

Section 5. Informed Consent

This section provides information on informed consent procedures for MTN 001. MTN 001 involves three types of informed consent:

- Informed consent for screening
- Informed consent for enrollment
- Informed consent for long term specimen storage and possible future research testing

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 random assignment, use of study products and completion of follow-up visits and procedures. For enrolled participants, informed consent for long term specimen storage and possible future research is optional. Participants may choose not to consent to long term specimen storage and possible future research testing and still be enrolled in the study. The participant can consent later in the study to long term storage and possible future research testing (does not have to consent at enrollment), as long as she gives her consent before the samples are stored.

This section contains general information and instructions applicable to all three types of informed consent required for MTN 001. In addition, detailed guidance is provided for the standardized approach to the enrollment informed consent process that must be followed at all 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 of these aspects of the process are described in greater detail below. Please also refer to Section 4.8 of the ICH GCP guideline and the informed consent section of the DAIDS SOP for Source Documentation for further guidance on the informed consent process and documentation requirements.

As noted above, for MTN 001, 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 possible future research testing. Participants may choose to not have their specimens stored for possible 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 a site has been “activated” for study implementation, the site-specific informed consent form specifies all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate informed consent form. It also is 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

If the participant is not literate, an impartial literate witness must be present during the entire informed consent process/discussion with the participant. As part of the documentation steps detailed below, the witness will be asked to sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant. The ICH GCP guideline identifies an “impartial” witness as a person who is independent of the study, who cannot be unfairly influenced by people involved with the study. The MTN CORE received guidance from the US Food and Drug Administration’s GCP office stating that the witness need not be “totally unaffiliated with the study. It may be possible, for example, to designate a "subject advocate" who would be available at each site ...” Please refer to Section Appendix 5-1 of this manual for a summary of considerations for obtaining informed consent from illiterate participants.

When a witness is present during the informed consent process, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the participant, with emphasis on the fact that the witness is there as a protection for the participant, not as an agent of the study per se.

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 SOP for Source Documentation. 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, including specification of who may serve as a witness to 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 the many 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
- Procedures to document and identify participants that have consented to participate in the 21-Week In-depth interview (for applicable sites)
- 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

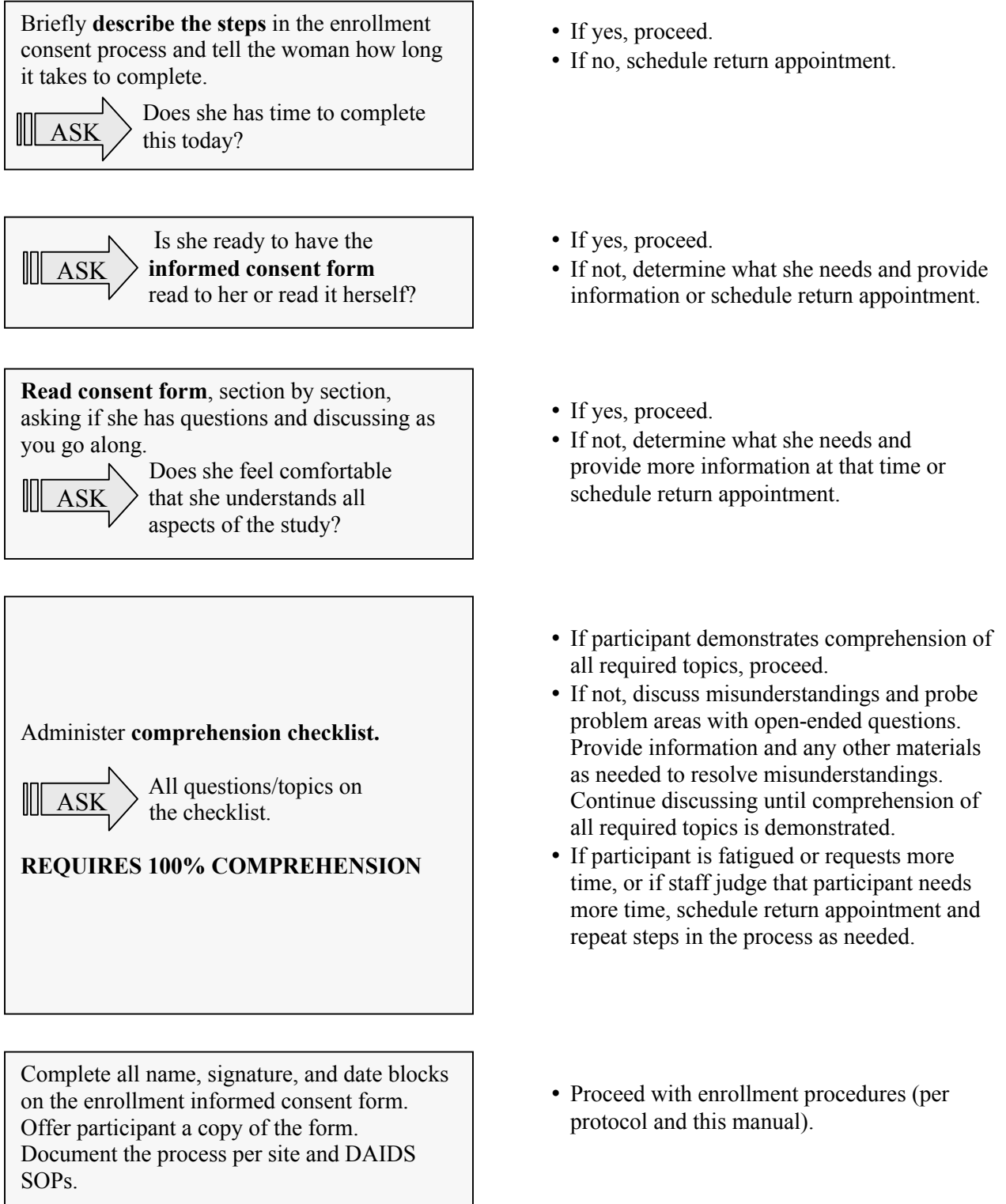
At each study site, the informed consent process for enrollment will be conducted according to site SOPs. However, site SOPs must reflect the standardized approach to the enrollment informed consent process that is described in this section. Informed consent for enrollment must be obtained prior to performing 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 all sites must be reviewed and approved by study site IRBs/EC and DAIDS 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 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 (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. Care must be taken to use the correct forms for long term specimen storage and possible future research testing.

**Figure 5-1
Overview of MTN 001 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 gel applicator
- Sample pill container
- Sample product carton
- Urine specimen cup
- Watch (for recording time of study product dosage for PK measures)
- Blood collection tubes
- Vaginal and/or pelvic model
- Speculum
- Sample randomization envelopes
- Other randomization explanation visual aids (e.g., sack or box containing six items of different colors)

When using 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.

When using a vaginal model to demonstrate gel use, be sure to lubricate the sample applicator before insertion. If this is done while the participant is present, point out that women normally have some lubrication, and you are just adding some to the model to make it more realistic. 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. After inserting the applicator, point out that there is plenty of room for the applicator inside.

When using a pelvic model to demonstrate gel use, it may be necessary to first orient the participant to the model and the anatomical parts shown. Be sure that all staff who may use the model are able to explain what each part is. Point out that the vaginal opening starts at the outside edge of the plastic model. Hold the applicator in the middle of the barrel and also hold your fingers against the outside edge of the model, so that the applicator is only inserted half-way. Otherwise, it could appear to the participant that the applicator is jabbing against the cervix.

Regardless of use of the vaginal and pelvic models, study staff who take part in informed consent discussions should be prepared to “imitate” the application of gel with two hands between their legs.

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 sample MTN 001 Enrollment Informed Consent Comprehension Checklist (see 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. Sites may choose to adapt the checklist, however all checklists require approval from the MTN CORE (FHI) prior to use.

The comprehension checklist will be administered to each potential participant after she has completed the informed consent discussions described above and before she is asked to sign or mark 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, however this is not a requirement per se. 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 most recently spoke with her or 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 the sample checklist, Question 1 is “study is testing one gel and one oral pill.” 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 how many products are 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 may explain the correct information before proceeding to another question, or defer explanation of the correct information until after the entire checklist has been administered.

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 do not need to be repeated.

It is expected that study staff administering the informed consent process and checklist will be sufficiently knowledgeable about MTN 001 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 or marking of 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 Possible Future Research Testing

At each study site, the informed consent process for specimen storage and possible future research testing will be conducted according to site SOPs among enrolled study participants. For participants who do not consent to specimen storage and possible future research testing, specimens collected and stored on-site per protocol will be retained until the study is completed and all protocol-specified testing has been completed. Thereafter, any remaining specimens collected from these participants 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 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).

If the participant is not literate, the witness who was present during the informed consent discussion must sign and date the informed consent form to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant. The participant printed name, signature, and signature date blocks on the informed consent form should be completed as follows:

- The study staff member who completes the informed consent process/discussion with the participant should enter the participant's name below the "participant's printed name" block, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.
- The participant should make her mark in the "participant's signature" block.
- The study staff member who completes the informed consent process/discussion with the participant should enter the date upon which the participant made her mark on the informed consent form below the "participant signature date" block, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.

The DAIDS SOP for Source Documentation lists detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS SOP must be met. In order to also meet some of the suggestions listed in the DAIDS SOP, 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 001 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 SOP for Source Documentation. However, if an informed consent coversheet is used, it is not necessary to transcribe information recorded on the coversheet into the chart note.

Additionally, at site conducting the 21-Week In-depth Interview behavioral assessment, it is important the site develop a method to document and identify which participants have consented to participate in this interview.

Finally, 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 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 5-1
Summary of Considerations for Obtaining Informed Consent from Illiterate Persons

- Each site must specify procedures for obtaining and documenting informed consent from illiterate persons in its SOP for obtaining informed consent. These procedures must be consistent with the DAIDS SOP for Source Documentation and must be followed each time informed consent is obtained. It is recommended that each site seek IRB/EC review and approval of these procedures.
- An impartial witness must be present during the entire informed consent discussion with an illiterate participant. The witness must sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant.
- The site SOP for obtaining informed consent should define who may serve as the witness to the informed consent process.
- Take care to minimize the perception of coercion due to the presence of the witness.
- The study staff member who completes the informed consent process/discussion with the participant should enter the participant's name below the "participant's printed name" block, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.
- The participant should make her mark in the "participant's signature" block.
- The study staff member who completes the informed consent process/discussion with the participant should enter the date upon which the participant made her mark on the informed consent form below the "participant signature date" block, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.
- Refer to Section 4.8 of the ICH GCP guideline and the informed consent section of the DAIDS SOP for Source Documentation for additional information.

Section Appendix 5-2
Sample Informed Consent Coversheet for MTN 001

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?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ STOP. Participant is not eligible for MTN 001.
Date of informed consent process/discussion:	
Start 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 001?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Record and explain departures from site SOPs below.
Can the participant read?	<input type="checkbox"/> Yes <input type="checkbox"/> 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?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
Were all participant questions answered?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
Did the participant comprehend all information required to make an informed decision?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
Was the participant given adequate time/opportunity to consider all options before making her informed decision?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
Did the participant accept a copy of the informed consent form?	<input type="checkbox"/> NA (participant chose not to provide informed consent) <input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Offer alternative form of study contact information to participant.
End time of informed consent process/discussion:	
Notes/Comments (continue on back if needed):	
Signature of study staff person completing informed consent process/discussion (and this coversheet):	

Section Appendix 5-3
MTN 001 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 and oral pill		
		Testing to learn if women like using the gel and/or pill		
		Testing to learn if the products are safe		
2	What do you understand that you are being asked to do in this study?	Use condoms and study product daily		
		Have pelvic exams and HIV tests		
		Not get pregnant in the next 21 weeks		
		Come for follow-up visits for 21 weeks		
3	What do you understand are possible risks to being in this study?	Possibility of social harms		
		Gel or pill may have other side effects		
		Gel may irritate skin inside or outside vagina		
4	What will happen if you do not join the study?	No effect on access to care		
		Free to make her own decision about joining		
5	Please tell me about the different groups in the study.	There will be 6 different sequences of 3 different study periods		
		All women will take both of the study products but at different times		
6	How will the information about you be protected?	Participant information kept under lock and key		
		Only people working on study have access		
7	What are the benefits to participating in the study?	Counseling, tests, clinical care, benefit to science or community		
8	What should you do if you have any questions about the study?	Must articulate how to contact staff		
Outcome: <input type="checkbox"/> Demonstrated comprehension of all required points, decided to enroll in study. <input type="checkbox"/> Demonstrated comprehension of all required points, decided not to enroll in study. <input type="checkbox"/> Demonstrated comprehension of all required points, deferred enrollment decision <input type="checkbox"/> Did not demonstrate comprehension of all required points (yet), needs more time/discussion. <input type="checkbox"/> Unable to demonstrate comprehension of all required points, consent process discontinued. <input type="checkbox"/> Other (specify): _____			Optional Comment Categories: a. Answered correctly on first try b. Could not answer at first, but answered correctly after probing c. Answered incorrectly at first, but answered correctly after discussion d. Not able to answer correctly at this time e. Other (describe)	
Staff Signature:				