Section 5. Participant Follow-up

This section provides information on requirements and procedures for participant follow-up in MTN-014. Examples of visit checklists detailing the protocol-specified procedures that must be completed at MTN-014 study visits are available on the MTN-014 Study Implementation Materials webpage: http://www.mtnstopshiv.org/node/4665

5.1 Study Follow-up Plan and Participant Retention Targets

Once enrolled, each participant will remain in follow-up for approximately 10-20 weeks (depending on her menses schedule).

As this is a short-term Phase 1 study, a retention rate of 100% is targeted for each study visit. An average overall retention rate of 95% is targeted. Further information on retention definitions and procedures for MTN-014 is provided in Section 6 of this manual.

5.2 Types of Follow-up Visits

Scheduled Visits are those visits required per protocol. The protocol specifies that, after Screening, participants will have 2 Period Initiation visits, followed by 2 weeks of product administrations visits (Directly Observed Dosing (DOD)) for each period, and 2 Period End visits. In between periods she will return for a Washout Visit. Lastly, she will have 2 safety phone calls, approximately 7 days following the Period End visits. See section 5.3.1 below.

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 (for administrative or product related reasons, in response to AEs, for interim counseling and testing, etc). Site staff may be required to assign visit codes to interim visits for purposes of data management as described in Section 10 of this manual.

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

5.3 Follow-up Visit Scheduling

5.3.1 Target Visit Dates and Visit Windows

For MTN-014, assignment of the MTN-014 Randomization Envelope is the effective point of enrollment and the enrollment visit is considered Day 0. For each participant, follow-up visits are targeted to take place based on the participant's enrollment date and scheduled around a participant's menstrual cycle. Enrolled participants will have the following scheduled visits in MTN-014:

Visit 1	Screening Visit	≤ 42 days prior to enrollment
Visit 2	Enrollment/Study Product Administration Visit/Initiate Period 1	Day 0
Visits 3-15	Study Product Admin Visits (DOD)	13 consecutive days following Visit 2
Visit 16	Period 1 End Visit	Day 14 (Two weeks following Visit 2)
	Safety Phone Call	Day 21 (One week following Visit 16)
Visit 17	Washout Visit	Day 35 (Three weeks following Visit 16)
Visit 18	Study Product Admin Visit/Initiate Period 2	Day 56-119 (Approximately, three weeks following Visit 17)
Visits 19-31	Study Product Admin Visits (DOD)	13 consecutive days following Visit 18
Visit 32	Period 2 End/Final Clinic Visit	Day 70-133 (Two weeks following Visit 18)
Visit 33	Safety Phone Call/Study Termination	Day 77-140 (One week following Visit 32)

Note: Visit schedule will vary based on the participants menses. Period 1 and Period 2 Initiation Visits should occur approximately 3-7 days after the participant's last day of menses. Amenorrhoeic participants can be scheduled at any time within the visit window. It is suggested that staff contact participants prior to their scheduled Period 1 and Period 2 Initiation Visits as both a reminder and also to confirm that her visit is still on target with her final day of menses.

Acknowledging it will not always be possible to complete follow-up visits on the targeted dates, the MTN-014 protocol allows for visits to be completed within a visit window, if possible. For the Initiate Period Visits, Washout Visit, Period End Visits, and Safety Phone Call/Termination Visits, there are visit windows specifying on which study days the visit is 'allowed' to be completed. If it is not possible to complete the required visit on the target date, the site should complete the visit within the visit window. Study Product Administration Visits (visits 3-15 and 19-31) do not have visit windows as these visits are completed on consecutive dosing days. A complete listing of visit windows is available in Section 10 of this manual.

The MTN Statistical and Data Management Center (SDMC) will provide the site with a visit scheduling tool that can be used to generate follow-up visit schedules for enrolled participants. Every effort should be made to schedule participants within the timeframes as specified above.

5.3.2 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 (e.g., because 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. When this occurs, the visit is considered a split visit. As described in Section 10 of this manual, all case report forms completed for a split visit are assigned the same visit code (even though the dates recorded on the case report forms may be different).

NOTE: Study Product Administration Visits cannot be split because of the required consecutive daily schedule. In addition, PK/PD specimens should always be collected on the target day (14 days post product initiation) to avoid complicating interpretability. If it is not possible to do so, the site should contact the MTN-014 Management Team as soon as possible for guidance on the next best time to schedule the participant for that visit.

5.3.3 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 10 gives detailed information regarding the completion of the Missed Visit form.

If a participant does not attend a Study Product Administration Visit in the clinic, and inserts the unobserved dose at home, this is still considered a missed visit and the Missed Visit form should be completed. In addition, if the dose was inserted at home, it should be documented on the Directly Observed Dosing form. In this instance, if the participant reports an adverse event via telephone, the site should still document the missed visit on a Missed Visit form and also document the adverse event on the AE log form (with the same visit code as the missed visit marked in item 10).

5.4 Follow-up Visit Locations

All visits are expected to be conducted at the site clinic.

5.5 Study Product Supply/Dispensing during Follow-up

One applicator of study product will be dispensed daily at each Study Product Administration Visit. In addition, 2 extra applicators of study product will be dispensed at the Period 1 and 2 Initiation Visits (Visit 2 and Visit 18). Record these doses on the Product Dispensation and Returns CRF. In the event that a participant is unable to return to the clinic for DOD, she will use these extra doses to insert at home. Product replacement will occur only in the event of lost or damaged product that must be replaced. For complete details of study product replacement during follow-up please see Section 7 of this manual.

At Visits 15 and 31, study staff will collect all unused study product (if any) and record the number of unused study applicators returned on the Product Dispensation and Returns CRF. If the participant forgets to bring unused study product to these visits, she should be reminded to return product at the Period End Visits. Site staff will determine if the participant remains eligible for continued study product use per protocol specifications. Protocol Section 9 lists conditions under which participants should be discontinued from study product use, either temporarily or permanently. Furthermore, prior to initiating product for Period 2 (Visit 18) the PSRT must be consulted regarding product use management for any participant who has unresolved abdominal or genital (pelvic or anorectal) AEs of any grade, or unresolved Grade 3 or 4 AEs. The site Investigator of Record (IoR) is responsible for ensuring that these protocol specifications are followed for all participants.

The MTN-014 Prescription will be used by clinic staff to communicate the study product to be supplied to each participant at the Enrollment/Study Product Administration Visit/Initiate Period 1 and at the Study Product Administration/Initiate Period 2 Visit (Visit 18). The MTN-014 Study Product Request Slip will be used by clinic staff to dispense 1 applicator of study gel at Study Administrative Visits (3-15 and 19-31) and to communicate to the pharmacy if study product needs to be re-placed at any visit as needed. The Study Product Management Slip will be used to communicate to the pharmacy if product use needs to be held, resumed, or discontinued.

5.6 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Section 7 and Appendix I. Further guidance on completing protocol-specific follow-up procedures is incorporated into visit checklists and the sections below.

5.7 Directly Observed Dosing

At Study Product Administration Visits (2-15 and 18-31), clinic staff will directly observe participants insert study gel in the clinic at approximately the same time of day as all other daily doses. No curtain or alternative method of privacy should be used, as it is important for the site staff to directly observe the gel insertion. Alternatively, site staff may insert the gel for the participant if preferred by the participant and/or if the participant is having difficulty with insertion.

5.8 Follow-up Procedures for Participants Who Become Pregnant

Participants who become pregnant after enrollment will be permanently discontinued from study product and they will be terminated from the study. Participants who are pregnant at their scheduled termination visit will continue to be followed only to ascertain the pregnancy outcome (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained).

5.9 Follow-up Procedures for Participants Who Become Infected with HIV

Participants who become infected with HIV after enrollment will be counseled and referred for available sources of medical and psychosocial care and support. Participants will be permanently discontinued from study product and they will be terminated from the study. RNA and HIV drug resistance testing will be done on those participants if clinically indicated, per discussion between the site IoR and the MTN Laboratory Center.

5.10 Modified Follow-up Procedures for Participants Who Permanently Discontinue Product

Participants who are permanently discontinued from study product, for any other reason other than HIV seroconversion and pregnancy, may be terminated from the study by the site IoR, after consultation with the PSRT. Follow-up of AEs should continue until resolution or stabilization, per Section 8 of this manual. If the site IoR decides to allow the participant to continue in the study, despite being permanently discontinued from study product, the following study procedures will not be conducted:

- Study Product Administration Visits and procedures
- Provision of study product, product use instructions and product adherence counseling
- PK/PD/mucosal gene expression microarray, histology, and proteomics specimen collection
- Pelvic and rectal exams (unless these are needed to follow-up on AEs)

5.11 Directly Observed Dosing Assessment Questionnaire

The Enrollment DOD Assessment (EDE-1) CRF and the DOD Assessment (DE-1) CRF are interviewer-administered questionnaires conducted with study participants at Enrollment and Period End Visits, respectively. Ideally, the staff person administering the questionnaires will not be the same person observing DOD during follow-up. The Enrollment DOD Assessment should occur prior to the participant inserting her first dose.

During the interviews, the interviewer will provide brief synopses of the participants' responses in chart notes for those items that require response codes. Site staff should also document in chart notes any additional participant comments or suggestions related to the DOD experience beyond what is asked on the CRF. When conducting the questionnaire, staff may find it helpful to audio-record the participant's responses to aid in the completion of the questionnaire itself. Together with the chart notes taken during the interview, site staff may use the audio-recordings, if available, to complete these items on the CRF after the participant has left. Site staff should also utilize the SCHARP provided Response Code List as a reference to ascertain and document participant responses.

As with all study-related documents, the audio-recordings of the DOD Assessments should be confidentially maintained along with her study records. Once the staff person transcribes notes from the audio-recording, either directly onto the CRFs or in chart notes, the audio file should be erased/destroyed.

5.12 Biopsy Procedural Counseling

All participants will undergo biopsy collection. Prior to biopsy collection, biopsy procedural counseling will be conducted. See Section 12 of this manual for counseling and documentation requirements.

5.13 Product Use Instructions, Product Adherence, and Protocol Adherence Counseling

See Section 7 of this manual for guidance on product use instructions. See Section 12 of this manual for product and protocol adherence counseling and documentation requirements.

5.14 Prohibited Practices

Protocol section 6.7 lists prohibited practices. See Section 12 of this manual for counseling and documentation requirements.

5.14 Visit Checklists

The visit checklists included in the MTN-014 Study Implementation Webpage are designed to guide site staff in proper study procedures as well as to serve as source documentation of procedures performed at study visits. Note, however, that checklists alone may not be sufficient for documenting all procedures. For example, chart notes may be required to:

- Explain why procedures in addition to those listed on a checklist were performed
- Explain why procedures listed on a checklist were not performed
- Document procedures performed at interim visits
- Document the content of counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements)

See Section 3 of this manual for detailed information on source documentation requirements. Tips for completing visit checklists in accordance with these requirements are as follows:

- Enter the participant identification number (PTID) and visit date in the top section of each checklist. If information is written on the front and back of the checklist, enter the PTID and visit date on both sides.

- For screening visits, enter the screening attempt number in the top section of the checklist.

- For interim visits, enter the visit code in the top section of the checklist.

- Enter your initials only beside the procedures that you perform. Do not enter your initials beside procedures performed by other staff members. If other staff members are not available to initial checklist items themselves, enter, initial, and date a note on the checklist documenting who completed the procedure, e.g., "done by {name}" or "done by lab staff."

- If all procedures listed on a checklist are performed on the date entered in the top section of the form, the date need not be entered beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item.

- If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why on the checklist (if not self-explanatory); initial and date this entry.

5.14.1 Sequence of Procedures

The sequence of procedures presented on the visit checklists is a suggested ordering. In consultation with the MTN LOC (FHI 360), site staff may modify the checklists to maximize the efficiency of site-specific study operations. The site may alter the sequence of procedures to suit local staffing and logistical requirements, with the following exceptions:

- Informed consent for screening and enrollment must be obtained before any screening procedures are performed. Screening procedures are listed in protocol Sections 7.1.

- On the day of enrollment, random assignment must take place **after** collection of blood for plasma archive, and final confirmation of eligibility.