Section 4: Informed Consent

4. Introduction

This section provides information on informed consent procedures for MTN-035. Informed consent is required for Screening and Enrollment, for which MTN-035 uses one consolidated Informed Consent Form (ICF). For this study, consent for possible participation in in-depth interviews (IDI) is imbedded within the main consent form. No additional signatures are needed for this component of the study

Depending on IRB/EC 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.

This section contains general and specific information and instructions for administering ICFs. In addition, detailed guidance is provided on standardized approaches to the informed consent process that all sites must follow.

4.1 Overview of Informed Consent Requirements and Procedures

Informed consent is a process whereby 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 Section 4.8 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 IoR, and all delegated study staff involved in the informed consent process, to provide 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 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

Given the nature of certain study activities, including CASI and SMS assessments, participants must be able to read and write in the applicable language in order to be in this study.

4.2 Site-Specific Informed Consent Forms

A sample ICF is provided in protocol Appendix III. Sites are 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.

Sites are responsible for following procedures outlined in the MTN MOP and DAIDS Protocol Registration Manual when drafting and, if applicable, translating their site-specific ICFs. Unless waived by the local IRB/EC, site-specific ICFs must address the eight required elements of informed consent, as required by U.S. federal regulations at 45 CFR 46.116. All ICFs (English and, if applicable, translations and back-translations) must be reviewed and approved by MTN LOC (FHI 360) prior to IRB/EC submission. After ethics approval, ICFs must be submitted to and approved by the DAIDS PRO prior to their initial use.

Each site is responsible for preparing bulk supplies of its approved ICFs and for only using the currently-approved ICF version(s) during the study. It is recommended that sites consider the use of color-coding or other techniques to ensure that the various study ICFs be easily distinguishable and used appropriately. A 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) indicating when a particular version was in use. If additional guidance on version control tracking is needed, sites are encouraged to ask the MTN LOC (FHI 360) for assistance.

Upon receiving final IRB/EC and any other applicable regulatory approval(s) for an amendment to the ICF(s), sites should implement the ICF(s) immediately and submit updated versions 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, each site must establish an SOP describing the steps for conducting the IC process and obtaining informed consent from potential study participants. This SOP should contain, at minimum, the following:

- Information about applicable local laws, regulations and institutional policies pertaining to the IC process
- The minimum legal age to provide independent IC for research at the study site
- Procedures for determining participant identity and age
- Procedures for determining participant literacy

- Procedures for providing all information required for IC to the participant
- Procedures for determining participant comprehension of the required information
- Procedures to ensure that IC is obtained in a setting free of coercion and undue influence
- Procedures for documenting the IC process
- Storage locations for blank ICFs
- Storage locations for completed ICFs
- Procedures (e.g., color-coding) to ensure that different versions of the study ICF are easily distinguishable and used appropriately
- Procedures for implementing a change in version of the ICF 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 with the participant at Screening. 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 Enrollment 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 chart notes.

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

4.5 Informed Consent Support Materials

Factsheets have been developed for MTN-035 and are available on the MTN-035 web page (https://mtnstopshiv.org/research/studies/mtn-035/mtn-035-study-implementation-materials) for use with participants, partners, and community members, as study staff deem appropriate. These factsheets include information on the MTN-035 study. Factsheets should be translated into local languages, as appropriate, and approved by IRBs/ECs before use. Once approved for use, the factsheets may be used during the informed consent process or at any other time throughout the study.

Use of visual aids, in addition to the factsheets, is encouraged throughout the informed consent process to facilitate participant comprehension. Each site should determine the most appropriate visual aid(s) for its study population and ensure these aids are available in each room where informed consent discussions take place.

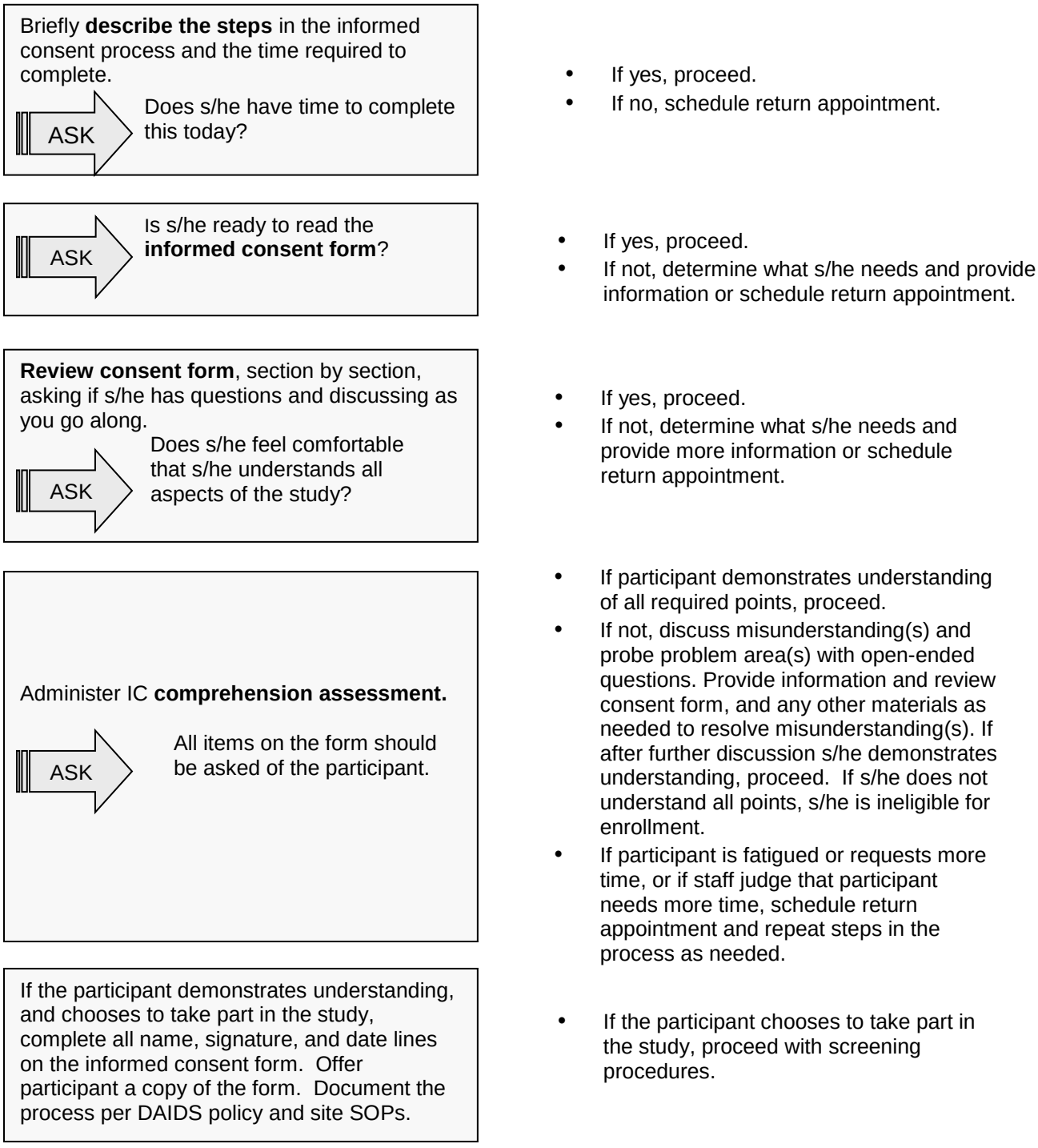
In addition to site-specific visual aids, it may be helpful to point out such things as a locked file cabinet, a referral clinic across the way, or a calendar on the wall. It may not be necessary to use each visual aid with each participant. Study staff should use their judgment as it applies to each participant's information needs and how best to address them. Suggested visual aids for sites to consider using include:

- Calendar with study visit schedule
- Sample placebo rectal insert, placebo rectal suppository and/or an empty douche bottle with covered rectal tip

- Urine specimen cup, blood collection tubes and/or sample throat swab
- Anoscope
- Pelvic or rectal illustrations/models*
- Lubricant sachet

**If using a model to demonstrate product placement, it may be necessary to first familiarize the participant with the model and the anatomical parts shown. Be sure that all relevant staff are able to explain what each part is and, if demonstrating product use, are comfortable inserting the sample study products using the model. Staff that take part in informed consent discussions should be prepared to demonstrate the various insertion positions and "mime" the insertion of each product, if necessary.*

Figure 4-1
Overview of MTN-035 Informed Consent Process



4.6 Comprehension Assessment

The participant must not sign the ICF until s/he fully understands the information contained therein, including that pertaining to visit procedures. Site SOPs should explain the procedures that study staff are responsible for implementing to ensure that each participant understands the screening process and the study prior to signing the ICF and undertaking any study procedures, respectively.

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 s/he is asked to sign the ICF. It is expected that staff administering the informed consent and assessing comprehension be sufficiently knowledgeable about MTN-035 to make good judgments about the potential participant's understanding of the required information.

4.6.1 Comprehension Assessment Tools

A sample comprehension assessment tool is available on the Study Implementation Materials section of the MTN-035 webpage. Sites may use the tool as provided or may adapt it for local use. Any comprehension assessment tool(s) a site wishes to use should be submitted to local IRBs/ECs for approval prior to use. The tool should not be presented to participants as a "test," but rather as a way of ensuring that participants have all the information they need to make an informed decision about enrolling in the study. If/when participants indicate a misunderstanding of any item on the IC comprehension assessment tool, staff should provide clarification on the applicable topic before proceeding to the next question. Detailed instructions for using any comprehension tool must be specified in the site SOP for obtaining informed consent.

A template open-ended comprehension assessment tool is available on the MTN-035 webpage. This tool is structured around open-ended questions that correspond with the required elements of informed consent for research. Each question should be read to potential participants, giving them 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 assessment specifies points that must 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, staff should review those aspects again until the participant fully understands them.

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 ICF to screen/enroll in the study. Similarly, if the participant has concerns about possible adverse effects of participating in the study or indicates that s/he may have difficulty adhering to the study requirements, do not ask him/her to sign the ICF.

4.6.2 Documenting the Comprehension Assessment

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, 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, a template of which is available on the MTN-035 webpage under Study Implementation Materials. All required points must be satisfactorily addressed by the participant before proceeding to the final informed consent decision and signing of the ICF.

After the informed consent process is completed, the outcome of the process should be recorded directly on the comprehension assessment form (or in a chart note) and the staff member who completed the form should record his/her signature in the space provided. Detailed information on how comprehension will be assessed must be specified in the site Informed Consent SOP.

4.7 Documenting the Informed Consent Process

It is essential that all informed consent documentation (i.e. ICFs, IC coversheet, IC comprehension assessment tool) indicate that participant informed consent was obtained before any study procedures were conducted.

US FDA regulations require that informed consent be documented by "the use of a written informed consent form approved by the IRB 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 his/her name using an initial for first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

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. To meet the suggestions listed in the DAIDS policy, sites are strongly encouraged to use an Informed Consent Coversheet similar to the template provided on the MTN-035 webpage under Study Implementation Materials. Sites choosing to use a coversheet should list the coversheet as a source document in their SOP for Source Documentation and should use the coversheet consistently to document all informed consent procedures undertaken with participants. The sample IC Coversheet 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 IC Coversheet, all elements of the informed consent process must be adequately described in the site SOP for obtaining Informed Consent and documented in detail in a signed and dated chart note.

Regulations require that participants be given a signed copy of the ICF(s). If a participant opts not to receive a copy or if site IRB/EC policy mandates that a blank ICF be provided, document this on the IC coversheet or chart note and ensure that an alternative form of study contact information (e.g., a contact card or appointment card) is provided in lieu of the full signed/dated ICF.

4.8 Reconsenting Requirements

There may be times when sites must reconsent participants, due to minor ICF modifications, LoAs, protocol amendments, etc. When reconsenting is required due to minor ICF modifications or the addition of new information resulting from an LoA, the consenting process may be abbreviated. 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.

Using the most current version of the applicable 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. The signature lines at the end of the consent for participant and staff, and witness (if applicable per local regulations) must also be completed in full.

Although an IC comprehension assessment form does not need to be completed in the circumstances described above, participant understanding should be assessed and all questions should be answered prior to signing the new ICF(s). Once comprehension has been evaluated and deemed sufficient, documentation of informed consent should be conducted. The participant should be offered an updated, signed copy of the ICF to take home.

If reconsenting of participants is required due to a protocol version change, a complete review of the ICF must be conducted. When changes to the ICF have been made as a result of protocol version changes, a new IC comprehension assessment form must be completed. Documentation of informed consent should be conducted and participants should be offered an updated, signed copy of the ICF to take home.

4.9 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 that used in the enrollment assessment. The key elements of informed consent should also 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 and descriptions of the study period. Should gaps in participant understanding about the study be identified, staff should provide counseling or additional education as needed to clarify potential misunderstandings, especially those that impact participant safety. This discussion should be noted in the participant's chart note for that visit date.