

Section 5. Participant Follow-up and Retention

This section provides information on requirements for follow-up visits in MTN-024/IPM 031. This section also presents information related to the definition, requirements and procedures for participant retention. Additional procedure-specific details can be found in the following locations:

- Visit Checklists
- Section 6 for product-related guidance
- Section 7 for clinical considerations
- Section 9 for counseling considerations
- Section 11 for data management

5.1 Study Follow-up Plan and Participant Retention Targets

After enrollment, each participant will be scheduled to complete three clinic visits and two follow-up phone calls. The clinic visits will occur at approximately 4-Week, 8-Week and 12-Week. The phone calls will occur one week following the Enrollment Visit and one week following the 12-Week Final Clinic Visit/Early Termination Visit. The total duration of their participation will be about 13 weeks.

5.2 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 three visits; 4-Week Study Visit, 8-Week Study Visit, and 12-Week Final Clinic Visit/Early Termination Visit.
 - **Scheduled phone calls** are those phone calls required per protocol. They are the 1-Week and 13-Week/Study Termination phone calls. Note: If the participant returns to the clinic for reassessment following her 12-Week Final Clinic, site staff may conduct the 13-week termination procedures at the time of the visit in lieu of the phone call.
- **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.

5.3 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-024/IPM 031 Study Implementation Materials webpage under Checklists: <http://www.mtnstopshiv.org/node/4924>.

5.3.1 1-Week and 13-Week Follow-Up Phone Calls

The two required phone calls to study participants which are scheduled at 1-Week and 13-Week/Study Termination serve the purpose of inquiring about AE's. More details are provided in protocol Section 7.4.1. 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-024/IPM 031 Study Implementation Materials webpage under Checklists: <http://www.mtnstopshiv.org/node/4924>.

Note: If a participant is requested to return to the clinic for further evaluation following the 12-Week/Final Clinic Visit, prior to study termination, site staff are able to complete required study termination procedures in clinic if the visit is within the 13-Week/Study Termination Visit window. The applicable termination study visit code should be documented on all required source documentation and CRFs.

5.3.2 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-024/IPM 031. For more information on visit codes for split visits see SSP Section 11.

While conducting all visit procedures 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)
- 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, behavioral questionnaire completion should occur on the same day and not split across days.

5.3.3 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. Section 11 gives detailed information regarding the completion of the Missed Visit form.

5.4 Modified Procedures for Participants Who Become HIV-infected (Per Appendix II)

HIV testing is required at Screening and the 12-Week Final Clinic Visit/Early Termination Visit. Any other HIV testing will only be conducted if clinically indicated. If a participant tests positive for HIV per the algorithm in Appendix II the following should occur:

- Contact the MTN-024/IPM 031 Management Team.
- Refer the participant to local care and treatment services. This should be documented on the applicable counseling worksheet and/or in chart notes.
- Offer additional counseling and support services to the participant.

Participants who become HIV-infected during the course of the study will permanently discontinue study VR use and will be terminated from the study. Additional laboratory testing (such as HIV viral load and HIV drug resistance testing) may be offered in consultation with the IoR/designee and NL.

5.5 Modified Procedures for Participants Who Become Pregnant

As participants are postmenopausal, pregnancy is not expected to occur. Pregnancy testing is not routinely conducted during follow-up. In the rare occurrence that a participant is confirmed as pregnant the following should occur:

- Refer the participant to local health care services. The referral should be documented in chart notes.
- Any results of testing already completed for the woman should be communicated to her as soon as they are received. A Pregnancy Report CRF must be completed to report the pregnancy. 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 who become pregnant during the course of the study will permanently discontinue study VR use and will be terminated from the study. Pregnant participants may be referred to MTN-016, if available at the site. They may be informed about MTN-016 upon first identification of their pregnancy, but should not be actively referred for screening and enrollment in MTN-016 until after the pregnancy confirmation requirements of MTN-016 are met. 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.

5.6 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.

The following procedures will occur at the visit in which the clinical product hold/discontinuation was initiated but will be omitted at subsequent visits should the participant choose to remain in follow-up:

- Provision of vaginal ring
- PK specimen collection
- Provision of counseling (adherence and product use)
- Pelvic exams (unless required for AE follow-up)

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.

5.7 Participant Transfers

Participant transfers are not expected to occur in this study due to the short study duration. In the unlikely event a participant leaves the area in which they enrolled in the study and relocates to another area where the study is taking place during the course of the study, participant transfers may be allowed. To maximize participant retention, participants who relocate 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. Detailed guidance on participant transfer procedures is outlined in the MTN Manual of Operational Procedures, section 13.2.4.

5.8 Voluntary Withdrawal/Early Termination

As stated in the informed consent form, a participant may choose to withdraw consent from the study and terminate their study participation for any reason at any time. If a participant wishes to discontinue participation in the study, her 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 (12-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 and the End of Study Inventory CRFs. When completing the Termination CRF, mark item 2c “participant refused further participation, specify”. No other CRFs should be completed, unless instructed otherwise by SCHARP.
- 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).

5.9 12-Week Final Clinic Visit/Early Termination

Procedural requirements for conducting the 12-Week Final Clinic/Early Termination visit is specified in protocol sections 7.4; further procedural guidance is incorporated in the 12-Week Final Clinic/Early Termination visit checklist which is available on the MTN-024/IPM 031 Study Implementation Materials webpage under Checklists: <http://www.mtnstopshiv.org/node/4924>. Provided in the remainder of this section is additional information related to key aspects of early termination visits.

5.9.1 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.

5.9.2 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 study termination, 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.

5.9.3 Referral to Non-Study Service Providers

After study termination, 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 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 can be tailored for use is available on the MTN-024/IPM 031 Study Implementation Materials webpage under Other Tools/Templates: <http://www.mtnstopshiv.org/node/4924>.

5.9.4 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. It is recommended that participant preferences be recorded on a study exit worksheet.

A sample study exit worksheet that may be tailored for use is available on the MTN-024/IPM 031 Study Implementation Materials webpage under Other Tools/Templates: <http://www.mtnstopshiv.org/node/4924>.

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.

A sample contact log is available on the MTN-024/IPM 031 Study Implementation Materials webpage under Other Tools/Templates: <http://www.mtnstopshiv.org/node/4924>.

5.10 Participant Retention

5.10.1 Retention Definitions

The term “retention” generally refers to completion of follow-up visits and procedures as specified in a study protocol. This definition must be operationalized for any study, and operational definitions usually reflect the primary objectives and endpoints of a study.

For MTN-024/IPM 031, the following retention measures are planned:

- During the study, retention for each regularly scheduled follow-up visit will be defined based on whether participants complete the visit within the visit window. Participants who complete a regularly scheduled visit within the visit window will be considered ‘retained’ for that visit.
- Overall study retention is calculated as the percentage of the total number of visits completed by all participants (within their allowable visit window) divided by the number of visits expected for all participants. A visit is considered expected for a participant once the allowable window closes, regardless of whether or not a participant is lost to follow-up or terminated early from the study.

The MTN Statistical and Data Management Center (SDMC) will post reports on their ATLAS portal presenting retention rates throughout the period of study implementation. The SDMC also will generate a final end-of-study retention rate after the study is completed.

5.10.2 Retention Requirements

Each study site will target retention of at least 95% of enrolled study participants for each scheduled follow up visit. The purpose of the 95% retention target is to ensure the accuracy of study results by minimizing bias that can be caused by missing data. Low retention rates can have serious impacts on the accuracy of the study results because it is unknown whether participants who do not return for scheduled study visits used the study product, liked the product or had adverse effects resulting from use of the product. To avoid these problems, and thereby avoid bias in the study results, high participant retention rates must be maintained throughout the study.

5.10.3 Retention SOP

Site staff are responsible for establishing a standard operating procedure (SOP) for participant retention to meet the study retention goal of 95%. This SOP should be re-evaluated and modified in response to lower than anticipated retention rates, or at any other time when retention strategies are modified. The SOP should minimally contain the following elements:

- Site-specific retention goals
- Methods for tracking actual retention versus retention goals

- Procedures for completing and updating participant locator information
- Site-specific definition of “adequate” locator information (for purposes of determining participant eligibility)
- Visit reminder methods and timeframes
- Methods and timeframes for identifying when a visit has been missed
- Planned retention methods (including what outreach/locator efforts are taken within 24 hours, 1-3 days, 1 week, or 2 weeks after a missed visit)
- Methods for timely evaluation of the utility of retention methods
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

5.10.4 Obtaining and Updating Locator Information

Successful retention begins with collection of locator information from each study participant. Provision of “adequate” locator information is a study eligibility requirement and each site must specify its definition of adequate locator information in its retention SOP.

Each study site is encouraged to develop an exhaustive locator form to maximize contact effectiveness and participant retention. Potential locator items include:

- Participant's full name, alias, and/or nickname; home address; home phone number; mobile phone number; work address; work phone number; fax number; or e-mail address; daytime and nighttime locations, meeting places and hangouts.
- Name, address, telephone number, and/or other contact information for stable contacts (i.e., participant family members and friends) who typically know the whereabouts of the participant.

Note: Although contact information for a participant's current primary partner will likely be useful, contact information for other contacts also should be collected, since the participant's relationship with this partner could change during the course of the study.

During the informed consent process and when collecting locator information, study participants must be informed that their locator sources will be contacted if study staff are unable to locate the participant directly. Study staff will negotiate with the participant how they will identify themselves when locator sources are contacted. Arrangements agreed upon with the participant should be documented on the locator form. Study staff should view every participant contact as an opportunity to update the participant's locator information. When updating locator information, actively review each item on the locator form to determine whether the information is still current (i.e., rather than simply asking “Has any of your information changed since your last visit?”). Site staff should also probe for additional information that the participant was not able or willing to provide at previous visits.

Study staff should document that they reviewed the locator information with the participant at every visit. Any updates to the locator form should use standard GCP corrections with initials and date of the staff member making the changes.

5.10.5 Retention Tips

Some general strategies for maximizing participant retention are as follows:

- Emphasize the value of the participant's involvement in the study during the study informed consent process and subsequently at follow-up visits. When participants complete scheduled visits, acknowledge and compliment their commitment, time, and effort devoted to the study.

- Keep locator information up-to-date and maintain thorough documentation of all efforts to contact the participant. Keep all this information in an organized manner, so that different staff members can easily review the information and contribute to re-contact efforts when necessary. Make use of all information collected on the participant's locator form. Even if a locator source is not useful/successful on one occasion, try it again later.
- Prepare a calendar of scheduled visits for each enrolled participant, based on her enrollment date, or offer a planner/calendar as an incentive and note all study appointments in the planner/calendar. Note the dates of all scheduled visits in the participant's file for easy reference.
- For participants who demonstrate a pattern of late or missed appointments, schedule follow-up visits for the beginning of the allowable visit window (i.e., up to one to two weeks before the actual target date) to allow maximum time for re-contact and re-scheduling if needed.
- Pay close attention to the allowable visit window and prioritize retention efforts for participants nearing the end of the window. Organize daily caseloads and work assignments based on these priorities.
- Make use of all available contact methods (e.g. phone, mail, home visits, email/internet).
- Dedicate adequate staff time and effort to retention efforts.
- Work with community members to identify the most applicable contact and retention strategies for the local study population, including the type and amount of participant incentives.
- Keep participants and community members up-to-date on study progress to foster a sense of partnership and ownership of the study (through the use of participant newsletters, for example).
- Inform local service providers who interact with the local study population about the study, so that they also can express their support for the study.
- Host gatherings, parties and/or other social events for participants. Host social, educational, and/or other events for participants' partners.
- Use tracking systems to identify when participants' scheduled visits are due and/or overdue. Establish routine mechanisms to remind both study staff and participants of upcoming scheduled visits.
- Follow-up on missed appointments with an attempt to re-contact/re-schedule within 24 hours (preferably on the same day). Continue these efforts per the site retention SOP until contact is made.