

Section 6. Participant Follow-up

This section provides information on requirements and procedures for participant follow-up.

6.1 Study Follow-up Plan

The target accrual of participants is expected to be completed within five months from the time of the first site activation. The protocol team will actively monitor and manage the accrual process to ensure that the enrollment occurs within the specified time frame. Each enrolled participant will be followed through the Follow-up Phone Assessment/Termination Visit, which may occur from Day 28 to Day 77.

To minimize bias and ensure accuracy of study results, each study site will target a minimum retention rate of at least 95% for all enrolled study participants.

6.2 Types of Follow-up Visits

Scheduled Visits are those visits required per protocol. The protocol specifies that, after Screening and Enrollment visits, follow-up visits occur at Treatment 1, Follow-up Phone Assessment, Treatment 2, Final Clinic Visit, and Follow-up Phone Assessment/Termination Visit. All scheduled follow-up visits are pre-assigned a visit code for purposes of data management as described in Section 13 of this manual.

Interim Visits are those visits that take place between scheduled visits. More specifically, a visit is considered an interim visit when a participant presents for additional procedures or assessments beyond the required procedures for a scheduled visit. There are a number of reasons why interim visits may take place (see protocol Section 7.8). Site staff may be required to assign visit codes to interim visits for purposes of data management as described in Section 13 of this manual.

Additional information related to the scheduling and conduct of scheduled and interim visits is provided in the remainder of this section.

6.3 Follow-up Visit Scheduling

6.3.1 Target Visit Dates

Enrolled participants will be scheduled to complete five follow up visits: three in-clinic visits and two follow-up phone calls during the course of the study. For MTN-007, randomization is the effective point of enrollment and enrollment is considered Day 0. Targeted visits dates are based on the day the previous visit was completed. Please refer to the data collection section of this SSP (Section 13) for further details.

The MTN Statistical and Data Management Center (SDMC) will provide each site with a visit scheduling tool that can be used to generate follow-up visit schedules for enrolled participants.

6.3.2 Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the protocol allows for visits to be completed within a visit window. For each required study visit, there is a visit window specifying which study days the visit is allowed to be completed. The study visit windows for MTN-007 are outlined in Section 13 of this manual.

Although the visit windows allow for some flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at specific intervals and every effort should be made to do so. The MTN SDMC will provide the Protocol Team with routine visit adherence reports for purposes of monitoring adherence to the visit schedule.

6.3.3 Visits Conducted Over Multiple Days: “Split Visits”

All procedures specified by the protocol to be performed at a particular follow-up visit ideally will be completed at a single visit on a single day. In the event that all required procedures cannot be completed on a single day, (for example, if the 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. See Section 13 for relevant visit coding and data collection instructions.

6.3.4 Missed Visits

For participants who do not complete any part of a scheduled visit within the visit window, the visit will be considered “missed” and a Missed Visit case report form will be completed to document the missed visit. Section 13 gives detailed information regarding the completion of the Missed Visit form.

6.4 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Sections 7.2 through 7.7. Highlighted for reference below are the primary procedural requirements required at each in-person clinic visit (Enrollment/Baseline Evaluation, Treatment 1 Visit, Treatment 2 Visit, and Final Clinic Visit):

- Review/update locator information
- Review/update medical history
- Review/update menstrual history (females only)
- Review/update concomitant medications
- HIV/STI Risk Reduction Counseling
- Urine Pregnancy Test (females of childbearing age only)
- Distribute condoms
- Provide reimbursement for study visit

Additionally, there are further procedures that are completed at certain visits, as follows:

- Document pre-existing conditions (Enrollment)
- HIV pre- and post-test counseling (Final Clinic Visit; only if indicated at Enrollment)
- Protocol Adherence Counseling (Enrollment, Treatment 1 and Treatment 2)
- Product Use Counseling (Enrollment, Treatment 1, and Treatment 2)
- Contraceptive Counseling (Enrollment, Treatment 1 and Treatment 2)
- Baseline Behavioral Questionnaire – CASI (Enrollment)
- Phone reporting system (between Treatment 2 and Final Clinic Visit)
- Product Acceptability Questionnaire – CASI (Final Clinic Visit)
- Physical Exam (Enrollment, Treatment 1, and Final Clinic Visit; only if indicated at Treatment 2)
- Rectal Exam (Enrollment, Treatment 1, and Final Clinic Visit; only if indicated at Treatment 2)
- AE Assessment (Treatment 1, Treatment 2, and Final Clinic Visit)
- Dipstick urinalysis (Final Clinic Visit)
- Blood draws
 - Complete blood count (Final Clinic Visit)
 - Complete metabolic panel - BUN, creatinine, ALT, AST (Final Clinic Visit)
 - Syphilis RPR (Final Clinic Visit; only if indicated at Enrollment)
 - HIV-1 serology (Final Clinic Visit; only if indicated at Enrollment)
 - Plasma archive (Enrollment)
- Rectal GC/CT by NAAT (only if indicated at Enrollment, Treatment 1, Treatment 2 and Final Clinic Visit)
- Urine GC/CT by NAAT (only if indicated at Enrollment, Treatment 1, Treatment 2, and Final Clinic Visit)
- Rectal swabs for microflora (Enrollment, Treatment 1, and Final Clinic Visit)
- Rectal sponge for cytokines (Enrollment, Treatment 1, and Final Clinic Visit)
- Normosol-R enema for rectal lavage to collect effluent for epithelial sloughing and fecal calprotectin (Enrollment, Treatment 1, and Final Clinic Visit)
- Anoscopy and rectal biopsies (Enrollment, Treatment 1, and Final Clinic Visit; only if indicated at Treatment 2 visit)
- Flexible sigmoidoscopy and rectal biopsies (Enrollment, Treatment 1, and Final Clinic Visit)
- Administration of study product (Treatment 1 and Treatment 2)
- Collection of used and unused study product (Final Clinic Visit)

There will also be two follow-up phone assessments: one completed within 24 hours after the Treatment 1 Visit and the other completed within 14 days of the Final Clinic Visit. The purpose of both follow-up phone assessments is to inquire about any possible adverse events the participant may experience as a result of study product use, application or procedures performed.

6.5 Follow-up Visit Locations

All visits will be conducted at the site clinics. No study specific assessments may be completed off-site. The exceptions to this are the Follow-up Phone Assessment and the Follow-up Phone Assessment/Termination Visit. Site staff will contact the participant to evaluate if the he or she has experienced any adverse events.

6.6 Study Product Supply/Dispensing during Follow-up

Because of the nature of the short dosing period and follow-up in MTN-007, there will be no routine product re-supplies. Participants will receive an in-clinic dose at the Treatment 1 Visit as well as an 8-day supply of study product at the Treatment 2 Visit. The supply of study product at the Treatment 2 Visit encompasses the full dosing for this study (7 days) plus one extra applicator. Product re-supply will occur only in the event of lost or damaged product that must be replaced. For complete details of study product dispensing please see Section 9 of this manual.

6.7 HIV Testing during Follow-up

In addition to HIV testing at screening, another HIV test will be done at the Final Clinic Visit. The algorithm to be followed for this final test can be found in Appendix II of the protocol. Full information on the procedural and documentation requirements of the algorithm and the processing of the HIV test can be found in Section 12 of this SSP.

6.8 Modified Follow-up Procedures

Participants who permanently discontinue study product will not routinely be withdrawn from the study. Rather, every effort will be made to complete all protocol-specified visits and procedures with these participants with the following exceptions.

6.8.1 Participants Who Become Infected with HIV

Participants who become infected with HIV after enrollment will be maintained in follow-up. All participants who become infected with HIV will be counseled and referred to available sources of medical and psychosocial care and support, as well as to any available research studies for HIV-infected persons. For any participants who become HIV-infected and also become pregnant during follow-up, every effort will be made to facilitate access to interventions such as single-dose nevirapine to reduce the probability of HIV transmission to the participant's infant. Study staff will capture seroconversions on study case report forms (CRFs).

While in scheduled follow-up, all protocol-specified study procedures will continue to be conducted for HIV-positive participants, with the following exceptions:

- After HIV infection is confirmed per the algorithm and the participant's enrollment plasma specimen has been tested for evidence of HIV infection, if applicable, HIV testing will be discontinued.
- Provision of study product (product use will be permanently discontinued). Site staff will make every effort to recover any unused study product immediately after the site becomes aware of the participant's HIV status.
- Protocol and Product Use Adherence Counseling

- Counseling for HIV/STI risk reduction will be modified to address primary and secondary HIV/STI prevention for infected individuals.
- Anoscopy (unless clinically indicated)
- Flexible sigmoidoscopy (unless clinically indicated)

6.8.2 Participants Who Become Pregnant

Participants who become pregnant after enrollment will be maintained in follow-up. Participants who are pregnant at the Final Clinic 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).

While in scheduled follow-up, all protocol-specified study procedures will continue to be conducted for pregnant participants, with the following exceptions:

- Provision of study product (product will be permanently discontinued)
- Protocol and Product Use Adherence counseling
- Rectal Exam
- Anoscopy (unless clinically indicated)
- Flexible Sigmoidoscopy (unless clinically indicated)
- Anorectal swabs
- Qualitative hCG
- Contraceptive counseling

For all participants who become pregnant, regardless of study treatment group, a Pregnancy Report and History case report form must be completed to report the pregnancy. A Pregnancy Outcome case report form also must be completed to document the outcome of the pregnancy. Certain pregnancy outcomes also must be reported on Adverse Experience Log case report forms (see Section 13.6) and/or in the DAIDS Expedited Adverse Event Reporting System, as described in Section 11 of this manual. Whenever possible, pregnancy outcomes should be ascertained based on medical records or other written documentation from a licensed health care practitioner. When medical records cannot be obtained outcomes may be ascertained based on participant report.

6.8.3 Participants Who Voluntarily Discontinue Study Product

Participants who voluntarily discontinue study product after enrollment will be maintained in follow-up. Protocol-specified procedures will continue except:

- Provision of study product
- Protocol and Product Use Adherence counseling
- Anoscopy (unless clinically indicated)
- Flexible sigmoidoscopy (unless clinically indicated)

6.8.4 Participants Discontinued from Study Product by the Site Investigator

Participants who are discontinued study product by the discretion of the Site IoR after enrollment will be maintained in follow-up. All protocol-specified study procedures will continue except:

- Provision of study product (product will be permanently discontinued)
- Protocol and Product Use Adherence counseling
- Anoscopy (unless clinically indicated)
- Flexible sigmoidoscopy (unless clinically indicated)

6.9 Participant Transfers

The transfer of participants is not expected to occur in MTN-007, but the following instructions are provided should the rare participant transfer occur.

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.

- Upon identifying a need for a participant transfer, the transferring site will notify the receiving site as well as the MTN CORE (FHI), MTN SDMC, MTN NL and MTN Pharmacy Affairs.
- The MTN CORE (FHI) will provide further guidance for the transfer to the involved sites.

6.10 Study Exit Considerations

Procedural requirements for conducting study exit visits are specified in protocol Section 7. Further procedural guidance is incorporated in the Follow-up Phone Assessment/Termination Visit checklist in Section 7 of this manual. Provided in the remainder of this section is additional information related to key aspects of study exit visits.

6.10.1 Final Study Contacts

Although the Follow-up Phone Assessment/Termination Visit is the last scheduled study visit, a final contact may be required afterwards to provide the participant with his or her final study test results, post-test counseling, and treatment, if needed. Additional contacts also are required for:

- Participants with certain types of AEs that are ongoing at study exit
- Participants who are pregnant at study exit

Participants with positive or indeterminate HIV Western blot (WB) or Immunofluorescent antibody (IFA) 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.

6.10.2 HIV Counseling and Testing

HIV testing is performed at the Final Clinic Visit per the algorithm. If the WB or IFA is positive or indeterminate, additional specimen collection and testing will be required to clarify or confirm the participant's HIV status; therefore, additional visits may be required after the Final Clinic Visit. HIV pre- and post-test counseling provided at the Final Clinic Visit or the Follow-up Phone Assessment/Termination Visit should emphasize that additional counseling and testing will be provided to the participant after his or her Final Clinic Visit or Follow-up Phone Assessment/Termination Visit, if needed, to clarify or confirm his or her HIV status.

6.10.3 Study Product Completion (Gel Participants Only)

All participants randomized to receive gel are expected to complete study product use at the Final Clinic Visit. All used and unused study applicators should be collected from the participant and returned to the study clinic on the day of collection. Clinic staff will count the number of used and unused study applicators returned at the Final Clinic Visit and complete a Study Product Returns (SPR) case report form. In addition, clinic staff should add the participant's PTID to a cumulative listing of participants who have exited the study, which should be provided to pharmacy staff on a weekly basis.

Participants should be reminded to bring all used and unused product supplies to their Final Clinic Visit. In most cases this will only be 1 unused applicator and 7 used applicators returned. For participants who do not bring all used and unused supplies to their Final Clinic Visits, arrangements must be made to collect the remaining supplies as soon as possible. If the study product is not collected within five working days after the Final Clinic Visit, the MTN-007 Protocol Safety Review Team (PSRT) must be informed, using the PSRT Query Form. When informing the PSRT, please describe the reason for the product hold (i.e., study exit), actions taken to try to collect the unreturned study product, and plans and timelines for further action to collect the product.

6.10.4 AE Management and Documentation

All AE Log forms completed for each participant should be reviewed at the Final Clinic Visit as well as the Follow-up Phone Assessment/Termination Visit and updated as needed. For AEs that are ongoing at the last phone call (Follow-up Phone Assessment/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-faxed to SCHARP DataFax.

For any serious or expedited AEs (SAEs/EAEs) that are continuing at a participant's Follow-up Phone Assessment/Termination Visit, the IoR/designee must establish a clinically appropriate follow-up plan for the AE (see Section 11.1 of this manual for more information on SAEs and EAEs). At a minimum, the AE must be re-assessed by study staff 30 days after the participant's Follow-up Phone Assessment/Termination Visit; additional evaluations also may take place at the discretion of the IoR/designee. The same approach must be taken for any AEs that are found to have increased in severity at the Follow-up Phone Assessment/Termination Visit. It is recommended that AE follow-up plans be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-9.

For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date. The MTN-007 PSRT may advise study staff as to whether any additional follow-up may be indicated on a case by case basis.

For AEs that are re-assessed after the participant's Follow-up Phone Assessment/Termination Visit, information on the status of the AE at the time of re-assessment will be recorded in source documents only. No updates should be made to AE Log case report forms based on the re-assessments. All information related to the re-assessment of AEs should be documented in the participant's chart notes, including all efforts to contact the participant.

6.10.5 Referral to Non-Study Service Providers

After completing their final study contacts, participants will no longer have routine access to services provided through the study, such as health care and HIV counseling and testing. Participants should be counseled about this, ideally before and during their Final Clinic Visits and Follow-up Phone Assessment Visits/Termination 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 that can be used when discussing this issue with exiting participants, as well as written referral sheets that can be given to participants at their Final Clinic Visit (Note: the sample scripts and referral sheets must be approved by each site's IRB/EC before they can be used).

6.10.6 Post-Study Contacts

It is expected that all participants will be re-contacted by study staff approximately three to nine months after study completion, when it is expected that study results will be available for dissemination to participants.

To facilitate post-study contact with participants, locator information should be actively reviewed and updated at all Follow-up Phone Assessment/Termination Visits, and participants should be counseled to contact the study site should their locator information change after exiting the study. 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.