

Section 5. Informed Consent

This section provides information on informed consent procedures for HPTN 035. HPTN 035 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 gels (if applicable), 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.

This section contains general information and instructions applicable to all three types of informed consent required for HPTN 035. In addition, detailed guidance is provided for the standardized approach to the enrollment informed consent process that must be followed at all sites.

NOTE: Effective with Version 2.0 of this section, prior references to the HIV Prevention Trials Network (HPTN) have been replaced where applicable with references to the Microbicide Trials Network (MTN).

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 HPTN 035, 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 HPTN protocol development and study activation processes, there is adequate assurance that once a site has been “activated” 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 HPTN 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 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
- 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

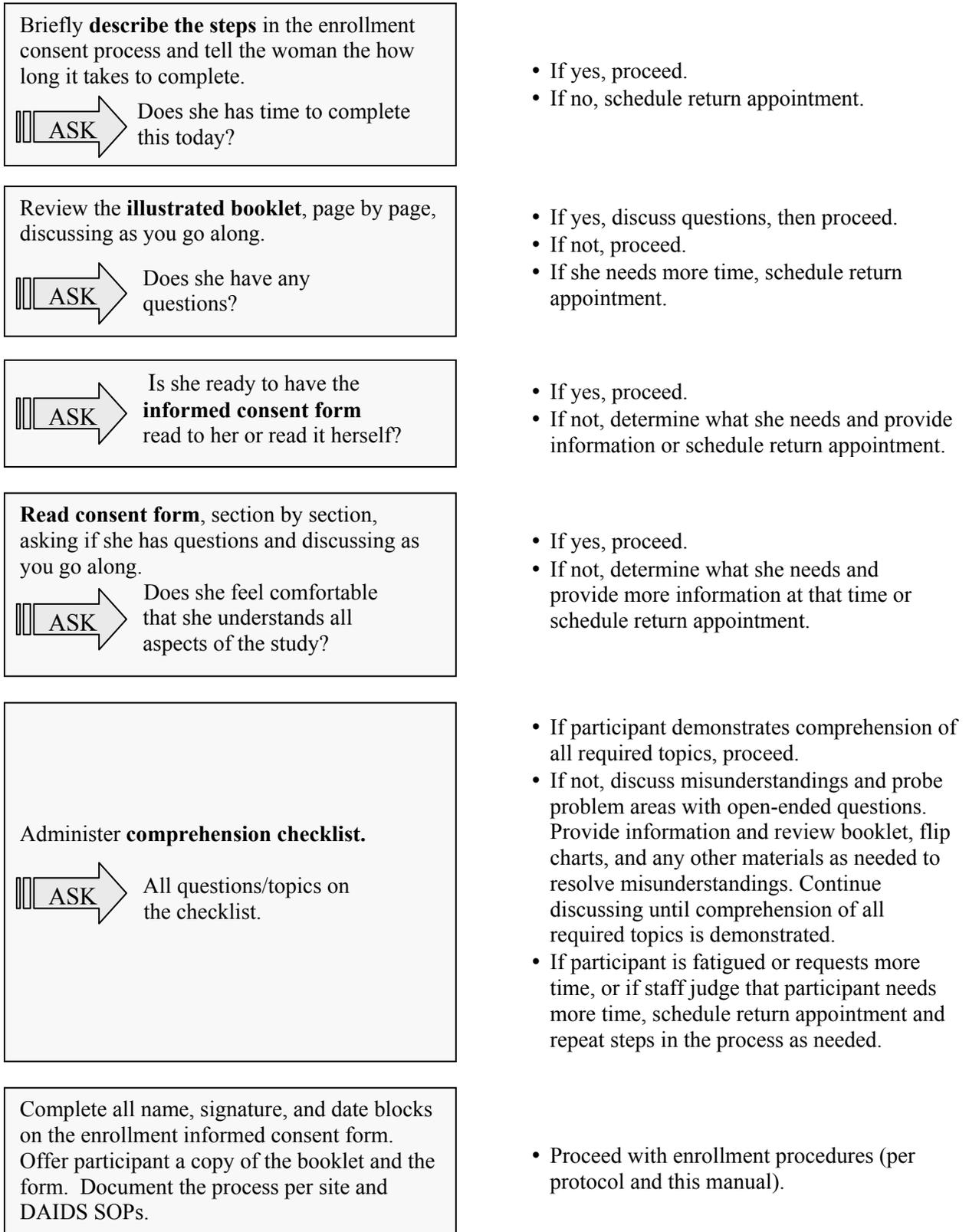
At each study site, the informed consent process for enrollment will be conducted according to site SOPs. However, site SOPs must reflect the standardized approach to the enrollment informed consent process that is described in this section. Informed consent for enrollment must be obtained prior to performing 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. At the beginning of the study, bulk supplies of the Phase II/IIb informed consent forms only should be prepared. For sites performing colposcopy among a subset of participants, care must be taken to use the correct forms after the colposcopy subset has been fully enrolled. Similarly, care must be taken at the time of transition between the Phase II and Phase IIb portions of the study to ensure that the correct forms are used for Phase IIb participants.

**Figure 5-1
Overview of HPTN 035 Enrollment Informed Consent Process**



- **HPTN 035 Microbicide Gel Study Information Booklet:** The illustrated informational booklet was developed to aid in introducing HPTN 035 to potential study participants and in explaining the information contained in the enrollment informed consent form. The booklet contains information corresponding to the eight elements of informed consent that US regulations require to be conveyed in any informed consent discussion. The booklet does not substitute for the enrollment informed consent form, since additional site-specific details are provided in the informed consent form. Also, participants who decide to take part in the study must sign or mark the enrollment informed consent form (as described in Section 5.5).

Each site should determine how best to use the booklet with its study population, and specify the preferred approach in its SOP for obtaining informed consent for HPTN 035. The booklet was designed to be given to women who have screened as eligible for the study, at least through Screening Part 1. Community input was sought and pilot testing was done at each site to develop the content of the booklet and to help each site decide how best to use the booklet. The recommended approach and an alternate approach are described below. Provided in Section Appendix 5-2 is a page-by-page guide to reviewing and explaining the booklet to potential study participants.

- **Recommended Approach:** When the time comes (per site SOPs) to begin the enrollment informed consent process, a study staff member will sit with the potential participant and first explain the purpose of the consent session. After answering any initial questions about what they are going to do together, the staff member will read through the booklet with the potential participant. Staff will decide if it is best to sit side-by-side, at a desk, and/or use the table top flip chart (described below) in addition to the booklet. The potential participant will be encouraged to ask questions throughout the reading. If the participant seems shy, embarrassed or nervous, the staff member may ask her questions and engage in conversation about the illustrations, to set the tone for free discussion. For example, the illustration on page 2 of the booklet shows a woman hearing about a study. Staff might ask the potential participant where she first heard about the study to help create rapport and make the participant feel more at ease.

Staff should discern the potential participant's literacy level (per site SOP) and make adjustments accordingly. If a participant is deemed literate, she might be given time to read through the entire booklet on her own, and then she and the staff member would review the booklet page by page. If a participant is not literate, staff may choose to read each page word for word, and then discuss before going to the next page. For semi-literate participants, a page by page review may be appropriate, with staff paraphrasing the content. After the booklet has been reviewed and discussed, staff should ask if the participant has any additional questions or concerns before proceeding to reading the enrollment informed consent form.

- **Alternate Approach:** Based on results of piloting, sites may choose to read the enrollment informed consent form first, and then use the booklet to provide additional information or explanation. If reading the informed consent form first, staff may read section by section, with discussion as needed before moving to the next section. The booklet could then be used as a review or reinforcement of the information provided in the consent form. As in the recommended approach, adjustments should be made based on participant literacy levels.

- **HPTN 035 Microbicide Gel Study Flip Charts:** Table-top flip charts have been prepared based on the content of the informational booklet. The flip charts include the illustrations from the booklet as well as one additional illustration that is not in the booklet: an illustration of a woman having a pelvic exam. This illustration was not included in the booklet because of its more sensitive nature. However, since some study participants may not fully anticipate what is required in a pelvic exam, it was felt that this illustration could be useful during the informed consent process.

The flip charts are intended to be used as a reference and review tool during informed consent discussions, to provide a brief overview or reminder when needed. The flip charts also may be used in group educational sessions as well as during ongoing informed consent discussions with enrolled study participants.

Additional pages can be added to the flip chart at the discretion of each site. Consideration should be given to adding the illustrated instructions for gel use (for subsequent use with participants assigned to gel). Illustrations that demonstrate proper condom use, or a map to the site, also may be useful additions.

- **Visual Aids:** Use of visual aids — in addition to the booklet and flip chart — 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 product carton
- Urine specimen cup
- Blood collection tubes
- 5 L jug
- Vaginal and/or pelvic model
- Speculum
- Sample randomization envelopes
- Other randomization explanation visual aids (e.g., sack or box containing four 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)

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 (you might also joke that it seems pretty realistic already). 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 “mime” 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 HPTN 035 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.

The 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.

The checklist is structured around eight 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 two experimental gels." 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 gels 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 are 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 HPTN 035 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 (see Section 16) listed 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 5-4. Sites choosing to use a coversheet should list the coversheet as a source document in their SOPs for Source Documentation for HPTN 035 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.

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.

5.6 Ongoing Assessment of Participant Comprehension

Per the HPTN 035 protocol, ongoing assessments of participant comprehension of informed consent topics will be undertaken among a sub-sample of participants during follow-up. These assessments will serve a quality assurance function for the study-specific enrollment informed consent process described in Section 5.3 above. It is expected that the assessments will help to identify aspects of the enrollment informed consent process that are, and are not, optimally effective for study participants. The assessments also may identify rumors or misperceptions about the study that require a response by the Protocol Team, either across sites or on a site-by-site basis. The Protocol Team overall, and each site individually, will use the data generated from the ongoing assessments to problem-solve, identify staff training needs, and develop strategies to provide information/education refreshers on topics that are identified as not well understood by study participants.

5.6.1 Frequency of Ongoing Assessment

Ongoing comprehension will be assessed quarterly with 20 participants per site, using the HPTN 035 Ongoing Informed Consent Comprehension Checklist included in Section Appendix 5-5.

Each quarter, the 20 participants will consist of participants presenting to the study clinic for scheduled monthly visits, beginning on a day randomly selected by the MTN SDMC. Every effort should be made to complete assessments with all eligible participants on the selected day. If 20 eligible participants do not present to the clinic on the selected day, the assessments will continue on consecutive days after the selected day. If the assessments must be continued on a second or third day, every effort should be made to complete the assessments with all eligible participants on those days, until 20 participants have completed the assessment.

5.6.2 Administering the Ongoing Assessment

For each of the 20 participants each quarter, the ongoing comprehension assessment will be administered at the beginning of the participant's visit, or while she is waiting for her visit to begin. No review or discussion of informed consent topics should take place before conducting the comprehension assessment.

The assessment should be administered by a study staff member who is knowledgeable about the study and the enrollment informed consent process. This staff member should be able to respond to questions that participants may have about the purpose of the assessment, the assessment procedures, and the topics discussed during the assessment. Sites should consider designating one or two staff members to complete all of the assessments each quarter.

The staff member who administers the ongoing comprehension assessment will explain the process to the participant and emphasize that the purpose is not to "test" the participant, but to inform study staff of the information needs of participants, which is important for protecting the safety and rights of all participants. The staff member also will emphasize that participants will not be penalized or withdrawn from the study based on the outcome of the assessment.

The ongoing assessment will be administered in a discussion style similar to the enrollment assessment. However, the ongoing comprehension checklist is not completed in the same manner as the enrollment comprehension checklist. Per the instructions printed on the checklist, for the ongoing assessment, items on the checklist are only ticked if the participant is able to demonstrate comprehension of the items without additional explanation of correct responses to the item. It is acceptable to clarify or explain the questions to the participant, and to probe for more information in her response, but it is not acceptable to explain required points of comprehension while administering the checklist.

5.6.3 Responding to Participant Information Needs After Administering the Ongoing Assessment

Some participants may not be able to demonstrate comprehension of all ongoing comprehension checklist items without additional explanation of correct responses to the items. For items that the participant does not comprehend, study staff will provide additional information/education/counseling after the entire checklist has been administered, to ensure participant comprehension of all items before continuing with the remainder of her study visit. This is an essential step for protecting the participant's rights and safety, for improving compliance with protocol procedures, and for dispelling misinformation about the study.

5.6.4 Documenting the Ongoing Assessment

At each site, a memo to file should be prepared to document the time period during which the ongoing comprehension assessment is conducted each quarter. A sample memo to file is provided in Section Appendix 5-6.

For each participant, the HPTN 035 Ongoing Informed Consent Comprehension Checklist serves as the primary source document for the ongoing assessment. After the checklist is completed, assessment outcomes and comment codes will be transcribed from the checklist onto the Ongoing Informed Consent Comprehension DataFax form (ICC-1), which will then be faxed to the MTN SDMC.

In addition to documenting the ongoing comprehension assessment on the checklist, the staff member who performs each assessment must document the assessment in a signed and dated chart note. In order to minimize documentation burden, study staff may choose to use a worksheet such as the sample provided in Section Appendix 5-7 to document the details of the assessment. When such a worksheet is used, the chart note documenting the assessment may be quite brief, for example:

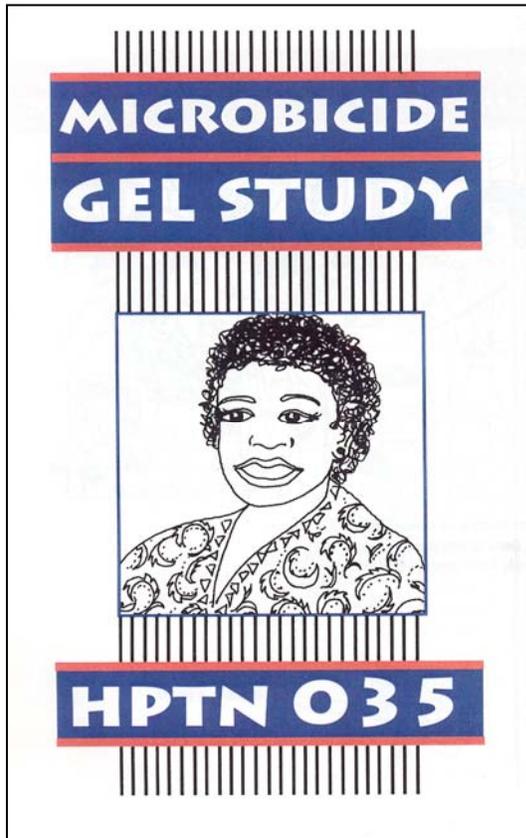
1 December 2006: Participant came to the clinic today for her scheduled Month 7 visit and was eligible to take part in this quarter's ongoing informed consent comprehension assessment. Assessment procedures were conducted per the SSP Manual prior to other visit procedures. See assessment checklist and worksheet for additional details. {staff signature}

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
Page by Page Review of the HPTN 035 Informational Booklet

Cover



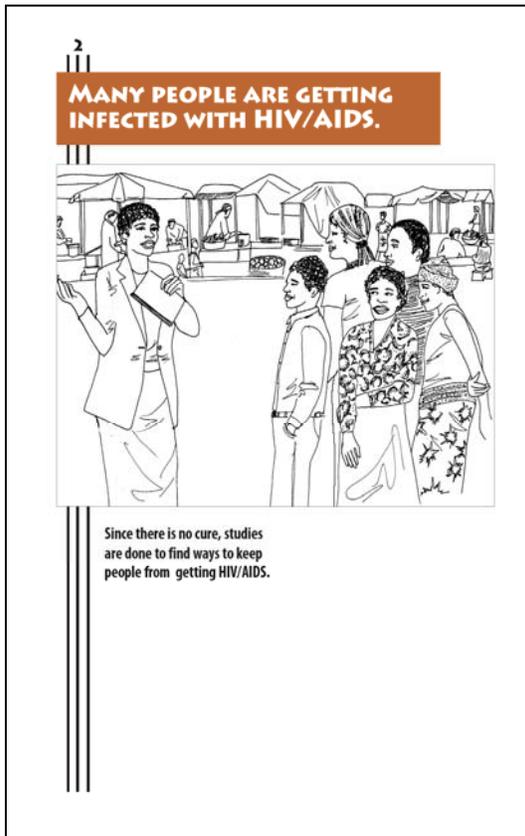
Suggested comments and discussion points to make:

As you told the potential participant earlier, before she can join the study she will need to sign or mark a consent form. We realize that some of the information in the consent form seems very technical and can be a bit overwhelming.

We want to make sure that she has as much information as she needs to make her decision about joining the study. Explain that you have a booklet that was developed to help people understand the information that is in the consent form.

Tell her that you'll go through the booklet with her and will her a copy to take home. After you've gone through the booklet, if she wants to take more time to decide, that's fine. She can take the booklet home, think it over, and share it with others who she might want to give her advice.

The cover shows "Serena" and the name of the study. Participants will be seeing Serena on a number of study materials from this point forward.



Discussion points to make:

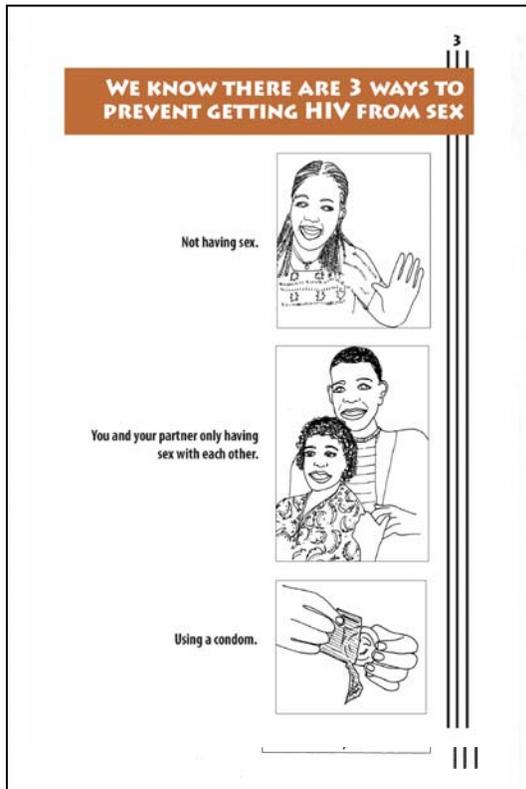
Even though AIDS has been with us for a long time, people are still getting infected.

She's probably heard about drugs that can help people who are HIV-positive live longer with HIV infection. But there is no "cure."

Because there is no cure, it is important to find ways for people to avoid infection. Health workers and researchers are conducting studies to try and find ways to help people avoid infection. You can mention some programs she may have heard about, or other projects or studies your site has conducted.

This page introduces the idea that AIDS is still a problem, and there is no cure.

Illustration shows people learning about how to prevent HIV, or hearing about a study.



Discussion points to make:

There are a number of strategies people use to avoid getting infected with HIV.

The three ways that are known to work in avoiding HIV are shown here.

- Not having sex. Since most people get infected through sex, not having any sex is one sure way to prevent infection.
- You and your partner only having sex with each other. That partner must not have HIV, though. And you have to be very sure that your partner is not cheating on you.
- Using a condom every time you have sex, and using it correctly. The condoms have to be good quality and not out of date.

For people who inject drugs, using clean needles is also an important way to prevent getting infected.

We know that many people find it hard to do all these things all the time to keep themselves safe. That's why researchers keep trying to find additional ways to help people stay safe.

This page reviews the basic HIV prevention messages (sometimes called "A B C").

Illustrations show abstinence, being faithful, and using a condom.

4

SOMETHING NEW MAY HELP PREVENT GETTING HIV



This is called a microbicide. A microbicide is a gel placed in the vagina before sex. As of today no microbicides have been shown to prevent HIV, but doctors are trying. There are many steps along the way. First, small studies are done to see if a microbicide is safe. Then, larger studies are done to see if a microbicide works to prevent HIV. You probably know about family planning methods to prevent pregnancy. It took many studies to develop those medicines, and many women took part in those studies.

Discussion points to make:

Researchers are trying to develop something new to prevent HIV infection.

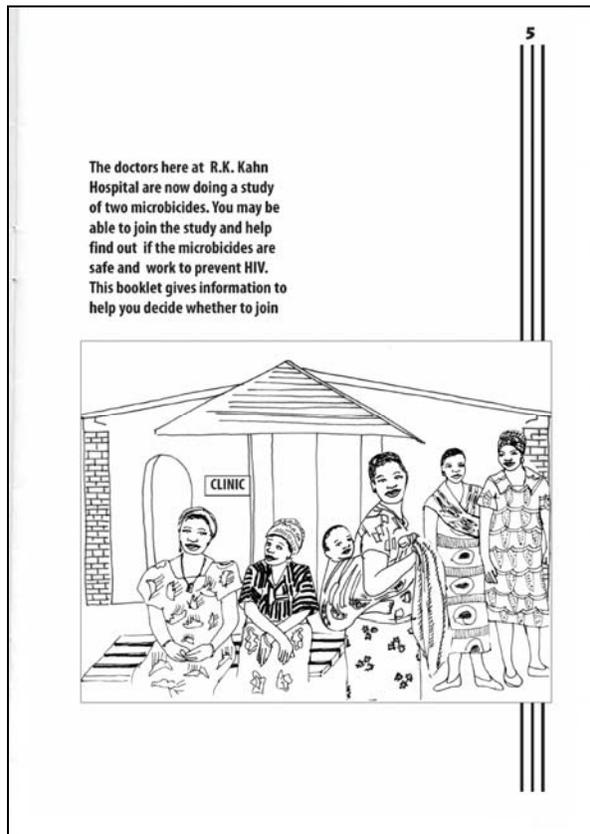
Read text on this page.

You might ask the woman if she remembers when Depo-Provera first came out. Remind her that each new drug requires a lot of research, and usually involves thousands of study volunteers. A lot of women tried Depo before it was shown to be effective and put on the market.

If other drugs, such as TB medications or measles vaccines are more appropriate, you can mention them here.

Be prepared for a discussion about people being used as “guinea pigs.” Have a plan for how to handle such questions. Remind women that sooner or later new drugs have to be tried on people, or no new medicines could ever be developed.

This page introduces the idea of microbicides. It also tells a little bit about how new drugs are developed, using contraceptives as an example. Illustration shows doctor doing research on new drugs.



This page makes the point that this site is helping develop microbicides, and that's why women are invited to join the study.

Illustration shows women at the site who may be taking part in a study.

Discussion points to make:

Point out that one thing that we really like about the idea of a microbicide is that it puts a prevention method in women's hands.

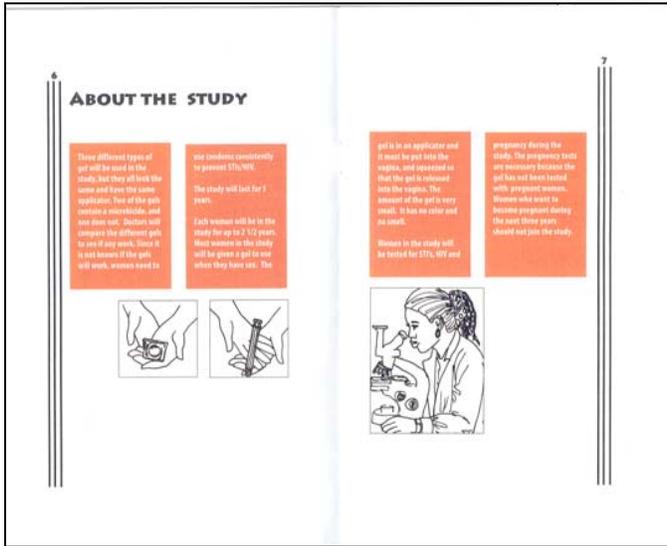
You might mention that some women may be able to use a microbicide without their partner even knowing about it, but this cannot be guaranteed for all women. In some earlier studies, some women have tried to use a microbicide secretly and others have told their partners about it. This will be up to women to decide.

In order to develop a microbicide that is safe and is known to really work, many studies are needed.

You can say that there are microbicide studies going on all around the world, and that the women in these studies want to help develop something they can use in the future to protect against HIV.

She may want to know where else this particular study is being conducted:

- Malawi
- South Africa
- United States
- Tanzania
- Zambia
- Zimbabwe



Discussion points to make:

Say that these pages provide more detail about the study.

Read the first paragraph.

Depending on when women join the study, they may be asked to stay in for up to 30 months. At the beginning of the study, focus on telling women about 30 months of involvement. Later on, toward the end of the study enrollment period, if you can estimate how long the participant will likely be enrolled, do so.

Describe the gel.

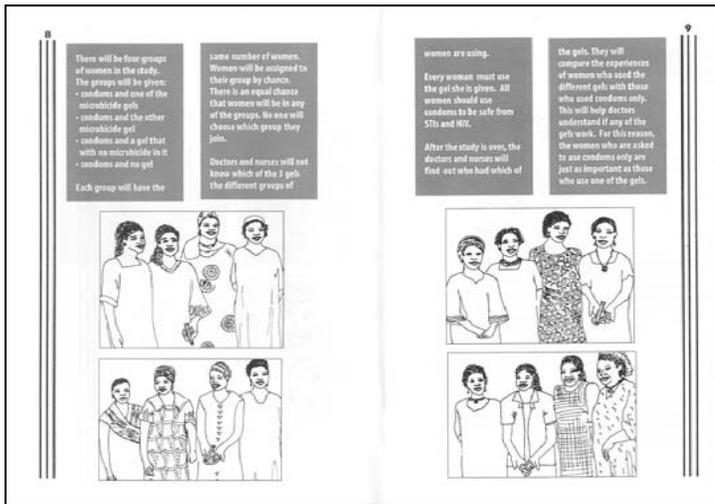
Visual aid – sample applicator: Demonstrate an assembled but empty applicator. Discuss if needed.

Visual aid – pelvic/vaginal model: If participant does not understand how the applicator is used, or is concerned that the applicator is big or long, consider demonstrating with a vaginal or pelvic model.

Talk about the regular pregnancy tests, STI tests and HIV tests during the study. Since the gels haven't been tested for use by pregnant women yet, point out that if she's planning to get pregnant any time over the next 2 ½ years, she shouldn't join the study.

These pages start to tell the details of the study.

Illustration shows a condom, a gel applicator, and researcher



Discussion points to make:

Read the first paragraph

Describe the four groups. Point out that the pictures show three groups with condoms and a gel applicator and one group with condoms and no applicator. Note that all groups have condoms because all women are counseled to use condoms to protect against HIV.

Point out that there are the same number of women in each group. Women were put into the groups by a random number that a computer generated, making sure each group has the same number of women.

Visual aid – randomization visual aid.

Observe that you can't really tell any difference between the groups unless you look really closely. They all have the same number of women, each group doesn't look much different from the other – just has different women in it. Also notice that you can't tell which of the gel groups got which gel. This is what we mean by blinding. No one, even the study doctors, can tell by looking which woman has which gel.

Describe the placebo. One of the three gels doesn't have any microbicide in it. You can't tell by looking which gel is which. The applicators are all identical.

Visual aid – visual aid for placebo and blinding

Be prepared to spend some time on this page!

These pages depict the four study groups, randomization, blinding and placebo. This may take some time to go through.

Illustration shows the four groups – conveying randomization, blinding, and placebo.

10

STUDY VISITS

Women in the study will see a nurse every month. Here's what will happen at the visits.

Every month women will have a urine test for pregnancy. They will answer questions about their health and use of the gel.

Every 3 months women will be examined and have their blood checked for HIV. They also will be counseled about how to stay safe and healthy.





Discussion points to make:

Women who join the study will be asked to have a clinic visit once a month, usually at the same time of the month.

Tell her we will take a urine specimen each month, and some routine questions will be asked.

Every three months the study staff will do a blood test for HIV. Reassure her that the amount of blood taken is small.

Visual aid – blood collection tubes, 5 L jugs

Say we'll do a pelvic exam every three months, to make sure that the gel isn't causing irritation, and just to make sure everything is going ok. For participants in the Phase II portion of the study, pelvic exams also will be done in each of the participant's first three months in the study.

Visual aid – flip chart illustration of pelvic exam, speculum.

This page provides details about what the woman will be asked to do during the study.

Illustrations:

- Calendar makes the point that she'll have an appointment at about the same time each month (not necessarily on the 14th).
- Serena is talking to the nurse at her regular study visit.
- Hand is holding a blood vial, to demonstrate that the amount taken is small

11



If women in the study have an STI, they will be counseled and treated. If women get HIV they will be counseled and referred to a clinic. If women become pregnant, they will be referred to a clinic for pre-natal care, and asked to stop using the gel. After the

baby is born, they may start using the gel again.

Since visits to the clinic take time, some money will be given. Women will be reimbursed for their transport and time for regular scheduled visits.

Discussion points to make:

Read the first paragraph.

Discuss:

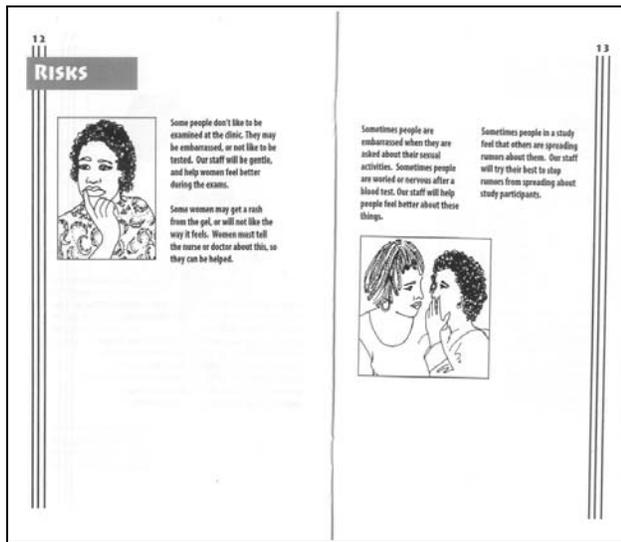
- STI counseling and treatment
- Referral for HIV treatment
- Referral for pregnancy
- No gel use during pregnancy

Pause before reading about reimbursements.

Make the point that since women have to take time to come in, they will be reimbursed for their transport and tell them whatever else your site has decided to say about the reimbursement.

This page tells them about counseling to be provided, STI treatment and pregnancy avoidance. Reimbursements are mentioned.

Illustration:
Serena and nurse are reviewing counseling information.



This page overviews risks.

Illustrations:

Serena holding her head could be embarrassed. She could have some physical symptoms or be worried. The two women whispering could be gossiping about Serena.

Discussion points to make:

Point out that Serena looks a bit stressed here. This could be from some risks associated with the study. Not all women will experience these, but some will.

Tell her that we know women may not like having regular exams at the clinic, so we'll be gentle when we do your pelvic and blood tests.

We realize that having to answer questions about sexual activities can be a bit embarrassing, so we have staff who are specially trained to make her feel more at ease when answering this kind of question.

We also understand that people may be nervous about the results of their tests, and we'll be very careful to give her all the information she wants about our testing procedures and what each test result means.

Some women may have side effects (like a rash), or just won't like how the gel feels. That's one reason for the monthly visits, so women can tell us about these if they happen, and we can try to take care of things quickly.

Sometimes people talk about others in a study. We've got our staff trained to be on the look-out for rumors about the study, so we can take care of them. Women may also have concerns about their partner's reactions, and again, we will offer to help if we can, by talking to him or providing additional information.

14

BENEFITS



If you decide to join the study you will be helping to find ways to stop HIV from spreading. We hope that microbicides can help, but we can't be sure until they are tested. There may be more studies after this one, before we can be sure that the microbicides work.

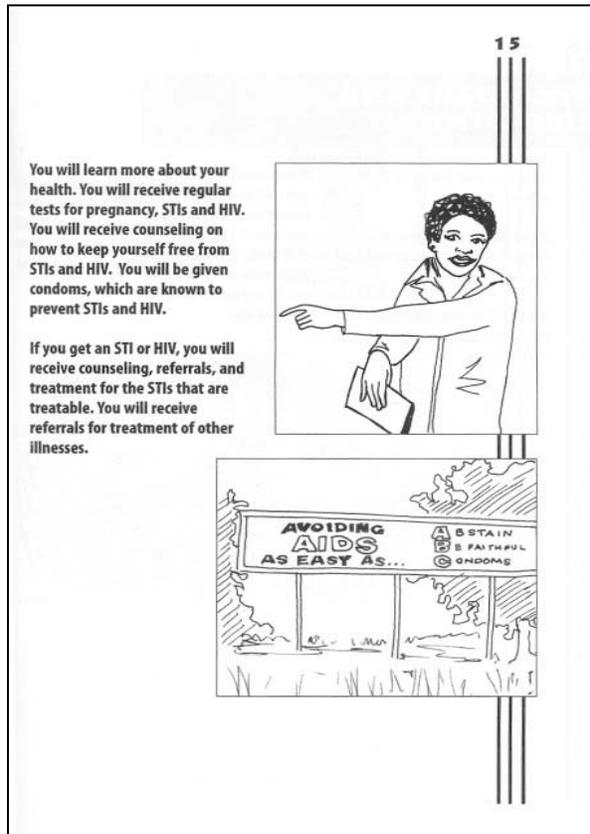
Discussion points to make:

One main benefit of taking part in this study is the sense of making a contribution to the fight against AIDS.

Women can be reminded that more studies may be needed after this one, and that there are many steps along the way. You might refer to what you talked about earlier on page 4, about the process of developing all new medications.

If the woman mentioned having friends or family who have had AIDS, you can mention that this is one way to try and help address the AIDS problem.

This page conveys the general good that comes from AIDS research. It appeals to people's notion of "doing the right thing," or "trying to help" with the AIDS problem.



Discussion points to make:

There are some personal advantages to being in the study. First, participants will learn about their health and how to avoid HIV. Remind women that they will be receiving regular exams, STI testing and treatment (for treatable STIs), regular pregnancy tests (so they'll know right away if they get pregnant), and a steady supply of condoms.

Remind the participant that these benefits are available to women in all four study groups.

Women also will receive referrals for other health problems that study staff cannot treat themselves.

The illustration is showing the nurse/doctor giving them a referral for treatment of health problems that surface during the regular study visits. The paper in her hand is a referral slip, and she is pointing to a referral location.

Visual aid – referral slip, information booklet.

This page provides information about additional things women might consider as “benefits.”

Illustration shows a staff member giving a referral slip and pointing to where the referral is located.

16

VOLUNTARY AND CONFIDENTIAL

Here are some things to think about.

If you decide not to join the study, it will not change the kind of health care you get at R.K. Kahn Hospital.

If you decide not to join the study, you may join other studies in the future.

If you decide to join the study, our staff are bound to keep all information about you in confidence. The staff will not talk about you with anyone other than themselves. We will keep your information locked away.



Discussion points to make:

This is where you should make the point that people are free to decide on their own if they want to join the study. Emphasize that if they decide not to join, it will not hurt them in any way. It will not prevent them from getting other services at the site, or anywhere else.

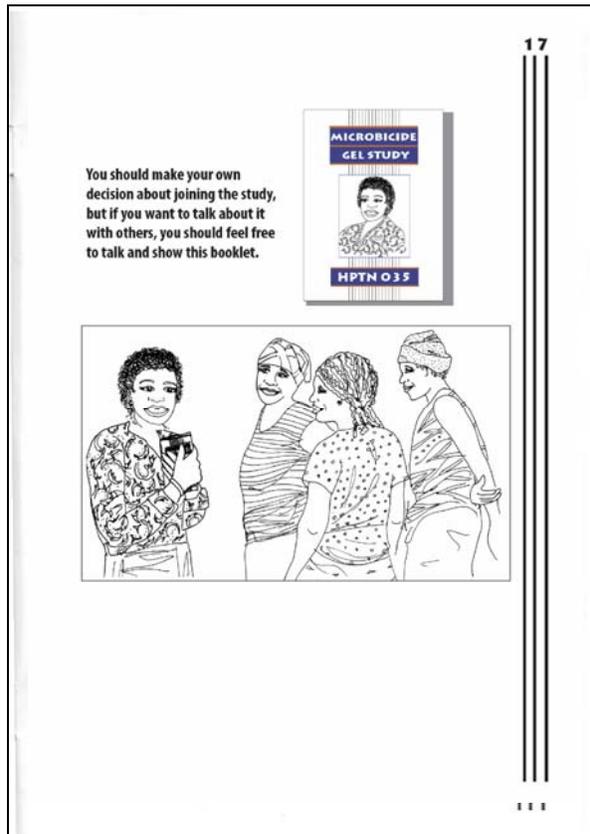
Tell her that since the study will collect personal and sensitive information about each participant, all records will be kept locked away.

Staff have been specially trained not to share or discuss information about participants with anyone who is not working on the study. We realize that sometimes people may know one another, or see one another in the community, and we want to maintain privacy and minimize embarrassment.

We can't absolutely "guarantee" that no one will ever know about their participation, but we are very good at maintaining privacy, and will make every effort to do so.

This page emphasizes that things are kept locked, secured, and confidential.

Illustration: Staff locking a file cabinet that has confidential participant information in it.



Discussion points to make:

Even though we will keep things confidential, we realize that women may want to talk to others to help them decide about joining.

Emphasize that even though we are obligated to protect their privacy, they have the choice about who else they might wish to tell, or consult.

Suggest that this booklet can be shared with friends, family, a partner, or other person whom the woman trusts.

Make the point that we hope women won't feel pressured to join or not join, but will make their own decision about what's right for them.

Right after promising to do our best to protect confidentiality, we tell women that they themselves are free to talk to others.

Illustration: Serena is talking with her friends about the study, and trying to decide if she should join. They are being supportive.

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It is important that women who join the study come for their visits and use the study gels for the full time. This will help to discover if the gels work to prevent HIV. However, people are free to quit the study if they feel they must. If you join, we really hope you will stay in the study until it is finished.

You may ask questions to help you decide to join the study. You may continue to ask questions any time.

We have a letter that you can show your partner, to help him understand what the study is about. If you'd like one of those letters, let us know and we'll give you one.

Discussion points to make:

We must tell women that they are free to quit the study if they feel they must for any reason. However, we want to stress the importance of staying in the study. Thus, on this page, we can make it clear that we want women to think carefully about their commitment if they join.

This is the point where we encourage them to ask additional questions before deciding. We encourage them to think through carefully what it will mean to join the study and what effect this might have on their lives.

Here we also mention that we have additional information they can give to their partner if they wish. If you have certain hours for male partners to come in, or male counseling sessions planned, mention these here.

We need to be mindful of balancing a stress on making a commitment with reminding women they are free to withdraw.

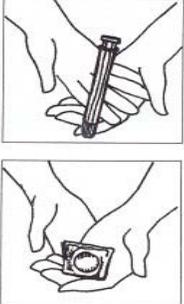
This page makes the point about how important it is to commit to the study.

The illustration shows Serena's partner being supportive of her.

19

There is much we do not know about microbicide gels. That is why we are doing this study. As you think about joining the study, please keep these things in mind:

- No one can tell who receives which gel until the study is over.
- One of the gels does not include any microbicide.
- It is not certain if the microbicide gels will work.
- To be really safe when having sex, you should use a condom.



Discussion points to make:

Remind the participant that:

- We don't know if the study gels work to prevent HIV.
- The study is blinded, so nobody will know which gel they get.
- One of the gels has no active ingredient.
- Condoms are the only proven method for HIV prevention.

It might be useful here to flip back to the booklet page showing the 4 randomization groups.

This page is another chance to remind women that the gels are experimental, and that condoms are the only proven method to prevent HIV.

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FOR ADDITIONAL INFORMATION OR QUESTIONS

This study is being conducted by:
HPTN under HPRU within the
Medical Research Council.

The study is being paid for
by the Division of AIDS at the
National Institutes of Allergy and
Infectious Disease, National
Institutes of Health, United
States Department of Health and
Human Services.

If you would like more
information about this study,
contact: Dr.
Roshini Govinden/Ms Kodwa
Mpepho, Medical Research
Council Clinic, R.K.Kahn
JHospital, 361 Chatsworth, Unit 6
Chatsworth.
Telephone: 031 401 415

Discussion points to make:

There are a number of important reference points on this page. Make sure the participant knows what each one is and verify that she knows how to reach someone if she has more questions.

Be prepared to explain the difference between the site and the study sponsor (NIH).

Encourage the participant to bring up any more questions that she may have at this time. You can flip back through the booklet to help answer these questions, or you might encourage the participant to flip back through the booklet to see if she has any questions.

Prepare a transition script, to let the participant know that if she has no more questions, you'll move on to the next step in the process.

This page has an array of contact information, and disclosure of who is funding and conducting the study.

Section Appendix 5-3
HPTN 035 Enrollment Informed Consent Comprehension Checklist, Version 1.1 (12 April 2006)

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 two experimental gels		
		testing to learn if gels are safe		
		testing to learn if gels may prevent HIV		
		study may not prove gels work		
2	What do you understand that you are being asked to do in this study?	asked to use condoms and perhaps gel with each act of vaginal sex		
		have pelvic exams and HIV tests		
		come for monthly visits for up to 30 months		
		not get pregnant in next 30 months		
3	What do you understand about possible risks that might happen as a result of being in the study?	gel may irritate skin inside or outside vagina		
		gel may have other side effects		
		possibility of social harms		
4	What will happen if you do not join the study?	free to make her own decision 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.	there are different gels		
		not everyone receives a gel		
		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 on the study have access		
7	What are the benefits to you of participating in this study?	counseling, condoms, tests, clinical care, benefit to science or community (should mention at least one from ICF)		
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: <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 to another visit. <input type="checkbox"/> Did not demonstrate comprehension of all required points (yet), needs more time/discussion, rescheduled for another visit. <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 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)	
Staff Signature:				

Section Appendix 5-4
Sample Informed Consent Coversheet for HPTN 035

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 HPTN 035.
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 HPTN 035?	<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 5-5
HPTN 035 ONGOING Informed Consent Comprehension Checklist (14 DEC 2006)

PTID:		Date:	
Random Assignment (circle one): Gel No Gel → <i>If No Gel, pre-mark items 4a and 4b as "NA."</i>			
Open-Ended Question/Statement	Required Points of Comprehension	✓	Comments
1 Please describe your understanding of the purpose of the study.	a. testing to learn if gels are safe		
	b. testing to learn if gels may prevent HIV		
2 Please tell me about the different groups of women in the study.	a. there are different gels		
	b. not everyone receives a gel		
	c. no one knows who receives which gel		
3 <i>For no gel participants, introduce this question as follows : We know this question may seem like it does not apply to you, because you do not use study gel, but we would like to know your thoughts on this one too.</i> If a woman always uses study gel, but does not use condoms, can she get HIV?	a. yes, such a woman can get HIV		
4 What do you understand about the possible risks of participating in this study?	a. gel may irritate skin inside or outside vagina		
	b. gel may have other side effects		
	c. possibility of social harms		
5 What are the benefits of participating in this study?	a. counseling, condoms, tests, clinical care, benefit to science or community (should mention at least one from ICF)		
6 What should women do if they have a question about the study or a problem related to being in the study?	a. contact the study staff		
7 Are women who join the study allowed to leave the study?	a. although clinic staff will ask women to consider options for staying in the study, and try to help women overcome any problems they may be having, yes, women can choose to leave without penalty		
INSTRUCTIONS: This checklist is not completed in the same manner as the enrollment checklist. Ask each main question and then tick each sub-item that the participant demonstrates comprehension of during discussion with you, <u>without further explanation of the correct answer</u> . Additional clarification of the questions and probing of responses may be done during administration of the checklist, but additional explanation of the correct answers should not be provided until <u>after</u> the entire checklist is administered. For sub-items that the participant is not able to demonstrate comprehension of, provide education/counseling after the checklist has been administered, but do not tick these items. Instead, use the comments column to document follow-up discussions and outcomes. For items that are ticked, comment category a or b should appear. For items that are not ticked, comment category c should typically appear, although category d also may appear. Complete the Ongoing Informed Consent Comprehension DataFax form (ICC-1), marking "yes" for each item with a tick mark recorded on this checklist.		Comment Categories: a. Answered correctly on first try b. Could not answer at first, but answered correctly after some probing c. Could not answer correctly with probing, but demonstrated comprehension after additional explanation/discussion/counseling d. Other (describe)	
Staff Signature:			

Section Appendix 5-6
Sample Memo to File for Quarterly Ongoing Informed Consent Comprehension Assessments

Memo to File

TO: HPTN 035 Study Files

FROM: [staff name]

DATE: [date name]

RE: Ongoing Informed Consent Comprehension Assessment

This memo serves to document that during the quarter beginning [date] and ending [date], ongoing informed consent comprehension assessments were performed on the following dates: [insert dates]. The first date for this quarter's assessment was chosen by the SDMC (see attached email message). The additional days were required in order to complete the assessment process with 20 participants presenting to the study clinic for scheduled monthly follow-up visits. The PTIDs of the participants who took part in this quarter's assessment are as follows:

SSS-XXXX-C	SSS-XXXX-C

Additional details on the assessment conducted with each participant can be found in the participants' study charts.

Section Appendix 5-7

Sample Worksheet for Documenting HPTN 035 Ongoing Informed Consent Comprehension Assessment

1. PTID:	
2. Name of study staff completing assessment:	
3. Date of assessment:	
4. Start time of assessment:	
5. Language of assessment:	
6. Was the assessment conducted according to the HPTN 035 SSP Manual?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Record and explain departures below.
7. According to the Ongoing Informed Consent Comprehension Checklist completed for this assessment, was the participant able to demonstrate comprehension of all checklist items?	<input type="checkbox"/> Yes ⇒ Skip to item 9. <input type="checkbox"/> No ⇒ Complete items 8a, 8b, and 9.
8a. For checklist items that the participant did not comprehend, was information/education/counseling provided to the participant?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
8b. For checklist items that the participant did not comprehend, was the participant able to demonstrate comprehension after receiving information/education/counseling?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
9. End time of assessment:	
Notes/Comments:	
Signature of study staff person completing assessment (and this coversheet):	