Section 6. Participant Follow-up

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This section provides information on requirements and study visit procedures for participants in follow-up. Additional procedure-specific details can be found on the template visit checklists available on the MTN-025 website (http://www.mtnstopshiv.org/node/7330). Also see Section 9 for all product-related guidance, Section 10 for clinical procedures, Section 12 for counseling procedures, Section 13 for laboratory-related procedures and Section 14 for data management.

6.1 Study Follow-up Plan

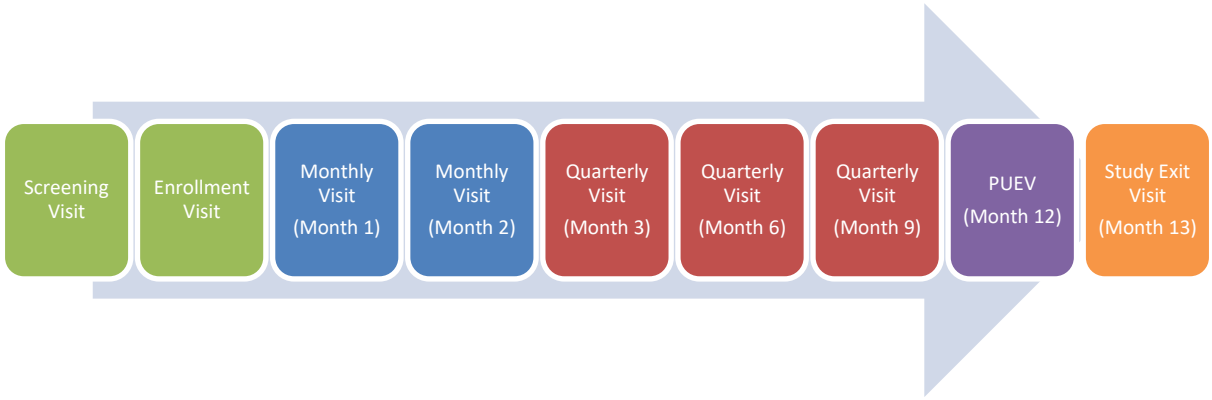
After enrollment, each participant will be followed approximately one year. An adjusted (shortened) follow-up period will be employed for women who enroll after the formal accrual period. Sites should contact the management team anytime a participant is enrolled after 15 September 2017 for guidance on their follow-up visit schedule. Please see detailed guidance on the adjusted follow-up period provided in SSP Section 4.

6.2 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. The protocol specifies that follow-up visits are targeted to occur monthly for the first three months, then quarterly thereafter. All participants will also be scheduled for a Product Use End Visit (PUEV) followed by a Study Exit/Termination Visit approximately 4 weeks later (Figure 1).

Figure 1: MTN-025 Scheduled Visits



- **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 product use, or to start or stop accepting study rings.
  - 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 14 for details about visit scheduling, and visit windows for scheduled and interim visits.

6.3 Follow-up Visit Locations

MTN-025 study visits will typically be completed at the study clinic. When necessary, follow-up visits may be conducted off-site at the participant's home or location suitable to the

participant with documented participant consent and allowable per site-specific SOPs. See Section 6.4.5 for more information on the conduct of off-site study visits.

6.4 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Sections 7.4 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 at follow-up visits is incorporated into the visit checklists which are available on the MTN-025 website. Information on the decliner population procedures is in SSP Section 2. Sites participating in the qualitative component of HOPE should reference SSP Section 17 for details regarding In-depth Interviews (IDIs).

As a general guide:

- **Month 1 and 2** visit procedures include:
  - Review/updating locator information, visit scheduling, and reimbursement
  - Provision of tailored protocol/adherence counseling (referred to as "HIV prevention options counseling'), which includes risk reduction counseling (Section 12)
  - HIV pre- and post-test counseling, including offering condoms (See SSP Section 12)
  - HIV-1 testing and urine pregnancy testing
  - Contraception counseling and, if needed, provision of contraception (Section 12)
  - Interval medical/menstrual/medication history including recording/updating any adverse events (AEs) and concomitant medications (Section 10)
  - If needed, a physical and/or pelvic exam, testing for UTI/RTI/STIs or other clinical conditions (Section 10)
  - Collection and storage of: a self-administered vaginal swab, blood for dapivirine testing and archive, and hair (required unless participant declines) (Section 13; Section 10 for guidance on how to collect the vaginal swab; section 12 on counseling for hair sample collection)
  - Provision of all available test results and treatment or referrals for UTI/RTI/STIs.
  - If applicable, collection of used ring for storage and future testing
  - Offer a study vaginal ring, and if accepted, provide ring for insertion and ring insertion instructions (as needed) (Sections 9 and 12)
  - If needed, a digital exam to check ring placement

- **Quarterly** visit procedures include <u>all monthly visit procedures</u>, plus:
  - ACASI (Month 3 visit only; Section 7)
  - Behavioral assessments (Section 7)
  - Social harms assessment (Section 11)
  - If indicated, provision/collection of up to 3 vaginal rings

- **Product Use End Visit (PUEV)** procedures include <u>most monthly and quarterly visit procedures,</u> with the following modifications:
  - HIV prevention options counseling will be modified to focus on risk reduction plans once the dapivirine ring is no longer accessible

- No vaginal rings are offered
- A physical and pelvic exam are required
- Testing for GC/CT, Syphilis, and Trichomonas is completed
- Blood for serum chemistries and CBC with platelets is collected
- PUEV/Discontinuers ACASI is completed

- **Study Exit/Termination Visit** procedures include most monthly visit procedures, with the following modifications:

  - No HIV prevention options counseling is completed, however, participants still receive HIV risk reduction counseling per site SOPs
  - No vaginal rings are offered or collected
  - A behavioral assessment is completed
  - Contraceptive counseling only occurs if indicated
  - Next visit scheduling only occurs if indicated

Note that with the exception of provision/collection of the study vaginal ring and associated instructions, all study procedures are conducted regardless of whether a participant chooses to accept a ring. Study procedures will be modified in the event of a clinical hold/discontinuation of product as per protocol sections 7.6.1-7.6.3.

While conducting all visit procedures for each scheduled visit is ideal, it is acknowledged that this might not always be possible. At a minimum, all of 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)
- HIV testing and Pre- and post-test counseling and pregnancy testing are required for product dispensation if this has not been done at the research clinic within the past 90 days
- If applicable, collection of Used/Unused Rings
- As needed, HIV Prevention Options Counseling/Product Use Instructions

See Section 9 for more information about study product dispensation.

6.4.1 Visits to Pick Up Rings During Quarterly Follow-up Schedule

Participants who do not want to receive 3 rings at their quarterly visits are permitted to come to the clinic each month to obtain a new vaginal ring each month instead (e.g., if they do not feel comfortable having a supply of two additional unused rings at home). Off-site visits can also be utilized for monthly ring provision, if the participant consents. Participants who opt for monthly ring pick-up should be scheduled for an interim visit at a time convenient to them at approximately 1 month intervals (i.e. about 4 weeks or 28 days) to exchange their ring. There are no formal visit windows or target dates for these visits. Note that monthly ring pick-ups should not be routine across the participant population, rather, they should be offered in the unique situation that a participant does not feel able to take 3 rings at a time. See SSP Section 9.1 for details on completing prescriptions for participants who choose to receive rings monthly.

Visits for the sole purpose of picking up a new ring during a quarterly schedule should be streamlined such that the participant spends as little time as possible in the clinic.

Sites should consider strategies for flagging these participants for fast-tracking through the clinic. The only procedures required are those necessary to collect her used ring (i.e. completing ring storage procedures and accountability documentation) and dispense a new ring (i.e. verbal check-in on AEs, negative HIV/pregnancy tests within 90 days, completing a ring request slip or new prescription, if applicable). These visits should be documented as an interim visit. Each site should determine their plan for reimbursement of visits to pick up rings. While visits exclusively for the purpose of picking up rings should not be at a cost to the participant, the amount reimbursed should not be so much as to incentivize participants to pick up rings on a monthly schedule.

6.4.2 Considerations for Interim Contacts During Quarterly Follow-up Schedule

Participants should be counseled as outlined in section 12.6 regarding the transition to quarterly visits at their Month 3 visit. Sites should consider strategies for supporting participants between quarterly visits with interim contacts such as by phone or through SMS. The goals of these contacts could range from general check-ins, to supporting retention (visit reminders), to supporting ring use or reminders to change rings. The frequency of contacts can be determined by the site team (e.g. monthly), however, routine contacts should not be so frequent as to be bothersome to the participant (e.g. daily). Permission for any method of contact must be obtained from the participant, for example, through documentation on the site locator form. Confidentiality should be considered when determining the content of any SMS messages, e.g. not to include information that would unwittingly disclose her study participation or ring use to others. If required by IRBs, regulatory approvals of SMS as a contact method and/or messages contained must be obtained prior to implementation.

6.4.3 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-025. For more information on study product considerations during split visits see Section 9.7.

Note that while a visit may be split, individual procedures should not be split. For example, HIV pre and post-test counseling and HIV testing should all occur on one day. ACASI questionnaire completion should also occur all on one day and should not be split across days. Guidelines in Section 3.3.2 regarding sequence of procedures should also be followed for split visits.

6.4.4 Missed Visits

If no procedures of a scheduled visit are conducted within the visit window a Missed Visit CRF is completed and entered into the clinical database. MTN-025 visit windows are contiguous, as such no procedures are required to be made-up at subsequent scheduled visits. Note that in the event of a missed visit, an interim visit may be required to resupply rings and conduct associated safety assessments and counseling as needed (see minimum procedures required to dispense rings outlined in section 6.4 above). If a participant misses her Month 3 visit, ACASI will be considered missed and will not be made up at subsequent quarterly

visits. Section 14 gives detailed information regarding the completion of the Missed Visit form. Section 9.8 provides guidance on study product considerations around missed visits.

6.4.5 Off-site Visit Procedures

MTN-025 protocol Section 7 specifies that visit procedures may be conducted off-site with participant consent. Note that it is generally expected that regularly scheduled study visits will be conducted at the study clinic, and off-site visit procedures should occur infrequently. Off-site visit procedures are distinct from participant contacts made for the purposes of retention/tracing or to collect product in response to a product hold/discontinuation; these procedures are described separately in SSP Section 8 and Section 10, respectively.

This section describes requirements which must be met prior to implementation of off-site visits, as well as situations which may warrant an off-site visit and what visit procedures will be permitted. It is strongly suggested that sites include the option of off-site visits for a defined set of reasons and procedures based on site capacity thus ensuring advance preparation to respond to adherence and/or retention issues. Site-specific procedures for off-site visits should be described in site SOPs.

6.4.5.1 Informed Consent

Off-site visit procedures (excluding site procedures for retention efforts and product collection due to product hold) may only be conducted if the participant has provided written consent to be visited by study staff outside of the clinic. Should a participant express interest in joining the decliner population, but wish to have this visit done off-site, staff should explain confidentiality/safety issues and confirm over the phone that the participant is agreeable to completing the visit at a location outside of the clinic (see SSP Section 2.4.2 for additional guidance). Decliner informed consent procedures can occur off-site provided that permission is granted, confidentiality and safety considerations are discussed via phone call before the visit. Sample text for off-site visit consent is included within the sample enrollment informed consent form. Should local IRB/ECs require a separate informed consent to conduct off-site visits; a template will be provided on request from MTN LOC.

During the administration of the informed consent for off-site visits, sites should discuss with participants any issues that may jeopardize participant confidentiality and/or safety, such as living situation (e.g., persons living with participant, availability of private space at participant's home or place of work). Also, in an effort to minimize the potential risk of social harm to participants and to study staff who will conduct off-site visits, discuss with participants whether they have disclosed participation in the study to family, neighbors, or others who may learn of these off-site visits. Where participation has not been disclosed, maximal effort should be made to ensure inadvertent unwanted disclosure does not occur as a consequence of the off-site visit.

Each time an off-site visit is warranted, clinic staff must verify consent for off-site visits. When communicating with participants ahead of off-site visits, when possible, the rationale and the procedures to be conducted for the visit should be clearly explained to her as well as the approximate time that will be needed to complete the required procedures. Every effort should be made to ensure that the time and location is convenient for the participant.

6.4.5.2 Reasons for Conducting Off-Site Visits

Site staff should use good clinical judgment and discretion when determining that an off-site visit is needed for a particular participant. Examples of situations which may warrant an off-site visit for MTN-025 include, but are not limited to:

- Participant does not have time or is unable to come to the clinic for the visit
- To conduct decliner population visit procedures (see SSP Section 2)
- Follow-up on an adverse event/ serious adverse event
- Collect samples that were inadequately collected or inadvertently missed at scheduled visits or compromised in transit to or at laboratory
- Collect confirmatory HIV samples
- Provide/collect study product
- Follow-up on a participant who:
  - is unable to come to the clinic and may potentially fall outside of the visit window for the current visit
  - has voluntarily withdrawn from the study, but is willing to have a final HIV test/ pregnancy test/ safety bloods drawn off-site

6.4.5.3 Permitted Locations, Visit Types, and Procedures

Off-site visits may occur at a participant's home or at other appropriate venues, provided that both participant and staff are comfortable with the venue and provided that safety and confidentiality can be maintained.

Any type of follow-up visit (i.e. interim, monthly, quarterly, PUEV, study exit/termination) may be conducted off-site. Generally, the required visit procedures should remain largely the same as they would for an in-clinic visit. However, it is recognized that some procedures may need to be modified or omitted due to limited capacity to conduct them off-site. For example, ACASI may be omitted for M3 or PUEV visits, and pelvic exams may be omitted for PUEVs done off-site. Site staff should document within participant records which visits were conducted off-site and what procedures were omitted or modified as a consequence (if any). As with any visit (in-clinic or off-site), participants have the right to decline/refuse completing any study procedures; site staff should clearly document refusals in the participant chart. Effort should be made to finish required visit procedures that are not conducted during an off-site visit as part of a split visit within the visit window.

The minimum procedures required to dispense study product from site pharmacy and deliver during at an off-site visit are the same as listed in Section 6.4 above for in-clinic visits.

NOTE: Per protocol, the IoR/designee may use his/her discretion to provide up to one additional ring. This provision may occur in the clinic, or be delivered to the participant as an interim off-site visit. Should the IoR/designee approve of dispensing an additional vaginal ring, this should be adequately documented. In this situation, provided that safety tests (e.g. HIV testing, pregnancy testing) were conducted within the last 90 days, the only procedures that need to take place are AE assessment and recording (this can be based on participant-report), and HIV prevention options counseling/product use instructions, as needed. However, as with in-clinic visits, it is best to conduct as many of the scheduled visit procedures as feasible when off-site.

6.4.5.4 Off-Site Visit SOP Requirements

Sites are required to have approved SOPs for off-site visits in place as part of study activation. Considerations that should be addressed in the SOP for off-site visits are as follows:

- Feedback and operational suggestions received from the MTN 025 Community Working group and Sites Community Advisory Board or Group as relevant with regard to conducting off-site visits.
- Procedures for contacting and scheduling participants for off-site visits.
- Procedures for verifying participants' consent prior to conducting off-site visits.
- Procedures to protect the safety of study staff, participants and any family members present during off-site visits, as well as confidentiality of participants.
- Identification of staff member roles and responsibilities for off-site visits:
    - In general, most off-site visits will require two staff members, including one who is able to provide clinical assistance in case of symptoms or AEs, perform phlebotomy, conduct and verify rapid tests results and assist with specimen processing
    - Ensure that at a minimum one of these staff members are conversant in the language of choice of the participant
    - Ensure that these staff members are thoroughly versed in confidentiality and pharmacy and lab chain of custody issues
    - Procedures for management of symptoms/illness requiring medical attention. Specifically, procedures for management of positive pregnancy tests, positive or discordant HIV rapids, STI symptoms, contraceptive use and potential SAE/EAE, as well as provision of any necessary referrals should be described.
        - NOTE: If genital symptoms are reported during an off-site visit, the participant should be asked to report to the clinic as soon as possible for a pelvic exam.
    - Generally, if any issues requiring further follow-up arise at an off-site visit, the participant should be referred (or brought) to the clinic as soon as possible for further evaluation. Depending on the severity of the issue, site staff may need to transport participant immediately from the off-site visit to the clinic or nearest healthcare facility.
- Description of how routine participant identification procedures will be modified for off-site visits.
- List of materials and supplies that will be needed for an off-site visit.

Lab considerations:

Sites may perform off-site visits to collect specimens for transport to an outsourced or site laboratory or to perform rapid HIV testing and urine pregnancy testing at the off-site location. Prior to off-site specimen collection or testing, sites must submit SOPs to the MTN LC and DCLOT to obtain authorization. It is recommended that the primary site SOP for off-site visits reference existing laboratory SOPs when possible, and these SOPs include components on off-site procedures (for example, performing HIV rapid tests and pregnancy tests off-site).

Considerations for collection of specimens for transport to an outsourced and on-site laboratory:

- Chain of custody, for specimens to be transported from off-site visits
- Safety considerations, including details on how biological specimens and bio-waste will be handled and procedures to prevent and respond to specimen accidents
- Adhering to allowable time intervals to get specimens to testing laboratories
- Specimen handling and transport methods
- All HIV rapid tests must have face-to-face post-test counseling conducted on the same day the test was conducted
- Equipment and supplies

Considerations for testing performed in an off-site location:

- Source documentation for test results
- Staffing: 2 staff members qualified in HIV rapid testing will be required to perform and review HIV testing results
- Safety considerations, including details on how biological specimens and bio-waste will be handled and procedures to prevent and respond to specimen accidents
- Equipment and supplies
- Appropriate area in off-site location to perform testing

NOTE: Staff should follow the same procedures specified in section 6.5 below in the event of a possible seroconversion (i.e., a reactive rapid HIV test) identified during an off-site visit. If possible and agreed upon by the participant, sites should offer immediate transport to clinic for directed post-test counseling, blood sample collection for seroconversion, and used study product collection for storage and future testing.

Source Document considerations:

- No *completed* CRFs or other source documents should leave the study clinic. This includes tablets or computers used for direct data entry into Medidata. It is recommended that paper CRFs be used in these instances and data-entered upon return to clinic. Blank CRFs and blank chart note pages should be taken off-site to allow visit documentation to occur in real time.
- Staff notes (summarizing source documents in the binder) may be necessary to follow up on AEs/symptoms/contraceptive use, etc. documented at the last visit. These may be *transcribed* from source documents in the participant binder or within Medidata Rave and brought off-site. The system for this should be outlined in the site off-site SOP.
- Updates to log CRFs (e.g. AE logs, Con Meds log) or other site-specific trackers can be made upon return to the clinic based upon chart notes taken during the visit, but documentation of the off-site visit should never rely on memory. CRFs that are considered source documents (e.g., interviewer-administered forms such as BA) must be completed during the visit. They should not be updated or completed after the visit based upon visit notes or memory.
- All documentation from the off-site visit should be filed in the participant binder and no documentation from the off-site visit should ever be destroyed (for instance, no notes should be jotted on scrap paper that is later thrown away at the clinic).
- Source Documentation and Data Management SOPs apply to off-site visit documentation and data collection/management just as they do for on-site visits.

Pharmacy considerations:

- Specifications on product supply procedures for off-site visits. *NOTE: All pharmacy procedures outlined in the MTN-025 off-site visit SOP should be reviewed and approved by an MTN pharmacist.*
  - Requesting participant-specific study product from the pharmacy prior to the off-site visit (should include how this will be documented as an off-site visit on the MTN-025 Vaginal Ring Request Slip and the time line for notifying pharmacy prior to the off-site visit).
  - Ensuring proper chain of custody of participant-specific study product from time of receipt from the pharmacy to time of delivery to the participant, including ensuring that participant-specific study product is delivered to the correct participant
  - Transporting participant-specific study product at appropriate temperatures from time of receipt to time of delivery to the participant
  - Handling/returning participant-specific study product when the participant cannot be located or refuses to receive the product dispensed for her
  - Handling of used and unused study product, including procedures for collection and transportation back to clinic for disposal
  - Documenting all of the above, and appropriately storing all documentation in either the study clinic and/or pharmacy (as per site SOP)

6.5 Procedures for Participants Who Have a Positive Rapid HIV Test Result

The following procedures must be **done the same day of a positive rapid HIV test result(s**) during follow-up:

- **Collect blood and send for Confirmatory Test (Geenius), HIV RNA, and CD4+ testing**. Record all results on a HIV Test Results CRF. The blood used for the Geenius must be collected and labeled separately from the sample used for the HIV rapid tests. RNA and CD4 tests should be run together with the Geenius and not postponed until Geenius results are received.
- **Collect blood for plasma storage** for future HIV infection confirmation testing. Document collection on HIV Test Results CRF.
  - If indicated, complete a **Vaginal Ring Request Slip** and **Clinical Product Hold/Discontinuation Log CRF** to document the product hold. Note, clinical hold documentation is completed regardless of whether the participant is currently accepting rings. However, VR request slips are only completed for participant who have ever had a prescription completed.
- Counsel the participant regarding her HIV status per SSP Section 12 and site SOPs; provide referrals per site SOPs.

Refer to protocol Sections 7.5.1 and 9.6 and the guidance below for additional information.

- Perform all of the procedures listed above even if a participant's rapid test results are discordant.
- The samples for Geenius, HIV RNA, CD4+, and plasma storage are collected separately from the sample used for HIV rapid testing.
- If a participant's HIV status is confirmed (positive Geenius Result) during the same visit, proceed immediately to guidance below regarding completion of documentation for permanent discontinuation, and administering and/or scheduling discontinuers

ACASI

Note: HIV-2 is rare in the countries where HOPE is conducted, but all HIV-2 positive or indeterminate results must be evaluated (see SSP section 13.7.2). In cases of HIV-2 positive or indeterminate results, product should continue to be held and the MTN-025 PSRT consulted on further product use management, including progression to permanent discontinuation if HIV-2 infection is confirmed, and clinical care.

LOA#1 specifies routine plasma collection at all visits post enrollment. See Section 13.7 of this manual for guidance regarding plasma storage at post enrollment visits where plasma must also be stored per the HIV algorithm after a positive HIV rapid result.

6.5.1 Modified Procedures for Participants Who Become HIV-infected (Have a Positive Geenius Result)

The following procedures must be done for participants whose HIV infection is confirmed per the algorithm in protocol Appendix III:

- **Step 1: Permanently discontinue participant from study product.** Once the participant is identified as HIV-infected, complete a new Vaginal Ring Request Slip if indicated (i.e. for participants who have ever had a prescription completed) to notify the Pharmacy (mark permanent discontinuation), update the status for the item "Was the participant instructed to resume study product use?" in the Clinical Product Hold/Discontinuation Log CRF (the one originally completed for the reactive HIV rapid test result) with the date of permanent discontinuation being the date the participant's HIV final status is confirmed, and update the participant's final HIV status in the HIV Test Results CRF to reflect the participant's HIV-infected status. You should not wait to inform the participant of her HIV-infected status to complete these items.
- **Step 2: Inform participant of her confirmed HIV-infection status.** Counsel and refer per SSP Section 12 and site SOPs.
- **Step 3: Administer PUEV/Discontinuers ACASI, complete the ACASI Tracking CRF.**
    - The PUEV/Discontinuers ACASI interview is administered either at the visit when participant is provided confirmation of her HIV result, or as part of a split visit within approximately 1 month. The ACASI Tracking CRF is also completed.
    - If the ACASI assessment is not done in error at one of the above specified time points, they are made up – they are reflected as missed assessments.

Participants with confirmed HIV infection will be offered the option to continue MTN-025 follow-up visits per their original study schedule. These participants will also be encouraged to enroll in MTN-015, regardless of study product use. For those who choose to remain in MTN-025 follow up (regardless of enrollment in MTN-015), the following procedures will be discontinued:

- HIV-1 testing, HIV pre- and post-test counseling
- Offer use of vaginal ring, instructions, product adherence counseling
    - Note: HIV prevention options counseling should continue and be modified to address primary and secondary infection prevention.
- Complete blood count

- Blood chemistries
- Plasma collection for DPV testing and storage (note seroconverter plasma collection will be initiated as per the guidance below if the participant does not enroll in MTN-015)
- Hair collection (note: collect at the visit when product hold is initiated and discontinue at visits moving forward after HIV confirmation)
- Vaginal fluid collection (note: collect at the visit when product hold is initiated and discontinue at visits moving forward after HIV confirmation)
- Scheduled MTN-025 Study Exit Visit. HIV-infected participants will be terminated once they complete the PUEV.

In addition, the following procedures will be added for HIV-infected participants as part of all scheduled MTN-025 study visits for the remainder of the follow-up period.

- Seroconverter plasma storage
- CD4+ T cell count
- HIV-1 RNA PCR
- HIV-1 Genotyping (standard resistance testing), will be performed on the stored plasma closest to the time of HIV-1 infection.
- HIV-1 RNA PCR or HIV-1 Genotyping may be performed at additional/alternate time points as requested by site IOR or at the discretion of the Laboratory Center.

Staff should complete the Seroconverter Laboratory Results CRF when results are available.

These procedures are discontinued if the participant enrolls in MTN-015, but the site should continue to complete the Seroconverter Laboratory Test Results CRF at the time points listed above (even if the participant enrolls in MTN-015).

For any participants who become HIV-infected and also become pregnant during follow-up, study staff will ensure access to current prevention of mother to child transmission regimens to reduce the probability of HIV transmission to the participant's infant (see also Section 6.6). Should a pregnant participant seroconvert or if a participant has a positive pregnancy test and positive rapid HIV results, the PSRT should be notified.

6.5.2 Participants With a Positive Rapid HIV Test Who Are Confirmed as HIV-uninfected

For participants who have a positive rapid HIV test result and are later confirmed HIV-uninfected per the algorithm in protocol Appendix III, product may be resumed if desired by the participant. Once product is resumed, clinic staff should inform pharmacy staff of the resumption in writing, using a Vaginal Ring Request Slip signed by an authorized prescriber (or a prescription if the participant has not previously been accepting product). Clinic staff should also update the Product Hold/Discontinuation Log form to document eligibility to resume product use. If the participant declines vaginal ring use in this case and has ever had a prescription completed, a Vaginal Ring Request Slip marked resume should still be sent to the pharmacy. On this same slip, clinic staff will also mark decline, to indicate that the participant is not accepting a ring for use at this time.

Moving forward, sites must adhere to all guidance provided by the LC for follow-up HIV testing plans for these participants (e.g. using alternate approved HIV rapid tests). In cases where an alternate HIV rapid kit is used, sites must have a system to alert testing personnel of

this in advance. The HIV algorithm must be initiated whenever there is an HIV positive rapid test.

6.6 Modified Procedures for Participants Who Become Pregnant

Pregnancy testing will be performed for all participants at scheduled visits. Testing will also be conducted if indicated at interim visits. Participants will be encouraged to report all signs or symptoms of pregnancy to study staff. The IoR/designee will counsel any participant who becomes pregnant regarding possible risks to the fetus according to site SOPs. This counseling may include messages such as:

- Like for any new medication, Dapivirine has not been formally evaluated in women who are pregnant – medications are usually studied in women who are not pregnant first.
- For that reason, women who become pregnant in HOPE are withdrawn from the study medication.
- Studies in animals, and studies in women of medications similar to Dapivirine, do not suggest harm to women who become pregnant or their babies.
- It is important to gather additional information in women for Dapivirine, and that is the reason that the study sites will follow women who become pregnant in HOPE and their infants.
- Participants who became pregnant in ASPIRE were/are also being followed in MTN-016, however the results from this study are not available yet. We will provide participants results of this study when known.

The IoR/designee also will refer the participant to antenatal care available per site SOPs; however, sites will not be responsible for paying for pregnancy-related care.

Participants who become both pregnant and infected with HIV will also be referred to prevention of mother-to-child transmission (PMTCT) services and will be offered expedited resistance testing at the MTN LC to provide information that may be useful for identifying optimal PMTCT regimens. Site staff should notify the PSRT promptly. HIV testing of participants' infants will be offered through the study if such testing is not otherwise available. All referrals and offers of additional testing available through the study will be documented in participants' MTN-025 study records.

Participants who become pregnant during the course of the study will temporarily hold study VR and will not routinely be withdrawn from the study. While in scheduled follow-up, all protocol-specified study procedures <u>including pregnancy testing</u> will continue to be conducted for pregnant participants, with the following exceptions:

- Offering a vaginal ring, product use instructions, and adherence counseling will be discontinued
  - Note: HIV prevention options counseling will continue and will be tailored to focus on HIV risk reduction plans during pregnancy that do not involve the vaginal ring
- Contraceptive counseling should continue during pregnancy, but can be abbreviated and should be tailored to changing participant needs over time. For example, early discussions may focus on what contraceptive method she was using prior to

pregnancy and whether the pregnancy was due to contraceptive failure or not, while discussions later in pregnancy may focus on method selection and initiation post-delivery.

- Pelvic exams and self-administered swab for vaginal fluid will be discontinued after 24 weeks of pregnancy, unless the participant indicates comfort with continuing vaginal procedures. It should be documented in chart notes (or other source documentation) that the participant was agreeable to these procedures post 24-weeks.

For participants who become pregnant, a Pregnancy Report and History CRF must be completed to report the pregnancy. Participants who are pregnant at the Study Exit/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). A Pregnancy Outcome CRF also must be completed to document the outcome of the pregnancy. When reporting a pregnancy outcome, complete the Pregnancy Outcome eCRF within the visit folder at which the pregnancy was reported (i.e., The Pregnancy Report and History and Pregnancy Outcome eCRFs should be documented at same study visit.) 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. All study sites are encouraged to use a pregnancy management worksheet similar to the one available on the HOPE website (http://www.mtnstopshiv.org/node/7330) to ensure proper documentation of the pregnancy and timely discontinuation of VR use, if applicable.

If the pregnancy occurs during the VR use period, site pharmacy staff must be informed of the product hold in writing using the Vaginal Ring Request Slip and a Clinical Product Hold/Discontinuation Log form (see Section 14) must be completed and submitted to the MTN SDMC (note: clinical hold documentation is completed regardless of whether participant was previously accepting rings, however, VR ring request slips should only be completed if a prescription has previously been completed). Note that a separate Clinical Product Hold/Discontinuation Log form must be completed if the participant delivers and begins breastfeeding (since the reason for hold has changed).

Product use may be resumed after birth (provided the participant is not breastfeeding) or termination of the pregnancy, as evidenced by a negative pregnancy test performed by study staff. In instances of a pregnancy loss, vaginal ring use should not be resumed earlier than 2 weeks after a 1st trimester loss, or earlier than 4 weeks after 2nd trimester or later loss (see Section 10). Product restart timelines should begin when the pregnancy is lost (i.e., bleeding, elective termination, etc). This restart timeline should only be based off a negative pregnancy test if the date of pregnancy loss is completely unknown. A pelvic exam must be performed prior to resumption to confirm the absence of any findings that would contraindicate resumption, in the opinion of the IoR/designee.

All pregnant participants also will be referred to MTN-016, regardless of study product use. Written referrals to MTN-016 are not required; documentation of referral (verbal or otherwise) should be present in participant chart notes. All discussions related to potential participation in MTN-016 must be fully documented in participant study records.

6.7 Modified Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product Use

The following procedures will be discontinued starting at the visit/contact during which site staff initiate a clinical product hold/discontinuation and will only resume should the participant be clinically eligible to be offered study product:

- Provision of vaginal ring
- Provision of product adherence counseling, product use instructions
  - Note: HIV prevention options counseling will continue and will be tailored to focus on HIV risk reduction plans that do not involve the vaginal ring

Participants who permanently discontinue from study product use should have the PUEV/Discontinuers ACASI administered at the visit they are discontinued from study product use (or as part of a split visit within approximately one month). If a participant permanently discontinues from study product use at her Month 3 visit, the PUEV/ Discontinuers ACASI is administered at this visit instead of the Month 3 ACASI. No future ACASI questionnaires will be administered to the participant.

6.8 Participant Transfers

During the course of the study, participants may leave the area in which they enrolled in the study and re-locate to another area where the study is taking place. To maximize participant retention, participants who re-locate from one study location to another should be encouraged to continue their study participation at their new location. To accomplish this, study staff at both the original site (called the "transferring" site) and the new site (called the "receiving" site) will complete the process of a participant transfer. An optional Transfer Checklist and Transfer Inventory Log is available on the MTN website which summarizes the guidance below. Before initiating this process, the transferring site should ensure that the receiving site will be able to conduct study procedures in a language spoken by the transferred participant.

Upon identifying the need for a participant transfer to another site, the transferring site will notify the receiving site as well as the MTN-025 study management team and the MTN Pharmacist. After the logistical details of the transfer have been discussed and agreed upon by the two sites, the following steps will be completed:

- The MTN SDMC will notify the transferring site of all outstanding data QC notes for the transferring participant; the transferring site will resolve these QCs.

- The transferring site will explain the transfer arrangements to the participant and obtain her written permission to provide copies of her study records to the receiving site. If the participant has already moved and cannot return to sign the records release, this may be accomplished by the transferring site faxing the release to the receiving site for completion by the participant.

- The transferring site will deliver certified copies of all of the participant's paper study records to the receiving site via courier or overnight mail service. Copies of participant-specific records maintained in the transferring site pharmacy must be sent to the receiving site pharmacy in a separate file clearly marked "Pharmacy Only" and

may be delivered in the same shipping envelope or carton as the clinic records. The transferring site (clinic and pharmacy) will document all materials sent to the receiving site and inform the receiving site of the shipment date and expected arrival date. The receiving site (clinic and pharmacy) will confirm receipt of the shipment.

- The transferring site will complete and submit a Participant Transfer case report form to the MTN SDMC (see Section 14 of this manual).

- The receiving site will establish contact with the participant, and obtain her written informed consent to continue in the study at the receiving site (using the receiving site's informed consent form).

- Upon receipt of the Participant Transfer CRF, the MTN SDMC will re-map the participant's PTID to reflect the change in site follow-up responsibility. The receiving site will now have access to the participant's casebook within Medidata Rave and can begin viewing and entering her data. Complete and submit the Participant Receipt CRF to the MTN SDMC. The participant's original PTID and follow-up visit schedule will remain unchanged.

- An authorized prescriber at the receiving site will be required to prepare an original signed and dated note* to pharmacy staff at the receiving site stating that the participant has provided written informed consent to take part in the study at the receiving site and that the prescriber authorizes the participant to continue study product use per the MTN-025 protocol at the receiving site (if applicable, i.e. if the participant chooses to accept study product). Clinic staff will deliver the original signed and dated note to pharmacy staff and retain a photocopy of the note in the participant's study chart. Upon receipt of the original signed and dated note, and a completed MTN-025 Vaginal Ring Request Slip (or MTN-025 prescription, if this is the participants first time accepting product), pharmacy staff at the receiving site will dispense a vaginal ring(s) to the clinic staff for the participant

    - **Note: if the participant has transferred from a different country, then a new prescription should be completed in lieu of completing the vaginal ring request slip and accompanying note. If more than one ring will need to be dispensed a request slip may also be needed to indicate the quantity.*

- The transferring site will retain responsibility for storage, and shipment to the MTN LC, if applicable, of all specimens collected from the participant prior to her transfer, unless otherwise instructed by the MTN LC.

6.9 Voluntary Withdrawal/Early Termination

As stated in protocol Section 9.8, participants may voluntarily withdraw from the study (withdraw consent) for any reason at any time.

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, during which the Early Termination Visit procedures (consisting of PUEV and Termination Visit

procedures) would be conducted. At the minimum, staff should try to perform a final HIV test (two rapid HIV tests).
- When completing the Termination CRF, mark "participant refused further participation, specify" as the Reason for Termination and provide additional details as to why the participant has refused further study participation.
- Record the reason(s) for the withdrawal in participants' study records.
- Update participant locator form.
- Complete the Study Exit Worksheet and Permission for Future Contact log (if applicable)
- Ensure all referrals are provided to participant as needed

If the participant chooses to withdraw consent after completion of her PUEV, but before the study end date, complete a Missed Visit CRF for the missed study exit visit as well as a Termination CRF (marking "participant refused further participation" as the Reason for Termination and specifying the reason).

As specified in protocol section 9.8, the IoR may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, in consultation with the PRST. It is recommended that site IoRs use their discretion with regards to terminating participants who relocate and cannot transfer to another study site or can no longer come to the clinic, and are unlikely to resume study visits after counseling efforts and discussions with appropriate study staff.

- If participants exhibit actions such as those listed above that indicate they may no longer be interested in study participation, it is recommended that they be offered a meeting with site leadership to discuss their desire to continue participation.
- When making termination decisions, study teams should weigh the advantages of keeping a participant in the trial against the negative impacts of a participant's poor retention on the study outcomes and clinic resources.
- Participant terminations should be viewed as a last resort and utilized only after other options have been thoroughly explored.
- Site teams are encouraged to discuss particularly challenging participants and potential terminations as a group and with the study management team, as needed.
- All discussions, counseling, and decisions about early termination should be adequately documented in the participant's study records. Consultation with the PSRT regarding early terminations per IoR decision should be printed and filed in the participant chart. PSRT consultation is not required for voluntary withdrawals.
- 'IoR discretion' should only be marked as the reason for termination on the Termination CRF if no other reason for termination applies.
- Site teams are encouraged to review their Retention SOPs to make sure any site-specific procedures are in line with this guidance (e.g. that site teams may consider early termination as one option for participants who permanently relocate). Updates should be sent to FHI 360 for review before finalization

For participants who have ever accepted a ring (i.e. has a prescription completed) and who are terminated early (regardless of reason) and have not been permanently discontinued from study product by the time of early termination, site staff should complete a Vaginal Ring Request Slip to inform the pharmacy that this has happened. The Vaginal Ring Request Slip should be marked "Product Use Period Completed" and specify the reason that the participant is being terminated early. A Clinical Product Hold/Discontinuation Log CRF is **not** needed to

document that a participant is ending eligibility for product use as a result of the early termination from the study.

6.9.1 Resumption of Study Participation After Voluntary Withdrawal

The protocol allows for participants who terminate early from the study to reverse their decision and re-join the study during their planned follow-up period, resume study procedures and follow-up at the investigator's discretion.

If such cases arise, study staff is advised to contact the mtn025mgmt@mtnstopshiv.org for additional guidance on how to manage various aspects of protocol implementation and data collection as the participant resumes participation in the study and to contact the PSRT to determine if the participant can be offered study product. If a participant rejoins the study, her PTID and follow-up visit schedule will remain the same. A clinical examination must be conducted prior to restarting product; procedures required should be confirmed by the PSRT. Resupply should be indicated on the Vaginal Ring Request Slip with a comment clearly stating that the participant has decided to rejoin the study and is clinically eligible to receive study product. If a participant has never previously accepted rings but wants to initiate ring use, a prescription should be completed for this initial dispensation.

Prior to performing any study procedure, the participant must provide written informed consent to document that she voluntarily rejoined the study. For re-consenting procedures, refer to Section 5.10 of this study manual.

Site staff should thoroughly document in the participant's chart notes her resumption of study follow-up, and if applicable, study product use and all communication with the study management team and PSRT.

6.10 Product Use End Visit and Study Exit Visit

The final two required follow-up visits for MTN-025 are the Product Use End Visit (PUEV) and the Study Exit visit (SEV).

- The PUEV occurs at the study's planned end of product use period, which for most participants will be her Month 12 visit (unless follow-up is extended based on need and requirements and with the necessary approvals—site teams will be notified should this occur; or if participants were enrolled after the formal accrual period has ended). A Vaginal Ring Request Slip marked Product Use Period Completed should be sent to the pharmacy for participant's who have ever received study product (i.e. ever had a prescription completed).
    - Note: Do not complete a new Product Hold/Discontinuation Log CRF at the PUEV. Completion of the PUEV CRFs tells SCHARP that the participant is expected to permanently discontinue study product use at this visit. This is true for participants who develop a new or increased severity AE at the PUEV that warrants product hold/discontinuation per protocol and for those participants who have a positive pregnancy or HIV rapid test at PUEV.
- The Study Exit visit occurs as the final follow-up visit for all participants with the exception of those who have become HIV infected prior to the PUEV (in this case, the participant will be terminated at her PUEV). The Study Exit visit takes place

approximately 4 weeks after the participant's PUEV. A participant's PUEV must take place prior to her SEV.

Separate operational guidance describing study closeout plans, including the HOPE study closeout checklist, will be circulated to the protocol team.

Note that the PUEV is conducted according to PUEV requirements (and is referred to as the PUEV) even if the participant had been permanently discontinued from study product, or is not accepting study product, prior to her PUEV. The same is true if a participant is on a clinical product hold at the time of her PUEV – the PUEV procedures are still performed as required.

If a participant has become HIV infected during follow-up, she is not required to complete a Study Exit visit (as the purpose of this visit is to identify delayed seroconversions in participants who are HIV-negative at the PUEV). The participant should be terminated once the PUEV is completed – complete a Termination CRF once the PUEV is completed.

Procedural requirements for conducting PUEV and Study Exit visits are specified in protocol Sections 7.4.2 and 7.4.3; further procedural guidance is incorporated in Operational Guidance #3 and in the PUEV/Early Termination/Termination Visit checklist on the MTN website. Provided in the remainder of this section is additional information related to key aspects of PUEV and Study Exit visits.

It is recommended that participant follow-up plans be documented on a study exit worksheet similar to the sample provided on the HOPE website (http://www.mtnstopshiv.org/node/7330).

6.10.1 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. See Section 8 for more detail on locator information.

6.10.2 HIV Counseling and Testing

HIV testing is performed at the study exit visit per the algorithm in Section 13. HIV pre- and post-test counseling provided at the study exit visit should emphasize that additional counseling and testing will be provided to the participant after her study exit visit if needed to clarify or confirm her HIV status. HIV counseling considerations are outlined further in Section 12.

For participants who test HIV positive at the study exit visit and have ambiguous HIV testing results (i.e., positive or discordant rapid tests and negative or indeterminate Geenius), study termination should be postponed until the algorithm is completed and all necessary samples are collected.

6.10.3 AE Management and Documentation

More information about the clinical management of AE's is discussed in the Clinical Management and AE Reporting Sections 10 and 11. 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 Study Exit/Termination visit, the status/outcome of the AE should be updated to "continuing at end of study participation" and the AE Log form should be re-saved within the Medidata Rave database. Information related to following up AEs after participant termination can be found in Section 11.

6.10.4 Final Study Contact

Although the Study Exit visit is the last scheduled study visit, a final contact may be needed after the exit visit to provide the participant with her final study test results, post-test counseling, and treatment, if needed. Additional contacts also are required for:

- Participants who are pregnant at study exit (note that if a participant is confirmed pregnant at the study exit visit she may be eligible for MTN-016), if eligibility criteria are confirmed during the visit
- Participants with certain types of AEs that are ongoing at study exit (see SSP Section 11)

As needed, a final contact should be scheduled based on the participant's overall clinical picture at study exit, as well as the time required to obtain all final study test results. Study staff may complete final contacts at the study site, by telephone, or at community-based locations, depending on site capacities and site and participant preferences. All final contacts must be documented in participant study records, but no case report forms are completed for these contacts.

6.10.5 Referral to Non-Study Service Providers

After completing their study exit visits and final study contacts, participants will no longer have routine access to services provided through the study, such as reproductive health care and HIV counseling and testing. Participants should be counseled about this —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 a sample script which can be used when discussing this issue with exiting participants, as well as written referral sheets that can be given to participants at their study exit visits (after obtaining IRB/EC approval of the written information). A sample script which may be tailored for use at each site is provided on the HOPE website (http://www.mtnstopshiv.org/node/7330).

6.10.6 Post-Study Contact

It is expected that all participants will be re-contacted by study staff when study results are 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. It is recommended that participant preferences be recorded on a study exit worksheet referenced in Section 6.10.4.

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. It is recommended that participant permission (or lack thereof) for future studies be documented on a study exit worksheet similar to the sample referenced in Section 6.10.4. In addition, for ease of retrieving information on participant permissions, it is recommended that study staff maintain future study contact permission logs similar to the example provided on the HOPE website (http://www.mtnstopshiv.org/node/7330).