Section 5. Informed Consent

This section provides information on informed consent procedures for MTN-013/IPM 026. MTN-013/IPM 026 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 product 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. Consenting to long term specimen storage is to be completed at the enrollment visit following the completion of the enrollment consent process.

This section contains general information and instructions applicable to all three types of informed consent required for MTN-013/IPM 026. 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 their willingness to participate in research, after having been informed of all aspects of the research that are relevant to her decision. 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 also 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.

In MTN-013/IPM 026, informed consent is first obtained for screening procedures only. Then, for participants found to be eligible, informed consent is obtained for enrollment. Written informed consent must be obtained for all participants prior to the performance of any protocol-specified screening or enrollment procedures and assessments. For enrolled participants, informed consent is 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, vaginal and/or cervical fluid, and cervical tissue specimens for possible future research testing. The specimen storage informed consent process must take place at the enrollment visit and after the participant provides written informed consent for enrollment. Participants may choose to not have their specimens stored for possible future research testing and still 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 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 able to read (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. An "impartial" witness is defined as a person who is independent of the study (though need not be "totally unaffiliated'), who cannot be unfairly influenced by people involved with the study. Refer to Section Appendix 5-1 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. 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.

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 on *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 review and approval of the SOP:

- 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 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 to ensure that the many different study informed consent forms are easily distinguished and used appropriately (e.g., color-coding)
- Procedures for implementing a change in the version of the informed consent form used

- Staff responsibilities for all of the above
- 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. Consent for Screening will be documented on the Enrollment DataFax CRF.

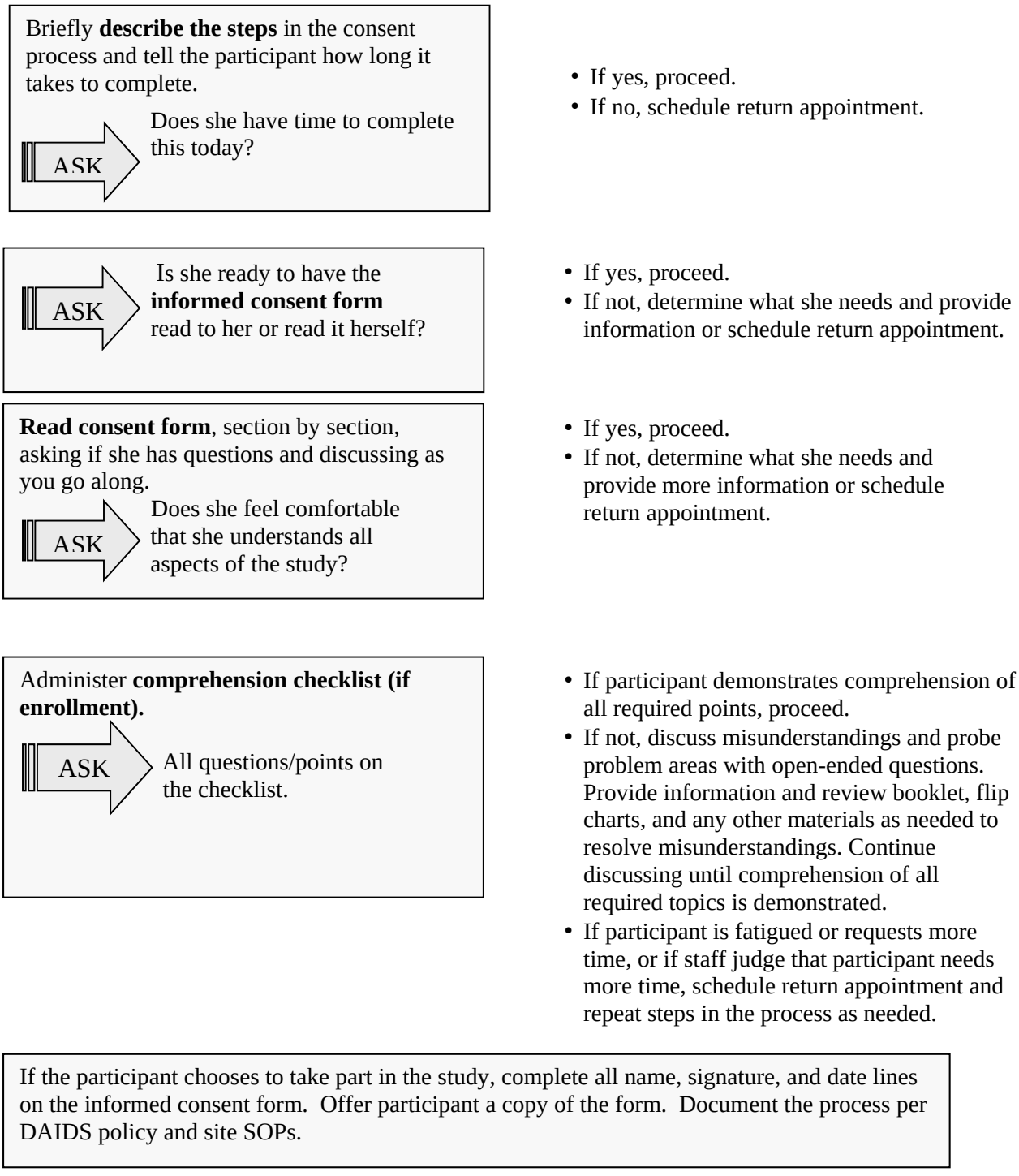
5.3 Informed Consent for Enrollment

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. Consent for Screening will be documented on the Enrollment DataFax CRF.

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 for each enrolled study participant. Participants must indicate on the form whether she agrees to storage and future testing of blood specimens, storage and future testing of vaginal and/or cervical fluid specimens, and/or storage and future testing of cervical tissue any time during study participation. 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. Consent for long-term specimen storage will be documented on the Eligibility Criteria DataFax CRF.

Figure 5-1
Overview of MTN-013/IPM 026 Informed Consent Process



5.5 Informed Consent Support Materials

Site-specific informed consent forms: The informed consent forms used at all sites must be reviewed and approved by MTN CORE (FHI360), study site IRBs and the DAIDS Protocol Registration Office 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.

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. 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 vaginal ring
- Blood collection tubes
- Urine specimen cup
- Vaginal and/or pelvic model
- Sample randomization envelopes
- Speculum
- Other randomization explanation visual aids (e.g., sack or box containing four items of different colors)
- Visual aids to explain placebo (e.g., sugar with and without vitamin A)

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 and rapport to help make the participant feel comfortable with the models. When using a vaginal model, hold the vaginal ring in the middle of the ring and insert it so that half is inserted inside and half is visible on the outside of the vagina.

Regardless of use of the vaginal and pelvic models, study staff who take part in informed consent discussions should be prepared to demonstrate the various insertion positions and imitate insertion of the vaginal ring.

5.5.1 Comprehension Assessment

Study staff are responsible for determining whether potential participants comprehend all information required to make an informed decision about study participation before proceeding to make a final enrollment decision. Sample *MTN-013/IPM 026 Enrollment Informed Consent Comprehension Tools* (see Section Appendix 5-3 and 5-4) 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 tool will be administered by the study staff member to each potential participant after she has completed the informed consent discussions and before she is asked to sign or mark the enrollment informed consent form. The tool 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 required. If more than one staff member spent time with the potential participant during the informed consent process, the assessment should be administered by the person who spent the most time with the participant.

The tool 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.

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 obtain a response about that point.

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. However, 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 do not need to be repeated.

It is expected that study staff administering the informed consent process and checklist will be knowledgeable about MTN-013/IPM 026 to make good judgments about potential participants' understanding 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 at another visit may be suggested or 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. 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 is recorded in the space provided.

5.5.2 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 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 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-013/IPM 026 and should use the coversheet consistently to document the informed consent processes with all participants. The sample coversheet is available as a separate electronic file on the Study Implementation Materials section of the MTN-013/IPM 026 web page.

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 and all other documentation (e.g., the informed consent form, the coversheet) document that informed consent was obtained before any study procedures were conducted. In particular, the documented date and end time of the informed consent process must precede the documented date and time of randomization. The chart note recorded to document the informed consent process should also document adherence to the requirements of the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. If an informed consent coversheet is used, a chart note is still required, but it is not necessary to transcribe all information recorded on the coversheet into the chart note.

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.

5.6 Re-Consenting Process for Participants who were not previously tested for HBV and HCV

In the event a participant was previously screened and/or enrolled, she must undergo a re-consenting process to continue participation in the study regardless of any previously documented written informed consent. Once Letter of Amendment #01 is approved at each site, all participants enrolled will need to be re-consented. Follow site SOPs for obtaining informed consent when documenting the informed consent process.

In the event a participant was screened but not yet enrolled into the study prior to receiving IRB approval for LoA #01, the participant must be consented using the IRB approved revised Enrollment informed consent form and tested for Hepatitis B and Hepatitis C at their next visit. In the event a participant is enrolled into the study prior to receiving IRB approval for LoA #01, the participant must be re-consented to continue study participation using the IRB approved revised Enrollment informed consent form and tested for Hepatitis B and Hepatitis C at their next visit.

The documentation requirements for the new written informed consent documents are the same as the requirements for participants joining the study for the first time (See Section 5.5).

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-013/IPM 026

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-013/IPM 026.	
Type of informed consent process/discussion	☐ Screening ☐ Enrollment	
Date of informed consent process/discussion:		
Start time of informed consent process/discussion:		
Language of informed consent process/discussion:	English	
Was the informed consent process/discussion conducted according to site SOPs for MTN-013/IPM 026?	☐ 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:	Version Number:	Date of Approved Informed Consent Form:
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.	
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

Sample MTN-013/IPM 026 Enrollment Informed Consent Comprehension Tools (1 of 2)

Question	Answers	✓	Comments
Please describe your understanding of the purpose of this study.	Testing an experimental vaginal ring (VR)		
	Assess if the VR is safe to use		
	Testing to see if the how the drugs in the VRs are absorbed in the body		
	Evaluate if women like using the VRs and if they use it as instructed		
Please tell me about the different groups of women in the study.	All women will use a VR which may or may not contain a drug		
	Groups will be randomly assigned one of four different VRs		
	All groups are important to the study		
	No one knows which VRs they will receive		
What do you understand that you are being asked to do in this study?	Use the VRs for approximately 28 days without removing it (unless instructed to by a study clinician)		
	Have pelvic and physical examinations		
	Provide a sample of urine, blood and vaginal fluid/tissue samples (biopsies)		
	Use an effective birth control method and agree not get pregnant while in the study		
	Avoid engaging in receptive sexual activity (including anal, oral, and vaginal) and using tampons		
What do you understand about possible risks that might happen as a result of being in the study?	VR may cause bad effects i.e. may irritate the vagina (must mention at least one)		
	Risks of study procedures (i.e. discomfort and pain from biopsies, mild bleeding)		
	Possibly of social harms i.e. others may treat participants unfairly for being in the study		
What will happen to you if you decide not to join the study?	Free to make her own decision about joining the study and can withdraw from the study at any time		
	No change to her regular medical care/benefits whether she joins the study or not		
How will the information about you be protected?	Information about participants is confidential, private, and locked away		
	Only people working on the study have access to her information		
What are the benefits to you of participating in this study?	Counseling, medical exams and tests, clinical care, helping to find way to prevent HIV (must state at least one)		
What should you do if you have any questions about what is happening in this study?	Must state 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
□ Did not demonstrate comprehension of all required points, needs more time/discussion
□ Unable to demonstrate comprehension of all required points, consent process discontinued
□ Other (specify):_____

Staff Signature:_____ Date:_____

Optional Comment Codes:

a. Answered correctly on first try
b. Could not answer at first but answered correctly with probing
c. Answered incorrectly at first but answered correctly after discussion
d. Not able to answer correctly at this time
e. Other (describe)

Section Appendix 5-4
Sample MTN-013/IPM 026 Enrollment Informed Consent Comprehension Tools (2 of 2)

1. If you wanted to tell a friend or family member about this study, how would you describe it to them?
   - ☐ Study objectives/purpose
   - ☐ Study population
   - ☐ Overall study design: duration, visit and procedures schedule, clinic visit locations

2. How do you think it would affect your day-to-day life to be in this study?
   - ☐ Study duration: 7 ½ weeks
   - ☐ Perceived risks and benefits of study participation

3. What do you think you will get out of being in this study?
   - ☐ HIV/STD education, counseling, and testing
   - ☐ Physical exams and medical tests
   - ☐ STI treatment
   - ☐ Personal satisfaction

4. Do you think being in this study could help you avoid becoming infected with HIV?
   - ☐ HIV education, counseling, and testing provided
   - ☐ Condoms provided at the final visit

5. Are there things about being in this study that you would be worried about?
   - ☐ Embarrassment/worry/anxiety when answering interview questions about sexual activities
   - ☐ Embarrassment/worry/anxiety when discussing HIV/AIDS and risk behaviors
   - ☐ Worry/anxiety while waiting for or after receiving test results
   - ☐ The side effects of using the vaginal ring

6. What kind of clinical procedures will you undergo in this study?
   - ☐ Blood and urine collection
   - ☐ Vaginal and/or cervical fluid collection
   - ☐ Physical examination
   - ☐ Pelvic examination

7. What happens to participants who become pregnant during the study?
   - ☐ Can remain in the study as originally scheduled if willing
   - ☐ Clinical procedures will change

8. What might the study staff do if you miss a study visit?
   - ☐ Mail, phone, other contacts to re-schedule the visit
   - ☐ Work through locator contacts to reach the participant

9. What are some reasons why the study staff might end your participation in the study?
   - ☐ The study is stopped or cancelled
   - ☐ The staff feel it would be harmful for the participant to stay in the study
   - ☐ If you become infected with HIV or become pregnant
   - ☐ The participant is unable to attend study visits or complete study procedures

10. What will the study staff do to protect your privacy and confidentiality during the study?
    - ☐ Keep information about study participation and all study records confidential
    - ☐ Maintain privacy and confidentiality when conducting locator activities
    - ☐ However some “outsiders” will review records