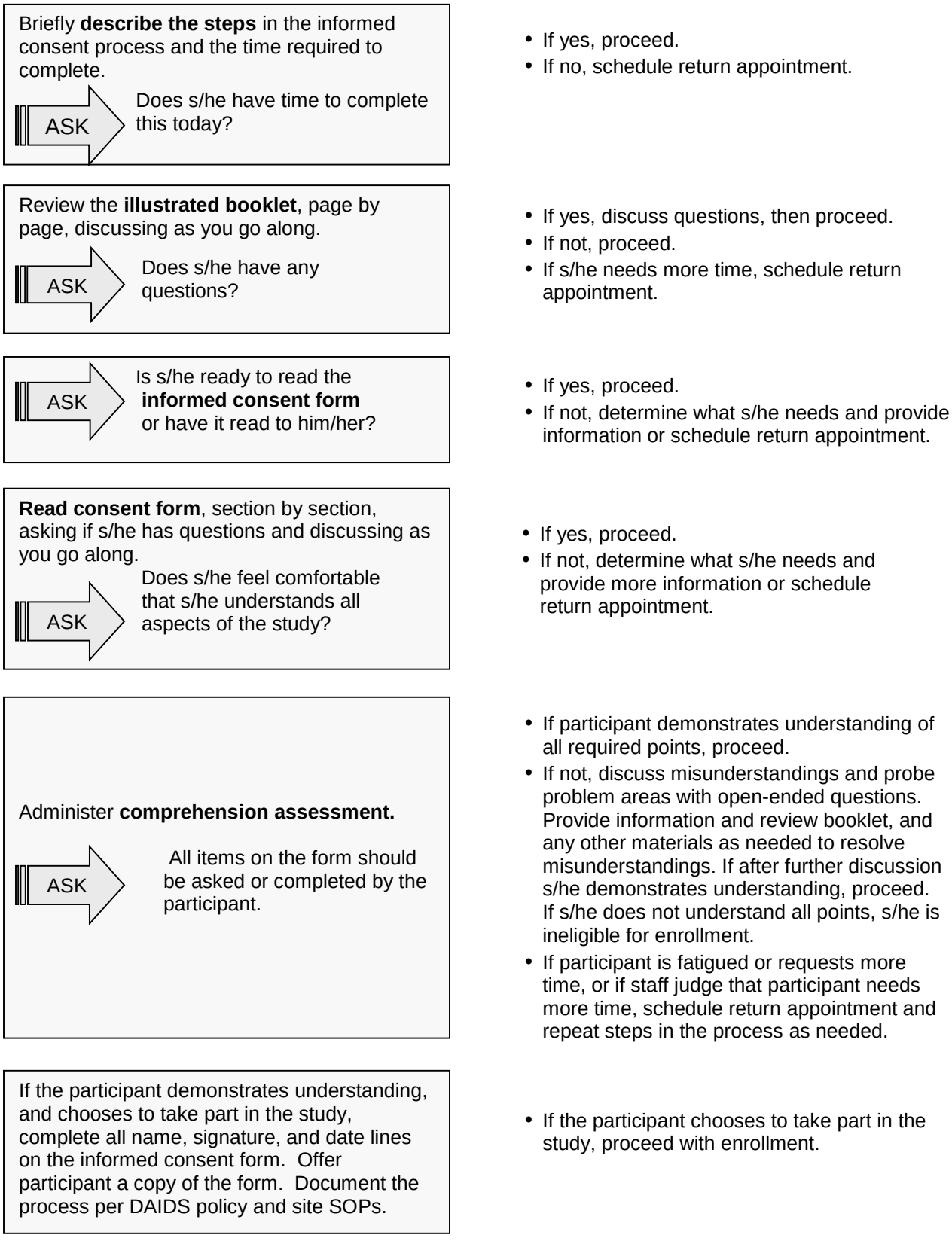
All study participants will be asked to provide informed consent to participate in an optional In-depth Phone Interview (IDPI). The IDPI will be conducted on a subset of 40 participants across all participating sites following the completion of the first 8-week product use cycle (visit 4). Participants who are interested and agree to participate in the IDPI must provide written informed consent at the Screening visit. Participants may choose to not participate in the IDPI and still enroll in the study. Further details on the IDPI can be found in SSP Section 6.

4.4.3 Informed Consent for Rectal Biopsy and Fluid Subset (Bangkok and Pittsburgh Sites Only)

Participants at the Bangkok and Pittsburgh sites will be asked to participate in this optional rectal tissue (biopsy) and fluid study activity. Participants who are interested and agree to participate

must provide written informed consent at the Screening visit. Participant understanding of the rectal tissue/fluid subset is crucial due to the intensive nature of collection procedures as well as associated risks. To ensure participant understanding of these additional procedures, sites must administer a comprehension assessment for this subset. The process for administering the comprehension assessment is presented in Section 4.6 below. The participant may choose to not provide rectal tissue and rectal fluid and still enroll/remain in the study. Further details on the rectal tissue and fluid subset can be found in SSP Section 5 including the sample size.

Figure 4-1
Overview of MTN-017 Informed Consent Process



4.5 Informed Consent Support Materials

4.5.1 MTN-017 Informed Consent Booklets

The illustrated informational booklet was developed to aid in introducing MTN-017 to potential study participants and in explaining the information contained in the informed consent form. The booklet contains information corresponding to the eight elements of informed consent that US regulations require to be conveyed in any informed consent discussion. The booklet is designed to supplement, not substitute, the informed consent form.

Each site should determine how best to use the booklet with its study population, and specify the preferred approach in its SOP for obtaining informed consent for MTN-017. The booklet was designed to be given to participants at their Screening visit for review prior to their Enrollment visit. The participant should be encouraged to take the booklet home for review before his/her enrollment visit and to share with people who are important to him/her.

4.5.2 Community Fact Sheet

Fact sheets have been developed for MTN-017 and are available in the Study Implementation Materials section of the MTN-017 web page for use with participants, partners, and community members, as study staff deem appropriate. The fact sheet includes information about the study products, target population, description of receptive anal intercourse (RAI) as well as information about potential risk and benefits. Factsheets should be translated into local languages at sites where applicable and IRB/EC approved before use. The fact sheet may be used at any time throughout the study once they are approved for use.

4.5.3 Other Informed Consent Visual Aids

Use of visual aids — in addition to the booklet and fact sheets — 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. Sample study products and supplemental study illustrations have been provided to each site to use as visual aids. 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 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 each site to consider using are as follows:

- Calendar
- Male and female condoms
- Sample pill bottle and gel applicator
- Urine specimen cup
- Blood collection tubes
- 5 L jug (to demonstrate the total blood volume in the human body)
- Tablet and Gel use instructions
- Sample randomization envelopes
- Other randomization explanation visual aids (e.g., sack or box containing two items of different colors)

4.6 Comprehension Assessment

The participant must 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.

Various methods (either oral or written) to assess comprehension may be utilized. 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 three assessment tools (open-ended, true/false, and multiple choice) are available as separate electronic files on the Study Implementation Materials section of the MTN-017 webpage. Sites may use the tools as provided or may choose to adapt for their local use.

- True/False and Multiple Choice Assessment Tools:

  These assessment tools are structured around questions that correspond with the required elements of informed consent for research. Sites choosing to utilize either the true/false or the multiple choice assessment tools should incorporate a scoring system into the assessment and 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, s/he 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.

- Open-Ended Assessment tool:

  The open ended-assessment tool is also structured around 11 open-ended questions that correspond with the required elements of informed consent for research. Each question should be read to the potential participant, giving him/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."

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 him/her to sign the informed consent form or screen /enroll in the study. Similarly, if the participant has concerns about possible adverse impacts on him/her if s/he were to take part in the study, or indicates that /s/he may have difficulty adhering to the study requirements, do not ask him/her 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 s/he has completed the informed consent discussion described above and before s/he is 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-017 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); however, this is not required. 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/her signature is recorded in the space provided.

All comprehension assessment tools should be translated into local language(s) (only bolded left hand column questions on the open-ended assessment tool template) and 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 his/her name using an initial for her 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 s/he agrees to storage and future testing of biological specimens, in-depth phone interview, and, where applicable, Rectal Tissue and Fluid Subset (unless the site has chosen to create stand-alone ICFs for these topics, in which case these forms should be completed separately). The participant may decline any of these options and still enroll in MTN-017.

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-017 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-017 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 "Version number/date of informed consent form used during informed consent process/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 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., 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 Informed Consent Process for Participants who Resume Study Participation After Voluntary Withdrawal

In the event a participant voluntarily withdraws from MTN-017 and wishes to re-join the study, s/he must undergo a re-consenting process to restart participation in the study regardless of any previously documented written informed consent. Written informed consent must be obtained prior to any study procedures, including clinical procedures, and prior to any procedures to determine product use eligibility. Refer to SSP Section 5.7.7.1 for specific procedures related to study resumption.

Written informed consent for storage and future testing of biological specimens, IPDI, and, where applicable, Rectal Tissue and Fluid Subset is optional for participants re-joining the study. Participants may choose not to re-consent to storage and future testing of biological specimens, IDPI, and, where applicable, Extra Samples Group and still re-join the study.

The documentation requirements for the re-consenting process are the same as the requirements for participants joining the study for the first time (see Section 4.7).

4.9 Ongoing Assessment of Participant Comprehension

For enrolled participants, informed consent also must 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. Sites 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, either across sites or on a site-by-site basis. This discussion should be noted in the participant's chart note for that visit date.