Section 5. Informed Consent

This section provides information on informed consent procedures for MTN 004. MTN 004 involves three types of informed consent:

- Informed consent for screening
- Informed consent for enrollment
- Informed consent for specimen storage and future research testing of specimens

Potential study participants must provide written informed consent for screening in order to undergo protocol-specified procedures for determining eligibility for study participation. Potential participants who are found to be eligible for the study must then provide written informed consent to enroll in the study and undergo protocol-specified "on study" procedures, including randomized assignment, use of study gels, and completion of follow-up visits and procedures. Informed consent for specimen storage and future research testing is optional. Participants may choose not to consent to specimen collection and storage for future research testing and still be enrolled in the study.

This section contains general information and instructions applicable to all three types of informed consent required for MTN 004. In addition, detailed guidance is provided for the standardized approach (study specific SOP) to the enrollment informed consent process that must be followed at both sites.

5.1 Overview of Informed Consent Requirements and Procedures

Informed consent is a process by which an individual voluntarily expresses her willingness to participate in research, after having been informed of all aspects of the research that are relevant to 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 aspect of this process is described in greater detail below. Please also refer to Section 4 of the ICH GCP guideline and the informed consent section of the DAIDS Policy DWD-POL-CL-04.00: *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* for further guidance on the informed consent process and documentation requirements, which can be found at: http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/ClinicalSite.htm.

As noted above, for MTN 004, informed consent is first obtained for screening procedures only. Then, for participants found to be eligible, informed consent is obtained for enrollment. For both screening and enrollment, informed consent must be obtained prior to undertaking screening and enrollment procedures, respectively. For enrolled participants, informed consent also must be construed as an ongoing process that continues throughout the study follow-up period.

Enrolled study participants are asked to provide informed consent for long term storage of blood specimens for future research testing. Participants may choose to not have their specimens collected and stored for future research testing and still enroll/remain in the study.

US regulations (45 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 Investigator of Record (IoR), and by delegation all 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 Westat or MTN CORE (FHI) has "activated" a site for study implementation, the site-specific informed consent form contains all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate informed consent form. It is also the responsibility of the IoR and designated study staff to:

- 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 the process

Per Section 13.4 of the MTN 004 protocol, this study does not plan to enroll illiterate individuals. However, if an illiterate woman is interested in participating, the site must follow the ICH GCP guidelines for consenting an illiterate participant.

As a condition for study activation, each study site must establish an SOP for obtaining informed consent from potential study participants that ensures that all of the above-listed requirements are met. The SOP must be consistent with the DAIDS Policy: *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. It is recommended that the SOP contain the elements listed below and that each site seek IRB/EC review and approval of the SOP.

- The minimum legal age to provide independent informed consent for research at the study site
- Procedures for ascertaining participant identity and age
- Procedures for ascertaining participant literacy
- Procedures for providing all information required for informed consent to the participant
- Procedures for ascertaining 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
- Considerations and requirements for illiterate participants,
- Storage locations for blank informed consent forms
- Storage locations for completed informed consent forms
- Procedures (e.g., color-coding) to ensure that the different 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 responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

5.2 Informed Consent for Screening

At each study site, the informed consent process for screening will be conducted according to site SOPs. Informed consent for screening must be obtained prior to performing any study screening procedures. For participants who do not consent to screening, no screening procedures should be performed and no data that can be linked to the participant's name or other personal identifier(s) should be recorded.

5.3 Informed Consent for Enrollment

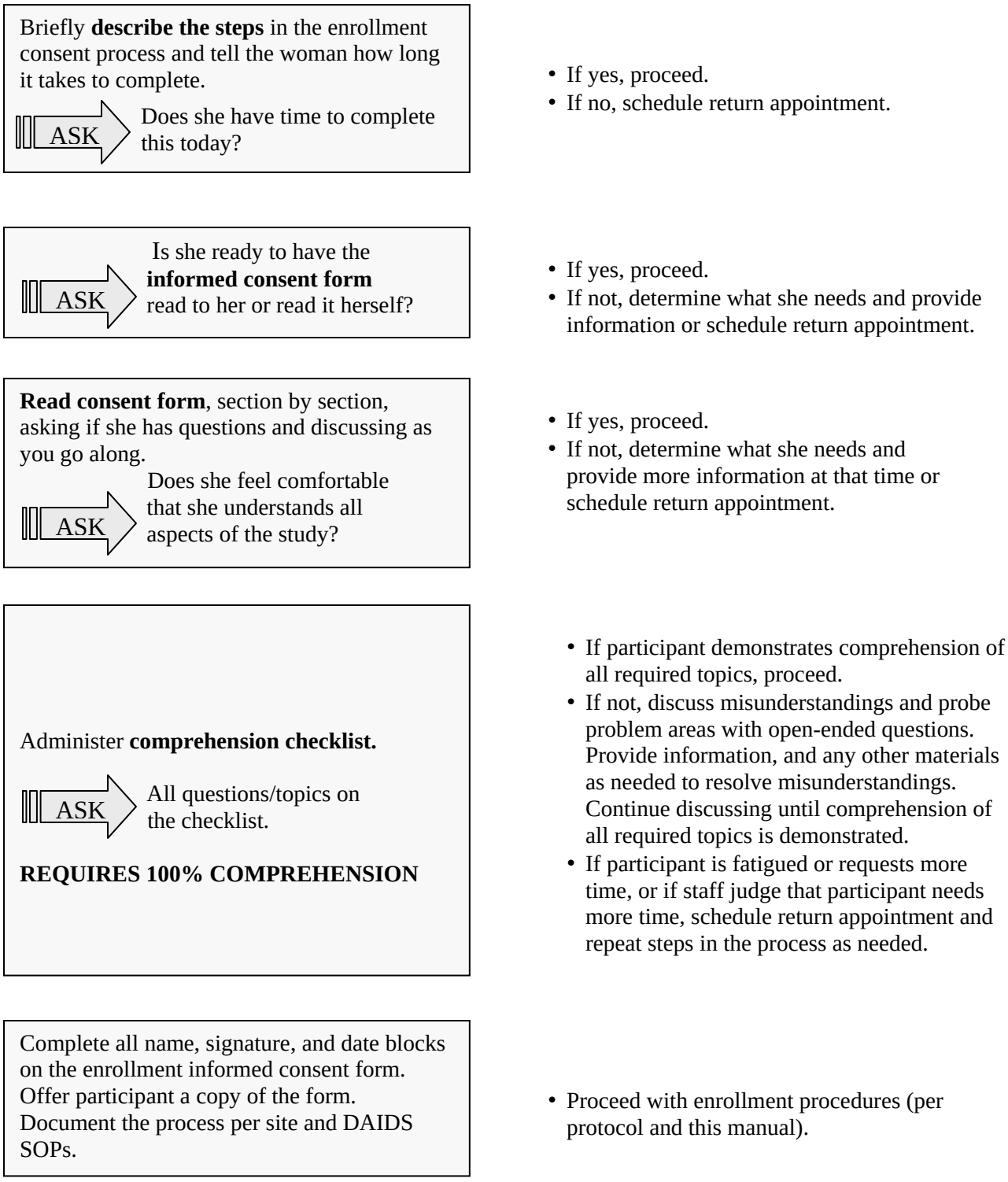
At each study site, the informed consent process for enrollment will be conducted according to site SOPs. However, site specific SOPs must reflect the standardized approach to the enrollment informed consent process that is described in this section. Informed consent for enrollment must be obtained prior to performing any study enrollment or "on-study" procedures. An overview of the standardized approach to the enrollment informed consent process is provided in Figure 5-1. Additional details related to key steps in the process are provided in the remainder of this section.

5.3.1 Informed Consent Support Materials

- **Site-specific informed consent forms:** The informed consent forms used at each site must be reviewed and approved by study site IRBs/ECs prior to their use. After the forms are approved, each site is responsible for preparing bulk supplies of their approved forms and for only using the currently approved versions of the forms at all times during the study.

  It is recommended that each site consider the use of color-coding or other techniques to ensure that the study informed consent forms are easily distinguished and used appropriately (such as a yellow cover sheet for screening, blue for enrollment, etc.). At the beginning of the study, bulk supplies of the screening and enrollment informed consent forms should be prepared.

Figure 5-1
Overview of MTN 004 Enrollment Informed Consent Process



- **Visual Aids:** Use of visual aids 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 a calendar on the wall. It is not 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
  - Sample applicator
  - Sample product carton
  - Urine specimen cup
  - Blood collection tubes
  - Vaginal and/or pelvic model
  - Speculum
  - Randomization explanation visual aids (e.g., sack or box containing three items of different colors)
  - Placebo explanation visual aids (e.g., hair gels with and without straightener, food flavoring sauces in sweet and non-sweet versions)

  If the site personnel choose to use vaginal and pelvic models, remember that participants may not be familiar with such models. Introduce the models in a sensitive manner and use information, rapport, and humor to help make the participant feel comfortable with the models. Be sure that all staff that may use the model are able to explain the anatomical parts of the model as needed.

  When using a vaginal model to demonstrate gel use, suggest to the participant that she may wish to expel a small amount of the gel from the applicator to provide lubrication before inserting the applicator. Always hold the applicator in the middle of the barrel and insert it so that half is inserted inside and half is visible on the outside of the vagina. Once the applicator is inserted, push the plunger all the way in to illustrate how the study gel will be administered into the vagina. Remove the applicator and remind the participant that all used applicators should be discarded.

5.3.2 Comprehension Assessment

The staff person conducting the enrollment informed consent process with a potential participant is responsible for determining whether the participant comprehends the information provided to her. The MTN 004 Enrollment Informed Consent Comprehension Checklist (see sample in Section Appendix 5-3) will assist staff in assessing participant comprehension and targeting follow-up educational efforts to ensure that participants understand all information required to make an informed decision about whether to enroll in the study.

The sample checklist will be administered by study staff to each potential participant after she has completed the informed consent discussions described above and before she is asked to sign on the enrollment informed consent form. The checklist should not be presented to participants as a "test," but rather as a way of double-checking that study staff have fulfilled their responsibility to provide all information needed for the participant to make an informed decision about enrolling in the study.

It is expected that the checklist will be administered by the same staff member who conducted the enrollment informed consent discussion with the participant; this will increase the likelihood of an accurate assessment of the participant's comprehension. If more than one staff member spent time with the potential participant during the informed consent process, the checklist should be administered by the person who spent the most time with the participant.

The checklist is structured around open-ended questions that correspond with the required elements of informed consent for research. Each question should be read to the potential participant, giving 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. When the potential participant mentions one of the required points, study staff should check off that point. If the participant does not mention one or more of the required points, study staff should follow-up with another open-ended question to elicit a response about that point. For example, one of the required points in Question 1 is "study is testing an experimental gel." If the potential participant does not mention this in her initial response to Question 1, the study staff member may then ask "Can you tell me what is being tested in this study?" If the participant responds correctly, the point may then be checked off. All required points must be satisfactorily addressed by the participant, and checked off, before proceeding to the final informed consent decision and signing or marking of the enrollment informed consent form.

When responding to the various questions, potential participants may report back more information than is included on the checklist. This is acceptable, as long as the required information is reported back. If the additional information reported by the participant applies to another question on the checklist, study staff may go ahead and check off that point. If any misinformation is reported back, study staff should explain the correct information before proceeding to another question.

Once administration of the comprehension checklist discussion begins, it is possible that the participant may spontaneously mention many of the required points, without each separate question being asked. In these cases, study staff should check off the relevant points on the checklist and then ask the remaining questions, or probe about the remaining points. It doesn't hurt to ask a question that a participant may have already answered in her response to a previous question. However, if staff is confident that a previous response was adequate, the specific question and/or point does not need to be repeated.

It is expected that study staff administering the informed consent process and checklist will be sufficiently knowledgeable about MTN 004 to make good judgments about potential participants' grasp of the required information. It is possible that a participant might repeat the correct information, yet the staff member may not be convinced that she really understands it. In these cases the staff should decide if further explanation or discussion is needed before proceeding to the final informed consent discussion and signing the informed consent form. The further explanation or discussion could take place at the same visit or another visit might be suggested/scheduled.

Whenever additional information or explanation is needed, all the informed consent support materials may be used. Study staff should decide which materials may be most helpful to each participant. Some potential participants may be more comfortable interacting with the same study staff person throughout the informed consent process. However, another staff member may be consulted, if necessary or desired, to help explain problematic concepts and/or respond to participant questions or concerns.

The comprehension checklist is considered a study source document that should be completed, handled, and retained in the participant's study chart like any other source document. After administering the checklist, study staff should carefully review the checklist to verify that all required points have been satisfactorily addressed by the participant and that this is adequately documented on the checklist (i.e., with a check mark beside each point). Failure to document participant comprehension of all required points on the checklist will be considered an informed consent and enrollment violation. Comments may be recorded in the designated column on the checklist (and on the back of the checklist if additional space is needed), however this is not required. Lastly, after the enrollment consent process is completed, the final outcome of the process should be recorded in the bottom left corner of the checklist and the staff member who completed the checklist should ensure his/her signature in the space provided.

5.4 Informed Consent for Specimen Storage and Future Research Testing

At each study site, the informed consent process for specimen storage and future research testing will be conducted according to site SOPs among enrolled study participants. For participants who do not consent to specimen storage and future research testing, specimens will not be collected and stored for specimen storage purposes (specifically, plasma archive specimens at the Enrollment and the 2-Week Study Visits). Any leftover specimens collected for study procedures will be destroyed.

5.5 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 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 blocks on the informed consent form in black or blue 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 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).

The DAIDS Policy *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Regulatory) 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 may use an informed consent "coversheet" similar to the example included in Section Appendix 5-2. Sites choosing to use a coversheet should list the coversheet as a source document in their SOPs for Source Documentation for MTN 004 and should use the coversheet consistently to document all informed consent processes with all participants.

In addition to completing the documentation requirements on the informed consent form itself, each informed consent process must be documented in a signed and dated chart note. It is essential that the note (as well as the dates on the informed consent form itself) document that informed consent was obtained prior to the initiation of any study procedures. The note should also document adherence to the requirements of the informed consent section of the DAIDS Policy *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials.* However, if an informed consent coversheet is used, it is not necessary to transcribe information recorded on the coversheet into the chart note.

Finally, regulations require that participants be offered a signed copy of the informed consent forms. If a participant opts not to receive a copy, document this in a 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.

Section Appendix 5-2
Sample Informed Consent Coversheet for MTN 004

Participant Name (or PTID):	
Name of study staff person completing informed consent process/discussion (and this coversheet):	
Is the participant of legal age to provide independent informed consent for research?	☐ Yes ☐ No ⇒ STOP. Participant is not eligible for MTN 004.
Date of informed consent process/discussion:	
Time of informed consent process/discussion:	
Language of informed consent process/discussion:	
Was the informed consent process/discussion conducted according to site SOPs for MTN 004?	☐ Yes ☐ No ⇒ Record and explain departures from site SOPs below.
Can the participant read?	☐ Yes ☐ No ⇒ A literate impartial witness should be present during the entire informed consent process/discussion. Refer to site and DAIDS SOPs for specific instructions. Record name of witness here: Record relationship of witness to participant here:
Version number/date of informed consent form used during informed consent process/discussion:	
Was all information required for the participant to make an informed decision provided in a language that was understandable to the participant?	☐ Yes ☐ No ⇒ Explain below.
Were all participant questions answered?	☐ Yes ☐ No ⇒ Explain below.
Did the participant comprehend all information required to make an informed decision?	☐ Yes ☐ No ⇒ Explain below.
Was the participant given adequate time/opportunity to consider all options before making her informed decision?	☐ Yes ☐ No ⇒ Explain below.
Did the participant accept a copy of the informed consent form?	☐ NA (participant chose not to provide informed consent) ☐ Yes ☐ No ⇒ Offer alternative form of study contact information to participant.
Notes/Comments (continue on back if needed):	
Signature of study staff person completing informed consent process/discussion (and this coversheet):	

Section Appendix 5-3
Sample Enrollment Informed Consent Comprehension Checklist

PTID: **Date:**

Open-Ended Question/Statement		Required Points of Comprehension	√	Comments
1	**Please describe your understanding of the purpose of the study**	Study is testing an experimental gel		
		Testing to learn if the gel is safe		
		Testing to learn if women will like using the gel		
		The gel may not work to prevent HIV or any other sexually transmitted diseases		
		The gel does not prevent pregnancy		
2	**What do you understand that you are being asked to do in this study?**	Use the gel twice per day		
		Use condoms with each act of vaginal sex		
		Must not douche or insert other things into vagina		
		Have pelvic exams, and other laboratory tests		
		Come for weekly visits for 3 weeks		
3	**What do you understand about possible risks that might happen as a result of being in this study?**	Gel may irritate skin inside or outside vagina		
		Gel may have other side effects		
		Possibility of loss of privacy		
	What will happen if you do not join the study?	Free to make her own decisions about joining		
		No effect on access to care when decide to join or not		
5	**Please tell me about the different groups of women in the study**	The groups receive three different gels – VivaGel, VivaGel placebo, HEC placebo		
		No one knows who receives which gel		
6	**How will the information about you be protected?**	Participant information is kept under lock and key		
		Only people working in the study have access		
7	**What are the benefits to you participating in this study?**	HIV testing and counseling, referral for care if needed, (must mention at least one)		
8	**What should you do if you have any questions about what is happening in the study**	Must articulate how to contact study staff		

Outcome:
□ Demonstrated comprehension of all required points, decided to enroll in study
□ Demonstrated comprehension of all required points, decided NOT to enroll in study
□ Demonstrated comprehension of all required points, deferred enrollment decision to another visit
□ Did not demonstrate comprehension of all required points (yet), needs more time/discussion, rescheduled for another visit
□ Unable to demonstrate comprehension of all required points, consent process discontinued
□ Other (specify):_____

Staff Signature:

Optional Comment Categories:
a. Answered correctly on first try
b. Could not answer at first, but answered correctly after some probing/discussion
c. Answered incorrectly at first, but answered correctly after discussion
d. Not able to answer correctly at this time
e. Other (describe)