Section 4. Informed Consent

This section provides general information and instructions on informed consent procedures for MTN-024/IPM 031. MTN-024/IPM 031 utilizes one study informed consent form, which consists of:

- Informed consent for screening, enrollment, long-term storage and the in-depth interview
- Informed consent for the following optional activity: PK and Intensive PK Subset

4.1 Overview of Informed Consent Requirements and Procedures

Informed consent is a process by which an individual voluntarily expresses 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. Please refer to Section 4.8 of the *International Conference on Harmonisation (ICH) Consolidated Guidance for Good Clinical Practice* (GCP) and the informed consent section of the DAIDS policy, *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials,* for further guidance on the informed consent process and documentation requirements.

US regulations (44 CFR 46.116) specify the elements of informed consent that must be conveyed to research participants through the informed consent process. It is the responsibility of the Investigator of Record (IoR), and by delegation all study staff involved in the informed consent process, to deliver all required information to potential study participants.

Based on the technical and regulatory reviews that are completed as part of the MTN protocol development and study activation processes, there is adequate assurance that once a site is activated for study implementation, site-specific informed consent forms specify all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate informed consent form. It is the responsibility of the IoR and designated study staff to perform the following:

- Deliver all required information in a manner that is understandable to potential study participants
- Assure that informed consent is obtained in a setting free of coercion and undue influence
- Confirm that the participant comprehends the information
- Document the process

4.2 Site-Specific Informed Consent Forms

A sample informed consent form (ICF) is provided in the MTN-024/IPM 031 study protocol. Sites are responsible for adapting the sample as needed for local use. Local adaptation may include reformatting the consent form in accordance with local IRB/EC requirements. Unless waived by the IRB, the adapted ICF must still contain the eight required elements of informed consent as defined in 44 CFR 46.116. All ICFs must be reviewed and approved by MTN CORE (FHI 360) prior to IRB/EC submission. After IRB/EC approval, the ICF must be submitted to the DAIDS Protocol Registration Office (DAIDS PRO) prior to its initial use.

Each site is responsible for preparing bulk supplies of the approved ICF and for only using the currently approved version of the ICF 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. A system for tracking version control and approvals the ICF is also recommended. Upon receiving final IRB/EC and any other applicable regulatory approval(s) for an amendment to the informed consent form, sites should implement the consent form immediately and submit the updated version to DAIDS PRO per the timelines outlined in the protocol registration manual.

4.3 SOP for Obtaining Informed Consent

As a condition for study activation, each site must establish a standard operating procedure (SOP) for obtaining informed consent from potential study participants. This SOP should minimally contain the elements listed below.

- The minimum legal age to provide independent informed consent for research at the study site
- Procedures for determining participant identity and age
- Procedures for determining participant literacy. If the participant is not literate, she cannot enroll in this study
- 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 (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 training requirements and staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

4.4 Informed Consent for Screening and Enrollment

Informed consent must be obtained before performing any study screening and any enrollment “on-study” procedures. For participants who do not consent to screening and/or study participation, no procedures should be performed and no data that can be linked to the participant’s name or other personal identifier(s) should be recorded.

Participants who consent to study participation also provide informed consent for participation in the qualitative component (in-depth interview). Participants will be randomly pre-selected by SCHARP and each prescription/randomization document will indicate whether the participant will complete the in-depth interview at the 12-Week Final Clinic /Early Termination visit.

The informed consent should be reviewed with the participant at the Enrollment visit to ensure that the participant clearly understands all information and is still willing to participate in the study. Review of the informed consent process must be documented in the participant’s study files.

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

4.4.1 Informed Consent for Specimen Storage and Possible Future Research Testing

Enrolled study participants are asked to provide informed consent for long term storage biological specimens (such as blood, vaginal/cervical fluids and/or tissue, if applicable) and related health data for possible future research testing. Related health data may include demographic information such as race, ethnicity, sex, and medical conditions. Participants may choose to not have their specimens or health data stored for possible future research testing or withdraw their consent for specimen storage at any time and remain in the study.

For participants who do not consent to specimen storage and possible future research testing, all specimens are still collected and stored on-site per protocol requirements. These specimens will be retained until the study is completed and all protocol-specified testing has been done. Thereafter, any remaining specimens already collected from these participants will be destroyed. Participants who provide consent to specimen storage and possible future research testing are allowing for the remaining (leftover) samples to be kept and not destroyed at the end of the study.

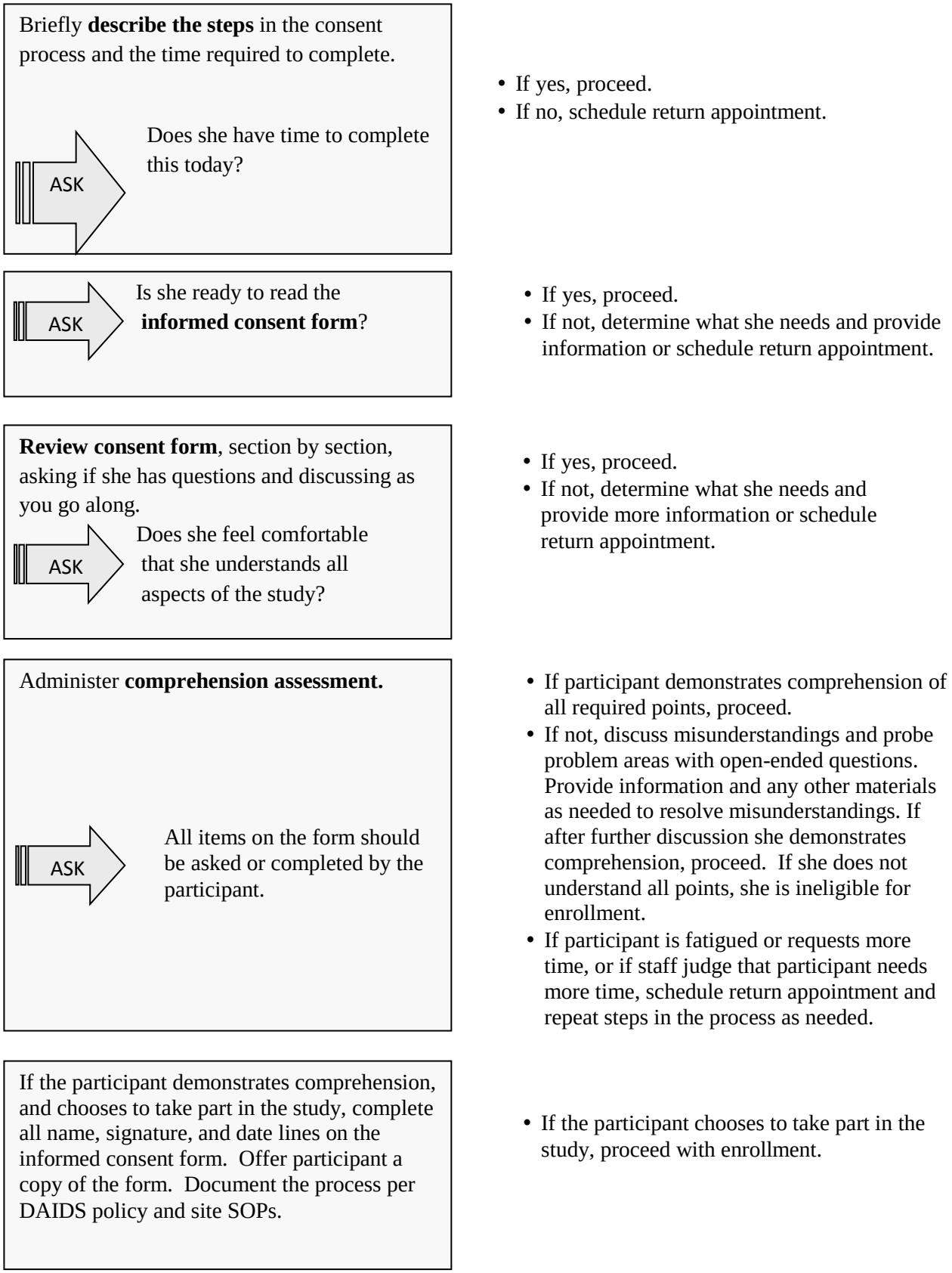
4.4.2 Informed Consent for PK and Intensive PK Subset

Participants will also be asked to participate in optional activities. This includes the collection of cervical tissue (biopsy) and/or vaginal fluid. Participants who are interested and agree to participate in these additional procedures must provide written informed consent. Participants must write their initials and date in the appropriate section of the informed consent to indicate they are willing to provide vaginal fluid or vaginal fluid and cervical tissue. Sites will need to develop a tool for easy identification of participants that have provided consent to participate in the subsets. Participants may choose to not participate in these optional procedures and still enroll in the study.

In additional to the protocol-specified eligibility criteria that participants need to meet to be able to join the study, participants in the subsets need to meet additional eligibility criteria, as listed in Section 5.2 of the protocol. The MTN-024/IPM 031 Eligibility Checklist has a row indicating assessment of these criteria.

Each participant will be offered participation in the optional activities as they enroll into the study. Accrual into the subsets will continue until the study target of 30 participants giving vaginal fluid and 15 additional participants giving vaginal fluid and cervical biopsy is met. Participant understanding of the subsets is crucial due to the nature of collection procedures as well as associated risks. To ensure participant understanding of these additional procedures, sites must administer a comprehension assessment for the subsets. The participant may choose not provide cervical tissue and/or vaginal fluid and still enroll/remain in the study. If one of the participants in the subsets terminates the study early and/or misses a subset sample collection, site staff should consult with the MTN-024/IPM 031 Management Team.

Figure 4-1
Overview of MTN-024/IPM 031 Informed Consent Process



4.5 Informed Consent Support Materials

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. Sample vaginal rings will be provided to each site to use as visual aids. 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 may not be 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
- Male condoms
- Sample vaginal ring and packaging
- Urine specimen cup
- Blood collection tubes
- 4 L jug (to demonstrate the total blood volume in the human body)
- Vaginal and/or pelvic model or illustrations
- Speculum
- Other randomization explanation visual aids (e.g., sack or box containing two items of different colors)
- Placebo explanation visual aids (e.g., sugar with and without vitamin A). Visual aids to explain placebos should look identical to each other.

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. If using a pelvic model to demonstrate ring placement, it may be necessary to first orient the participant to the model and the anatomical parts shown. Point out that the vaginal opening starts at the outside edge of the plastic model. Be sure that all staff members that may use the model are able to explain what each part is and, if demonstrating ring use, are able to insert and remove the ring with ease using the model.

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 "mime" the insertion of the ring.

4.6 Comprehension Assessment

The participant must not be asked to agree to take part in screening procedures, the study or to sign the informed consent form, until she fully understands the information contained in the informed consent form, including the visit procedures. Site SOPs should explain the procedures that study staff members are responsible for implementing to ensure that each participant understands the screening process and the study prior to signing the study informed consent form and undertaking any study procedures.

The Informed Consent Comprehension Tool serves to 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. Templates of two assessment tools (open-ended and true/false) are available on the MTN-024/IPM 031 Study Implementation Materials web page under Informed Consent Support Materials (http://www.mtnstopshiv.org/node/4924). Sites may use the tools as provided or may choose to adapt for their local use.

True/False Assessment Tool: This assessment tool is structured around questions that correspond with the required elements of informed consent for research. Sites choosing to utilize the true/false assessment tool should incorporate a scoring system

into the assessment and re-review the contents of the informed consent until the potential participant can answer all questions correctly. For example, if a participant answers less than 80% correctly, she should be re-counseled and the entire assessment should be repeated. This process should be repeated until it is determined the participant is unable to demonstrate adequate understanding. For participants that answer over 80% correctly, the questions not understood should be reviewed with the participant to ensure understanding of the information. The review and proper understanding of the information should be documented on the assessment tool, in the participant's chart notes or other site-specific source document.

Open-Ended Assessment tool: The open ended-assessment tool is also structured around open-ended questions that correspond with the required elements of informed consent for research. Each question should be read to the potential participant, giving her time to respond to each one. Each question should be satisfactorily answered by the participant before moving to the next question. For each question, the checklist specifies particular points that must eventually be included in the participant's response. These are identified on the tool as "Required Points of Comprehension."

Regardless of the method used to assess comprehension, if the assessment results indicate misunderstanding of any aspect of the study, site staff should review those aspects again until the participant fully understands them. Site staff should ensure 100% understanding of the IC prior to the participant providing written informed consent. If after all possible efforts are exhausted, the participant is not able to demonstrate adequate understanding of the study, do not ask her to sign the informed consent form or screen/enroll in the study. Similarly, if the participant has concerns about possible adverse impacts on her if she were to take part in the study, or indicates that she may have difficulty adhering to the study requirements, do not ask her to sign the informed consent form to screen/enroll in the study.

4.6.1 Administration of Comprehension Assessment

The comprehension assessment tool should be administered to each potential participant after she has completed the informed consent discussion described above and before she is asked to sign or mark the informed consent form. It is expected that study staff administering the informed consent process and assessment will be sufficiently knowledgeable about MTN-024/IPM 031 to make good judgments about potential participants' comprehension of the required information. The comprehension assessment tool should not be presented to participants as a "test," but rather as a way of assuring that study staff have fulfilled their responsibility of providing all information needed for the participant to make an informed decision about enrolling in the study. If any misinformation is reported back, study staff should explain the correct information before proceeding to another question.

The comprehension assessment tool 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 assessment tool, study staff should carefully review the assessment to verify that all required points have been satisfactorily addressed by the participant and that this is adequately documented. Consideration should be given to having two study staff members complete this verification because failure to document comprehension of all required points before proceeding with study procedures will be considered an informed consent process protocol deviation.

Comments may be recorded in a designated area on the form (and on the back of the form if additional space is needed) or on an informed consent coversheet. All required points must be satisfactorily addressed by the participant, before proceeding to the final informed consent decision and signing of the informed consent form.

After the informed consent process is completed, the final outcome of the process should be recorded directly on the assessment tool (or in a chart note) and the staff member who completed the assessment tool should ensure his/her signature is recorded in the space provided. All comprehension assessment tools utilized should be submitted to local IRB/ECs

for approval prior to use. Detailed information for how comprehension will be assessed must be specified in the site SOP for obtaining informed consent.

4.7 Documenting the Informed Consent Process

US FDA regulations and ICH E6 guidelines 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 lines on the informed consent form in dark ink. Legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a participant's full surname, and it is strongly recommended that initials not be used in place of a participant's full first name. However, if a participant commonly signs 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).

In addition to completing signature requirements as described above, the participant must indicate on the informed consent form whether she agrees to storage and future testing of biological specimens and, where applicable, participation in the PK and Intensive PK subset.

The DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* lists detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS policy must be met. In order to also meet some of the suggestions listed in the DAIDS policy, site staff are strongly encouraged to use an Informed Consent Coversheet similar to the sample included on the MTN-024/IPM 031 Study Implementation Material webpage under Informed Consent Support Materials (http://www.mtnstopshiv.org/node/4924). Sites choosing to use a coversheet should list the coversheet as a source document in their SOPs for source documentation and should use the coversheet consistently to document all informed consent processes with all participants. The first half of the coversheet (items up to and including "Version number/date of informed consent form used during informed consent process/discussion") should be completed at the start of the IC session. The remainder should be completed at the end of the informed consent session. If a site chooses not to utilize the Informed Consent Coversheet, all elements of each informed consent process must be documented in detail in a signed and dated chart note.

It is essential that all informed consent documentation (e.g., the informed consent form, the coversheet) document that informed consent was obtained before any study procedures were conducted.

Regulations require that participants be given a signed copy of the informed consent form. If a participant opts not to receive a copy, document this on the cover sheet or 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.

4.8 Ongoing Assessment of Participant Comprehension

For enrolled participants, informed consent also must be understood as an ongoing process that continues throughout the study follow-up period. Periodically, at study visits, staff should assess participants' comprehension using a discussion style similar to the initial assessment. Elements of informed consent can be reviewed at every visit, or periodically, as per site SOPs. Reviewing key elements of informed consent during follow-up visits may focus on the remainder of study participation. These informal assessments will help to identify aspects of the informed consent process that are, and are not, optimally effective for study participants. This discussion should be noted in the participant's chart note for that visit date.