

# Section 5. Study Procedures

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This section provides information on requirements for screening, enrollment and follow-up visits in MTN-023/IPM 030. Additional procedure-specific details can be found in the following locations:

- Visit Checklists (available on Study Implementation Materials webpage)
- Section 6 for product-related guidance
- Section 7 for clinical considerations
- Section 9 for counseling considerations
- Section 11 for data management

### **5.1 Visit Considerations**

Because of the nature of study procedures required to be performed during MTN-023/IPM 030, Screening, Enrollment, and Follow Up visits are expected to be completed at the study clinic only. However, per IRB regulations, sites may choose to consent either the participant or guardian/parent at an off-site location for convenience.

## 5.2 Eligibility Determination SOP

It is the responsibility of the site Investigator of Record (IoR) and other designated staff to ensure that only participants who meet the study eligibility criteria are enrolled in the study. Each study site must establish a SOP that describes how study staff will fulfill this responsibility. Minimally the SOP should contain the following elements:

- Eligibility determination procedures, including:
  - During-visit eligibility assessment procedures
  - Post-screening visit eligibility assessment and confirmation procedures (i.e. review of laboratory results)
  - Final confirmation and sign-off procedures prior to enrollment/randomization
  - Documentation of each eligibility criteria (met or not met)
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures (if not specified elsewhere)

Should study staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR/designee should contact the MTN-023/IPM 030 Management Team.

## 5.3 Visit Checklists:

Visit checklists are convenient tools designed to guide site staff in proper study procedures and may serve as source documentation if completed appropriately. These checklists alone may not be sufficient for documenting all procedures, but can be used to indicate that the procedure was completed. Visit checklist templates are available on the MTN-023/IPM 030 website under Study Implementation Materials.

Instructions for completing visit checklists in accordance with these requirements are as follows:

- Enter the participant identification number (PTID) and visit date in the top section of each checklist. If checklists are multiple pages, enter the PTID and visit date on each page.
- The “Procedures” column indicates when the item is required per-protocol. Complete staff initials next to procedures completed.
- Enter your initials only beside the procedures that you perform. Do not enter your initials beside procedures performed by other staff members. If other staff members are not available to initial checklist items themselves, make a note on the checklist documenting who completed the procedure, enter initials and date the entry, e.g., “done by {name} on dd/mmm/yy” or “done by nurse on dd/mmm/yy.”
- If all procedures listed on a checklist are performed on the date entered in the top section of the form, the date need not be entered beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable.
- If a procedure listed on the checklist is not performed, enter “ND” for “not done” beside the item and record the reason why on the checklist or in chart notes (initial and date this entry).

The sequence of procedures presented on the visit checklists templates is a suggested ordering. In consultation with the MTN LOC (FHI 360), site staff members are encouraged to modify the checklists to maximize the efficiency of site-specific study operations. Sites may alter the sequence of procedures, with the following exceptions:

- Informed consent/assent and parental/guardian permission must be obtained before any study procedures are performed. Study visit procedures are listed in protocol Sections 7.2-7.4.

- On the day of enrollment, random assignment must take place after final confirmation and verification of eligibility, administration of the Vaginal Practices CRFs, and collection of blood for plasma archive.
  - Note: The Baseline Audio Computer Assisted Self-Interview (ACASI) Questionnaire may be completed after randomization but prior to insertion of the study ring
- Pelvic exam procedures must be performed in the sequence shown on the pelvic exam checklist.
- If at all possible, behavioral assessment forms and ACASI questionnaires should be administered prior to the delivery of HIV and adherence counseling.
- It is recommended that procedures for determining eligibility for continued product use be conducted early in the visit to ensure that these procedures are conducted in the event that the participant needs to abruptly leave the clinic or is short of time.
- Vaginal Rings (VRs) should be removed immediately upon identification of conditions that require a hold or discontinuation. At visits with pelvic exams, timing of VR removal should be coordinated with the pelvic exam itself. At these follow-up visits, clinicians should not remove the current VR until the pelvic exam. Provision of a new VR for insertion should occur after the exam. At visits without pelvic exams, timing of VR removal may occur when it best fits into the clinic flow.

#### **5.4 Screening and Enrollment Timeframe**

All protocol-specified screening and enrollment procedures must take place within 56 calendar days of when the potential participant provides written parental/guardian and participant informed consent/assent. If participant and parent assent/consent occurs on different days, the screening window will begin with the first provision of consent. If all screening and enrollment procedures are not completed within 56 days of obtaining written informed consent, the participant will be considered ineligible for study participation. Participants may only re-screen once for MTN-023/IPM 030.

#### **5.5 Screening and Enrollment Logs**

Study sites are required to document screening and enrollment activity on screening and/or enrollment logs. Screening and enrollment logs should be updated in real time and completed once a participant provides informed consent for screening and when enrolled/randomized into the study. Participants who are approached, but do not provide informed consent should not be included on this log.

#### **5.6 Screening Visit**

The term “screening” refers to all procedures performed to determine whether a potential participant is eligible to take part in the MTN-023/IPM 030 study. The study eligibility criteria are listed in protocol Sections 5.2 and 5.3. Required screening procedures are listed in protocol Section 7.2.

##### **5.6.1 Screening Visit Procedures:**

Sites will be provided with an Eligibility Checklist to document participant eligibility for study participation. The Eligibility Checklist and Behavioral Eligibility Checklist provide further operational guidance on the timing of each assessment and suggested source documentation for each eligibility criterion. This document is available on the MTN-023/IPM 030 Study Implementation Materials webpage.

Screening procedures are specified in protocol section 7.2 (Table 5) and are reflected in the Screening Visit Checklist, which is available on the MTN-023/IPM 030 Study Implementation Materials webpage.

- Informed consent/assent and parental/guardian permission must be obtained prior to conducting any study procedures. After consenting, participants will be assigned a PTID and undergo a series of behavioral assessments, clinical evaluations, and laboratory tests.
- Locator information will be collected initially during the screening visit, and updated at subsequent visits throughout the study. Staff should confirm adequate locator information is provided prior to enrollment/randomization.
- Some eligibility criteria, which are based on self-report will be evaluated by administration of the Screening Behavioral Eligibility and Enrollment Behavioral Eligibility worksheets. It is suggested that staff administer these questionnaires early in the visit, so that more time-consuming clinical and laboratory evaluations can be avoided if the participant is determined ineligible due to behavioral criteria (unless sites decide to administer clinical and laboratory evaluations regardless of eligibility as a service to the participant). These worksheets are available on the MTN-023/IPM 030 Study Implementation Materials webpage.

Note: Eligible participants must have a history of sexual intercourse, at least one episode in their lifetime. For MTN-023/IPM 030, sexual intercourse is defined as penile-vaginal intercourse.

Clinical screening visit procedures are further detailed in Section 7 of this manual. In brief, clinical procedures include:

- Collection of medical and menstrual history including assessing concomitant medications, onset and progression of puberty, use of effective method of contraception, conducting a physical exam and a pelvic exam, and specimen collection.

Note: The study's protocol Section 5.2 (Inclusion criteria) specifies that a participant is required to report using an effective method for at least 30 days prior to enrollment. If a potential participant is currently using the contraceptive ring and agrees to switch to a protocol-allowed contraceptive method during screening; the site is not required to wait 30 days from initiation of the *new* method. The language in this section of the protocol, excluding use of the contraceptive ring is intended to exclude its use while in the study. The site may schedule enrollment given her history of using a reliable hormonal method.

- Evaluation of the use of prohibited medications such as PrEP, PEP and non-therapeutic injection drug use, assessing STI/RTI/UTIs, genital signs/symptoms, and overall general health.
- Undergoing HIV testing and urine pregnancy testing.
- Provision of all available test results and treatment or referrals for UTI/RTI/STIs.
- Provision of risk reduction, male condom, contraception, and HIV pre-and post-test counseling. Further considerations related to counseling requirements are detailed in Section 9 of this manual.

Details regarding laboratory tests and sample collection at screening are provided in Section 10 of this manual. In summary:

- Participants will undergo testing for STIs (Gonorrhea, Chlamydia, Syphilis, Trichomonas, and HIV), liver and kidney function (serum chemistries: AST, ALT and Creatinine), and a complete blood count with platelets.
- If indicated, participants may be tested for bacterial vaginosis, vaginal candidiasis, or herpes simplex virus (per local standard of care).

Designated staff will document the status of eligibility criteria assessed at screening, as applicable, by checking each set of "yes/no" checkboxes upon assessment and initialing and dating on the "Screening Visit" column of the MTN-023/IPM 030 Eligibility Checklist.

Between Screening and Enrollment, appropriately delegated site staff should review available lab results and other eligibility criteria and update the "Screening Visit" column of the MTN-023/IPM 030 Eligibility Checklist. No screening CRFs should be faxed to SCHARP until a participant is enrolled. Should a participant be ineligible for enrollment, the Eligibility Criteria CRF should be completed and faxed, and the screening file should be retained on site per the site's Data Management SOP. Refer to section 5.6.2 below for further information on the appropriate documentation, which should be included in the participant chart for those who screen-fail.

If the participant meets eligibility criteria at the end of the screening visit, she should be scheduled for her enrollment visit, making sure the enrollment visit takes place within the allowable 56-day time frame. Participants should be provided with study informational material, clinic contact information, and instructions to contact the clinic with any questions as needed prior to her scheduled enrollment visit.

### 5.6.2 Assignment of Participant ID Numbers

The MTN SDMC (SCHARP) will provide each study site with a listing of participant identification numbers (PTIDs) for use in MTN-023/IPM 030. The PTIDs will be provided in the form of a hard-copy MTN-023/IPM 030 PTID-Name Linkage Log (see Figure 5-1). Information regarding the storage and completion of the PTID-Name Linkage Log can be found in the site's Data Management SOP. Additional information on the structure and use of PTIDs can be found in the Data Collection section of this manual (Section 11). PTIDs will be assigned to all potential participants who provide informed consent/assent, regardless of whether they enroll in the study.

**Figure 5-1: Sample Site-Specific PTID-Name Linkage Log (PTID List)**

	Participant ID	Participant Name	Date	Staff Initials
1	XXX-00001-Z			
2	XXX-00002-Z			
3	XXX-00003-Z			
4	XXX-00004-Z			
5	XXX-00005-Z			
6	XXX-00006-Z			
7	XXX-00007-Z			
8	XXX-00008-Z			
9	XXX-00009-Z			
10	XXX-00010-Z			

### 5.6.3 Participants Found to be Ineligible (Screen Failures)

Screening should be discontinued if the participant is determined to be ineligible. If a participant screens out due to a clinical condition requiring follow-up, appropriate referrals should be provided. Documentation of all referrals should be included in the participant chart. All lab results should be provided and explained to participants within a reasonable timeframe, regardless of eligibility determination. For all screened out participants, the following documentation should be in place:

- Completed informed consent/assent and parental/guardian permission form
- Reason(s) for ineligibility, with date of determination, as per the completed Eligibility Checklist

- Completed Eligibility Criteria CRF, updated with screen failure reason(s) and faxed to SCHARP
- Necessary referrals on file (as appropriate) and documentation that any clinically significant abnormalities (labs, etc.) were communicated to the participant (even if referral is not necessary)
- All source documentation complete up until the time that ineligibility was determined
- Chart notes complete up until the time ineligibility was determined
- Indication of what visit procedures were conducted (on visit checklists)

In addition, the Screening and Enrollment Log should be updated with date of discontinuation of screening and reason for screen failure. Once ineligibility status is determined, the MTN-023/IPM 030 Eligibility Checklist may be stopped and the remaining items may be left blank. Site staff should document in chart notes why items on the checklist were left blank.

## 5.7 Enrollment Visit

Participants will be considered enrolled in MTN-023/IPM 030 once they have been assigned an MTN-023/IPM 030 Randomization Envelope. Further information on methods and materials for random assignment is provided in Section 5.7.2.

### 5.7.1 Enrollment Visit Procedures

Study enrollment procedures are specified in protocol section 7.3 and reflected in the Enrollment Visit Checklist, which is available on the MTN-023/IPM 030 Study Implementation Materials webpage. Additional details regarding enrollment procedures are outlined below.

The following procedures should be completed as part of eligibility determination prior to randomization on the day of enrollment. The IoR or designated staff will confirm and document the criteria indicated on the “Enrollment Visit” column of the MTN-023/IPM 030 Eligibility Checklist prior to proceeding with randomization/enrollment per site SOPs.

Before randomization, the participant should undergo the following procedures:

- Confirm the informed consent/assent and parental/guardian permission form is signed and dated and the participant remains willing and able to participate in the study
- Confirm 56-day screening window has not been exceeded
- Update and re-confirm adequacy of locator information
- Confirm behavioral eligibility criteria through administration of the Enrollment Behavioral Eligibility worksheet and completion of the Eligibility Checklist
- Review/update medical/medication/menstrual history since screening visit. Re-evaluate use of prohibited medications, STI/RTI/UTIs, genital signs/symptoms and overall general health
- Perform pregnancy testing, HIV testing, and plasma archive (Note for sites not conducting finger stick HIV rapids: to reduce participant burden, sites should consider collecting plasma archive and HIV samples as part of a single blood draw, prior to randomization)
  - In conjunction with HIV testing, participants will receive HIV pre- and post-test counseling as well as risk reduction counseling, including provision of condoms.
- Provide contraceptive counseling
- Conduct a physical exam
- Conduct pelvic exam procedures in the sequence shown on the pelvic exam checklist
- Participants should receive all available test results and treatment or referrals for UTI/RTI/STIs

- Complete the following behavioral assessments: Vaginal Practices CRFs, and Baseline ACASI (Note: Baseline ACASI may be conducted after randomization but must occur prior to insertion of study ring)
- Protocol adherence and vaginal ring (VR) adherence counseling
  - NOTE: this may also be conducted after randomization, but it could be helpful to provide the participant with more information about the ring prior to her final decision to enroll in the study

Designated staff will document the status of eligibility criteria assessed at Enrollment, as applicable, by checking each set of "yes/no" checkboxes upon assessment and initialing and dating on the "Enrollment Visit" column of the MTN-023/IPM 030 Eligibility Checklist. A staff member and the IoR/designee must review and sign/date the MTN-023/IPM 030 Eligibility Checklist to document the participant's eligibility status is confirmed prior to enrollment/randomization. The Eligibility Criteria CRF must also be completed for all screened participants once the participant's eligibility/enrollment status is determined. If the participant is confirmed to be eligible based on procedures listed above, the IoR or designee should complete final sign-off of eligibility on the Eligibility Criteria CRF, have this verified by a second staff member who will also sign-off on the Eligibility Criteria CRF.

After randomization, participants will undergo the following procedures:

- Provision of VR instructions and one VR for self-insertion
- Digital (bimanual) exam to check for correct VR placement
- Reimbursement
- Schedule next visit

To ensure an accurate assessment of baseline conditions is documented and eligibility is confirmed on the day of randomization, the enrollment visit should not be conducted as a split visit. If for some reason the participant cannot complete the Enrollment visit in a single day, (e.g. participant has to leave early due to an emergency) follow the guidance below:

- If she has not been randomized, reschedule the participant for the Enrollment visit within the 56-day window. No CRFs from an incomplete Enrollment visit should be sent to SCHARP.
- If she has been randomized, the visit is considered her Enrollment visit regardless of whether all procedures post-randomization were completed. Document any procedures not done. If the participant did not receive a study ring at the Enrollment Visit, she should be scheduled to come in as soon as possible after Enrollment to receive her first study ring and associated procedures (first product use, digital (bimanual) exam etc.).

No missed Enrollment visit procedures should be made up prior to the 2-Week visit with the exception of ring provision (described above) and the collection of plasma archive. Ring provision should only be done if all eligibility requirements continue to be met. If blood for plasma archive was missed during the Enrollment visit, the site should make every attempt to bring the participant back as soon as possible to collect and archive this specimen as part of an interim visit. Contact SCHARP with any CRF completion questions if this situation occurs.

### **5.7.2 Random Assignment/Prescription Assignment**

Participants will be randomly assigned 3:1 to one of the two study arms.

The SDMC will generate and maintain the study randomization scheme and associated materials. Randomization Envelopes will be shipped from the SDMC to each study clinic. Envelopes are stored in the clinic and must be assigned in sequential order to each participant who has been confirmed as eligible and willing to take part in the study. Only one envelope may be assigned to each participant; once an envelope is assigned to a participant, it may not be re-assigned to any

other participant. All envelopes are sealed with security tape to ensure envelopes are not tampered with or opened prior to assignment to a participant. Sites should complete all randomization procedures as specified in the MTN-023/IPM 030 Randomization SOP.

Envelope assignment will be documented on the Randomization Envelope Tracking Record. The act of assigning a Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once the Randomization Envelope is assigned, the participant is considered 'enrolled' in the study. Once assigned, the prescription should be completed as outlined in Section 6 of this manual and provided to the pharmacy.

## 5.8 Follow-up Visits

After enrollment, each participant will be scheduled to complete seven clinic visits and two follow-up phone calls. The clinic visits will occur at approximately 2-Weeks, 4-Weeks, 8-Weeks, 12-Weeks, 16-Weeks, 20-weeks, and 24-Weeks following the enrollment visit. The phone calls will occur one week following the Enrollment Visit and one week following the 24-Week Final Clinic Visit/Early Termination Visit. The total duration of their participation will be about 25 weeks.

### 5.8.1 Follow-up Visit Procedures

Required follow-up clinic visit procedures are listed in protocol sections 7.4 and 7.5 and Appendix I. Several additional clarifications of the procedural specifications are provided in the remainder of this section. Further operational guidance on completing protocol-specific procedures during follow-up visits is incorporated into the visit checklists, which are available on the MTN-023/IPM 030 Study Implementation Materials. More information on components of follow-up visits can be found in the following locations within this manual:

- Section 6: Product Use Instructions and Study Product Dispensing Instructions
- Section 7: Clinical Considerations
- Section 10: Laboratory Procedures
- Section 11: Data Management and CRF completion
- Section 14: Behavioral Assessment Instructions (including ACASI, SMS, and IDI). As per Protocol Version 2.0, Letter of Amendment #01, dated 16 February 2016, all IDIs and SMS activities related to the secondary and exploratory endpoints of acceptability and adherence were discontinued in February 2016.

### 5.8.2 Pharmacokinetic (PK) Procedures

PK blood draws are collected at the 2-Week, 4-Week, 12-Week Study Visits, and the 24-Week Final Clinic Visit/Early Termination Visit. Vaginal fluid for PK is collected at the 2-Week, 4-Week, 12-Week Study Visits, and the 24-Week Final Clinic/Early Termination Visit. Blood and vaginal fluid PK Samples should be collected on the same day and within approximately one hour of each other.

### 5.8.3 Types of Follow-up Visits

Throughout study follow-up, the following types of visits will be conducted:

- **Scheduled visits** are those study visits required per protocol.
- **Scheduled phone calls** are those phone calls required per protocol.
- **Interim visits** are those visits that take place between scheduled visits. There are a number of reasons why interim visits may take place including, but not limited to:
  - For product-related reasons, e.g., a participant may need a replacement vaginal ring or want to discuss problems with adherence to ring use.
  - In response to AEs, SAEs, or social harms.
  - For interim STI counseling and testing in response to STI symptoms, or interim HIV counseling and testing in response to presumed exposure to HIV.



- All scheduled and interim visits will be documented in participants' study records and on applicable CRFs. Site staff should also refer to Section 11 for details about visit scheduling, visit windows, and visit codes for scheduled and interim visits.

#### 5.8.3.1 1-Week and 25-Week Follow-Up Phone Calls

The two required phone calls to study participants which are scheduled at 1-Week and 25-Week/Study Termination serve the purpose of inquiring about AE's and any updates to concomitant medications. More details are provided in protocol Section 7.4.5. Sites should include how they will reimburse participants for these phone calls in their site-specific informed consent form. Call attempts should be documented per site SOP or on the Phone Call visit checklist, which is available on the MTN-023/IPM 030 Study Implementation Materials webpage. Note: sites may conduct the required visit procedures for the 1-week and 25-week phone calls via phone call or an in-person clinic visit. For example, if a participant returns to the clinic for AE follow-up after the 24-week visit, that visit may take the place of the phone call and be considered the termination visit (provided the visit takes place within the 25-week phone call window). Sites should contact the MTN-023/IPM 030 Management Team for additional guidance, as needed.

#### 5.8.3.2 Split Visit Procedures

All procedures specified by the protocol to be performed at a particular follow-up visit ideally will be completed on a single day. In the event that all required procedures cannot be completed on a single day (e.g. a participant must leave the study site before all required procedures are performed), the remaining procedures may be completed on subsequent day(s) within the visit window. When this happens, it is referred to as a "split visit" (required visit procedures are split across more than one day within the visit window). Split visits are permitted for any type of follow-up visit in MTN-023/IPM 030. For more information on visit codes for split visits, see SSP Section 11.

While conducting all visit procedures in a single day for each scheduled visit is ideal, it is acknowledged that this might not always be possible. At a minimum, the following procedures must be conducted in order to dispense study product:

- AE assessment and reporting (verbal report of symptoms is acceptable; if symptoms indicate that further evaluation is necessary, this must be conducted prior to dispensing study product)
- Pregnancy test
- Collection of used or unused vaginal ring, if available or applicable
- Adherence counseling/vaginal ring use instructions, as needed

Note that while a visit may be split, individual procedures should not be split. For example, ACASI completion or collection of the PK blood draw and PK vaginal swab should occur on the same day and not be split across days.

#### 5.8.4 Missed Visits

If no procedures of a scheduled visit are conducted within the visit window, a Missed Visit CRF should be completed and faxed to SCHARP as soon as the visit window ends. If feasible, and the participant is willing, schedule the participant to return to the clinic for an interim visit. At the interim visit, conduct the missed visit procedures and complete the applicable CRFs using the interim visit code. The site must also document this occurrence on a protocol deviation CRF, using the reason code for a "visit completed outside of window". The site should also clearly document in chart notes that the site staff attempted to schedule the visit per protocol, but the participant was unable to make the appointment. Section 11 gives detailed information regarding the completion of the Missed Visit form and interim visit codes.

## 5.8.5 Follow-up Procedures for Participants Who Discontinue Study Product

Section 7.5 of the protocol provides information on the procedures for participants who discontinue study product. Participants that discontinue study product will be encouraged to remain in the study, if they are willing, until their scheduled end-date.

### 5.8.5.1 Participants Who Become Infected with HIV-1

Study product use must be held immediately for participants with a positive EIA result, or an indeterminate result. Clinic staff should inform the pharmacist of the product hold in writing, using a Study Product Request Slip, and should complete and fax a Clinical Product Hold/Discontinuation Log form to the MTN SDMC.

Participants who seroconvert during study follow-up will discontinue the following study procedures:

- HIV testing
- Provision of study product and associated procedures
- Product Use Adherence assessments\*
- Pelvic exams, unless required for AE follow-up
- PK specimen collection (blood and pelvic samples)\*
- Provision of counseling (HIV pre/post-test, product use adherence)
- HIV/STI risk reduction counseling will be modified to address primary and secondary prevention for infected women.

\*Perform at the first visit where study product is discontinued, but omit at subsequent visits.

Participants who are confirmed HIV positive during follow-up will undergo the following additional procedures:

- CD4 testing
- HIV RNA testing
- HIV drug-resistance testing
- Consent to notify the participant's medical care provider of the participant's involvement in MTN-023/IPM 030
- Referral to available resources in the area for HIV testing, treatment, and support. Refer to protocol sections 7.5.1, 9.3 and 9.7.

### 5.8.5.2 Participants Who Become Pregnant

All study participants are required to be using an effective method of contraception according to Protocol Section 5.2. Study staff will provide contraceptive counseling to enrolled participants throughout the duration of study participation and will facilitate access to contraceptive services through direct service delivery. Study staff also will provide participants with condoms and counseling on use of condoms ideally during every sex act during study participation.

Pregnancy testing is performed at all study visits and may be performed as indicated at interim visits. In addition, participants are encouraged to report all signs or symptoms of pregnancy to study staff. If a participant becomes pregnant during follow-up, the following should occur:

- Counsel participant regarding possible risks to the fetus according to the study product's Investigator's Brochure.
- Refer the participant to local health care services. The referral should be documented in chart notes.
- A Pregnancy Report and History form must be completed to document the pregnancy and relevant history.

- A Pregnancy Outcome CRF also must be completed to document the outcome of the pregnancy. Whenever possible, pregnancy outcomes should be collected from medical records or other written documentation from a licensed health care practitioner. When medical records cannot be obtained, however, outcomes may be based on participant report.

Participants will be permanently discontinued from VR use and will be instructed to return the study VR. The participant will be offered the option to continue follow-up visits per her original study schedule until her originally scheduled study exit date. For those who choose to remain in follow-up, protocol-specified procedures will continue except the following:

- hCG testing\*
- Samples for PK\*
- Provision of contraceptive counseling
- Provision of study product and associated procedures
- Provision of product adherence counseling
- Pelvic exams, unless required for AE follow-up
- Product Use Adherence assessments\*
- Consent to notify the participant's medical care provider of the participant's involvement in MTN-023/IPM 030

\*Perform at the first visit where study product is discontinued, but omit at subsequent visits.

Participants who are pregnant at the 24-Week Final Clinic/Termination Visit will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Outcomes meeting criteria for EAE reporting also are reported on EAE forms.

#### **5.8.5.3 Modified Procedures for Visits When Product Is Not Dispensed (Participant is on a Clinical Hold/Discontinuation or Refuses to Accept Study Product)**

This section applies to situations where study product will not be dispensed to the participant, either because the participant has been placed on a clinical product hold/discontinuation by study staff, or she refuses to accept/use study product.

A "clinical" hold or discontinuation is one which is initiated by study staff. Clinical product holds/permanent discontinuations require documentation on a Clinical Product Hold/Discontinuation Log CRF.

Note: Instances where a participant declines or refuses study product should not be documented as product holds/discontinuations on a Clinical Product Hold/Discontinuation CRF.

For those who choose to remain in follow-up, protocol-specified procedures will continue except the following:

- Samples for PK\*
- Provision of study product and associated procedures
- Provision of product adherence counseling
- Product Use Adherence assessments\*
- Pelvic exams, unless required for AE follow-up

\*Perform at the first visit where study product is discontinued, but omit at subsequent visits.

Completion of these procedures will resume if/when study product use is restarted.

Participants who have voluntarily chosen to not use study product but are willing to continue in follow-up should be approached at all remaining visits about restarting VR use. This should be documented in chart notes.

### **5.8.6 Voluntary Withdrawal/Early Termination**

As stated in the informed consent form, a participant or her guardian may choose to withdraw consent from the study and terminate their study participation for any reason at any time. If a participant/guardian wishes to discontinue participation in the study, their wishes must be respected.

If the participant decides to withdraw from the study, staff should complete the following:

- Ask participant if she is willing to complete one last visit, which would count as her termination visit. If the participant is willing, site staff should conduct all required early termination procedures at this final visit. Early termination procedures will be done per Section 7.4 of the protocol (24-Week Final Clinic Visit/Early Termination Visit) and will be documented via completion of all required CRFs for this visit including completion of the in-depth interview, if randomized
- Site staff should complete the Termination CRF and mark item 2c "participant refused further participation"
- Update participant locator form, and document how the participant would like to receive any follow up test results (as needed) and be informed of study results

At the time when the participant states that she wishes to discontinue participation, study staff must document, in participants' study records, the participant's stated wishes in detail. The following information should be obtained if possible:

- Why the participant wishes to leave the study.
- Whether the participant is willing to have any further contact with study staff in the future and, if so, for what purpose, at what frequency, and through what methods. For example, a participant who is not currently able to complete study visits may be willing to have study staff check in with her in several months' time to see if her circumstances may have changed. In this case, study staff must document the timing and type of contact that the participant agreed to (e.g., in person, telephone, delivery/mail), as well as the participant's preferences for the location of the contact (e.g., at her home, at a family member's home, at her workplace).
- If the participant has any pending laboratory test results, whether and how she is willing to be contacted for purposes of receiving her results.
- Whether and how the participant wishes to be contacted for purposes of learning the results of the study or unblinding (when available).

### **5.8.7 24-Week Final Clinic Visit/Early Termination**

Procedural requirements for conducting the 24-Week Final Clinic/Early Termination visit is specified in protocol section 7.4; further procedural guidance is incorporated in the 24-Week Final Clinic/Early Termination visit checklist which is available on the MTN-023/IPM 030 Study Implementation Materials webpage. Provided in the remainder of this section is additional information related to key aspects of final clinic/early termination visits.

#### **5.8.7.1 Participant Locator Information**

Accurate participant locator information will be needed for post-study contact with study participants. As such, locator information should be actively reviewed and updated at all study exit visits and all participants should be counseled to contact the study site should their locator information change after study exit.

### **5.8.7.2 AE Management and Documentation**

More information about the clinical management of AE's is discussed in Sections 7 and 8 of this manual. All AE Log forms completed for each participant should be reviewed at the study exit visit and updated as needed. For AEs that are ongoing at the 25-Week Follow-up Phone Call, the status/outcome of the AE should be updated to "continuing at end of study participation" and the AE Log form should be re-faxed to MTN SDMC DataFax. Information related to following up AEs after participant termination can be found in Section 8 of this manual.

### **5.8.7.3 Referral to Non-Study Service Providers**

After the 25-Week Follow Up Phone call, participants will no longer have routine access to services provided through the study, such as routine health care and HIV counseling and testing. Participants should be counseled about this —ideally before and during their study exit visits — and provided information on where they can access such services after study exit. It is strongly recommended that all study sites develop written referral sheets that can be given to participants at their study exit visits.

### **5.8.8 Post-Study Contact**

- It is expected that all participants will be re-contacted by study staff after study completion, when study results will be available for dissemination.
- To facilitate post-study contact with participants, locator information should be updated at the study exit visit, and participants should be counseled to contact the study site should their locator information change after study exit. In addition, participant preferences for methods to be used for contacting them when study results are available should be documented in participant study records.
- Lastly, for participants whom study staff may wish to contact regarding participation in future studies, permission for such contact should be sought from the participant and documented. In addition, for ease of retrieving information on participant permissions, it is recommended that study staff maintain future study contact permission logs.