

Section 6. Participant Follow-up

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

6.1 Study Follow-up Plan and Participant Retention Targets

Each enrolled participant will be followed through week three post enrollment. The target accrual is expected to be completed within 14 months. The protocol team will actively monitor and manage the study accrual process to ensure that the enrollment plan occurs.

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. Further information on MTN 004 retention definitions and procedures is provided in Section 8.

6.2 Types of Follow-up Visits

Throughout the study follow-up period, two types of follow-up visits may be conducted:

- **Scheduled visits** are those visits required per protocol. The protocol specifies that follow-up visits occur on a weekly basis. Within the category of scheduled visits, the term “weekly visits” is used to refer to those visits scheduled to take place in follow-up at Weeks 1, 2, 3. All scheduled follow-up visits are pre-assigned a visit code for purposes of data management as described in Section 14.
- **Interim visits** are those visits that take place between scheduled visits. There are a number of reasons why interim visits may take place (see protocol Section 7.6.8). Site staff may be required to assign visit codes to interim visits for purposes of data management as described in Section 14.

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 three follow-up visits. For each participant, follow-up visits are targeted to take place on a weekly basis for three weeks from the participant’s enrollment date. Each participant’s enrollment date is defined as the date upon which she is assigned an MTN 004 Clinic Randomization Envelope (or an MTN 004 Replacement Envelope, for replacement participants). For example, for a participant assigned an envelope on 16 September 2008, follow-up visits will be targeted to take place on 23 September, 30 September, and 07 October. The One-Week and Two-Week Clinic Visits have a visit window of one day prior to through one day after the target date. The Three-Week Clinic Visit has a visit window of one day prior to through three days after the target date. If the target date falls on a Friday and is missed, site staff should make every effort to schedule the visit on the following Monday.

6.3.2 Targeted Phone Call

Enrolled participants will complete a phone assessment at targeted Day 2 Post Enrollment. If it is not possible to conduct the phone assessment Day 2 post enrollment, the assessment can be done 2-4 days post enrollment.

6.3.3 Target Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, each follow-up study visit and telephone assessment has a visit window around the target date (i.e., \pm one day before or after the target date for the Day-2 Phone Assessment, One-Week and, Two Week Clinic Visits, and, \pm one day before or three days after the target date for Three-Week Clinic Visit). Figure 6-1 illustrates the target visit windows for follow-up visits.

Figure 6-1
Target Visit Windows for MTN 004

Screening 1 Visit	Screening 2 Visit	Enrollment Visit	Phone Call	1-Week Clinic Visit	2-Week Clinic Visit	3-Week Clinic Visit
DAY -36 or less	Day -36 or less	DAY 0	Day 2-4	DAY 6-8	DAY 13-15	DAY 20-24

Although the visit windows allow for some flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at one-week intervals, and every effort should be made to do so. Extreme deviation from one-week intervals must be avoided. However, in cases where a participant is unable and/or not available to complete a given scheduled study visit within the window, it is highly preferable to conduct the visit as an “early retained visit” (before the visit window opens) or as a “late retained visit” (after the visit window closes), rather than miss the visit entirely. Such visits should be conducted on a date as close as possible to the visit window. The MTN SDMC will provide the Protocol Team with routine visit adherence reports for purposes of monitoring adherence to the weekly visit schedule (see Section 16).

6.3.3 Incomplete Visits

All procedures specified by the protocol to be performed at a particular follow-up visit 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 because the participant must leave the study site before all required procedures are performed), the study site staff is to make every effort to complete the remaining procedures as soon as possible. *Note:* all Enrollment Visit procedures, with the exception of informed consent and web-based questionnaire, must be conducted on the same day.

6.3.4 Missed Visits

A regularly scheduled follow-up visit is considered “missed” when a participant does not complete any of the required visit evaluations [either as an “on-time retained” visit (within the visit window), an “early retained visit” (before the visit window opens) or a “late retained visit” (after the visit window has closed)], and the next visit window has opened. For example, a participant completed her One-Week Visit and then did not return to the clinic until the day her Three-Week visit window opened. She did not complete the Two-Week Visit during the Two-Week visit window, and did not complete the visit as an “early retained visit.” The Three-Week visit window has already opened, so she cannot make up the Two-Week Visit as a “late retained visit.” Therefore, the Two-Week Visit is considered “missed.” A Missed Visit case report form will be completed to document the missed visit (see Section 14). Additionally, clinic staff will document the missed visit in the participants’ chart notes and forward a copy of the signed, dated, chart note to the Pharmacy.

It is imperative that site staff conduct any procedures from the missed visit at the participant’s next study visit. For example, if a participant misses her Two-Week Visit, she should complete all Three-Week visit procedures at her Three-Week Visit, as well as any additional procedures missed at the Two-Week Visit (e.g., PK draw (SPL 7013 blood draw)), and completion of the Study Gel Adherence and Acceptability Assessment CRFs).

6.3.5 Follow-up Visit Scheduling Scenarios

Presented in Section Appendix 6-1 are several follow-up visit scenarios that may occur during MTN 004. These scenarios illustrate that the target visit windows impact whether a completed visit will be considered an “on-time retained” visit or an “early or late retained” visit. The examples also illustrate the complexities that may be encountered when scheduling and completing study follow-up visits in a “real world” setting. Given these complexities, all sites are encouraged to use Participant Visit Tracking Sheets similar to the example in Section Appendix 6-2 for each enrolled participant.

6.4 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Section 7 and protocol Appendix I. Highlighted for reference below are the primary procedural requirements:

- Urine pregnancy testing is done at every contact
- Colposcopy is done at Enrollment and Two-Week Clinic visits, and may be done at all other visits if clinically indicated
- Blood draws are conducted at Screening visit 1, Enrollment, One-Week, and Two-Week visits
- A Phone Call is conducted on Day 2 - 4
- In addition to the screening behavioral assessment, there are 5 different behavioral measures:
 - Baseline Behavioral (web-based) done at Enrollment
 - Adherence Assessment (CRF), done at One-Week and Two-Week Visits
 - Acceptability and Adherence Assessment (web-based) done at Two-Week Visit
 - Acceptability Questionnaire (CRF), done at the Two-Week Visit
 - Study Burden Questionnaire (web-based), done at the Three-Week Visit

- Abdominal exams and pelvic exams (with concomitant medication review) should be performed at all follow-up visits, and, when clinically indicated, at any interim follow-up visits.

In the event that any study procedures do not take place on the date of the visit (for example, if a woman is menstruating at the time of her One-Week Clinic Visit), those procedures should be completed as soon as possible, as part of a “split” visit. If the participant is unable to make up the missed procedures prior to the opening of her next study visit window, site clinic staff should make up the procedures at the next study visit.

6.5 Follow-up Visit Locations

All visits must take place on-site.

6.6 Study Gel Re-Supply During Follow-up

Steps will be taken at follow-up visits to determine whether a participant remains eligible for continued study gel use per protocol specifications. Protocol Section 9.4 and Protocol Appendix II lists conditions under which participants should be discontinued from study gel use, either temporarily or permanently. The site Investigator of Record (IoR) is responsible for ensuring that these protocol specifications are followed for all participants.

Section 9 of this Study-specific Procedures Manual contains detailed information on site clinic staff procedures for the dispensation of study gel, as well as the return of unused study gel supplies.

6.7 Procedures for Participants Who Discontinue Product

Regardless of the participant retention methods undertaken at each study site, participants may voluntarily withdraw from the study for any reason at any time.

Protocol Section 9.4 specifies procedures for participants who discontinue study gel use. Participants who discontinue study gel because of safety concerns or who become pregnant will be encouraged to remain in the study if they are willing, for safety evaluations according to the study follow up schedule, except no study gel will be dispensed. Study pharmacy staff must be informed of the product discontinuation in writing using the Study Gel Request Slip.

6.7.1 Modified Follow-up Procedures for Participants Who Become Pregnant

Participants who test positive for pregnancy after enrollment/randomization will be maintained in follow-up according to their original study follow-up schedule until their study exit date, or until such time that the protocol team decides to enroll another participant to replace her in the study. All protocol-specified procedures will continue except for study gel administration. In addition, a post-study contact will be completed to ascertain the participant’s pregnancy outcome. The site IoR will report the pregnancy to the PSRT.

Study pharmacy staff must be informed of the product hold in writing using the Study Gel Request slip. Clinic staff will attach to the Study Gel Request Slip a signed, dated chart note documenting the participant's pregnancy. Study gel supplies previously dispensed to the participant must be retrieved as soon as possible after pregnancy is confirmed, and a Product Hold/Discontinuation case report form must be completed and transmitted to the SDMC.

For all participants who become pregnant, a Pregnancy Report and History (see Appendix 6-5) form must be completed to report the pregnancy. A Pregnancy Outcome 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 14) and/or DAIDS Expedited Adverse Event Forms.

6.7.2 Premature Study Discontinuation for an Individual Participant

Under some circumstances it may be appropriate for the investigator to prematurely discontinue a participant from study participation. These are:

- Failure to attend two consecutive clinic visits
- Repeated non-compliance with treatment as prescribed including male condom use
- Request by participant to withdraw
- Request of primary care provider if the study is no longer in the best interest of the participant.

Section Appendix 6-1
Follow-up Visit Scheduling Scenarios for MTN 004

<p>6-1.1 Suppose Miss X enrolls in the study on September 18. What are the target and visit window dates for her visits at One, Two and Three Week Clinic Visits?</p> <table style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th style="text-align: center;"><u>Target</u></th> <th style="text-align: center;"><u>Visit Window</u></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">Week 1</td> <td style="text-align: center;">September 25</td> <td style="text-align: center;">September 24-26</td> </tr> <tr> <td style="text-align: center;">Week 2</td> <td style="text-align: center;">October 02</td> <td style="text-align: center;">October 01-03</td> </tr> <tr> <td style="text-align: center;">Week 3</td> <td style="text-align: center;">October 09</td> <td style="text-align: center;">October 08-12</td> </tr> </tbody> </table> <p>Why? Target dates are set every week from the study enrollment date. The target visit window for the One and Two Week Clinic Visits is \pm one day from the target date, and is – one day and + three days from the Week 3 Visit target date.</p>		<u>Target</u>	<u>Visit Window</u>	Week 1	September 25	September 24-26	Week 2	October 02	October 01-03	Week 3	October 09	October 08-12
	<u>Target</u>	<u>Visit Window</u>										
Week 1	September 25	September 24-26										
Week 2	October 02	October 01-03										
Week 3	October 09	October 08-12										
<p>6-1.2 Suppose Miss X has her Week 1 visit on September 28. What are the target and visit window dates for her visits at Two and Three Week Clinic Visits?</p> <ul style="list-style-type: none"> • Same as above in 6.1.1 <p>Why? Target dates always remain linked to the enrollment date. Target dates do not shift when a previous visit does not take place on the target date.</p>												
<p>6-1.3 Suppose Miss X does not have her Two-Week Clinic visit on the target date of October 02, but presents to the study site on October 4. What do you do?</p> <ul style="list-style-type: none"> • Conduct a Two-Week Clinic visit, per protocol, on October 04. <p>Why? Even though Two- Week window has closed, the Three-Week window has not yet opened. Therefore, the Two-Week visit should be conducted and will be considered as “late retained.”</p>												
<p>6-1.4 Suppose Miss X completes her One-Week Clinic visit on time but then does not present to the study site again until October 8. What do you do?</p> <ul style="list-style-type: none"> • On October 8 (the day the Three-Week visit window opens), consider the Two-Week visit missed; complete a Missed Visit form and fax it to SCHARP. • On October 8, conduct a Three-Week visit per protocol. Also perform any additional procedures from the missed Two-Week visit that are not already done as part of the Three-Week visit procedures and data collections. • If the participant reports an AE that requires clinical follow up, schedule a non-study, post-termination clinic visit to follow-up on the AE. Continue to follow-up on the AE until it resolves or stabilizes. <p>Why? The Two-Week visit window closed on October 03, and the Three-Week visit window opened on October 8. Therefore, the Two-Week visit is considered “missed”. Conduct the Three-Week Visit on October 8; it will be considered “retained” since it is within the Three-Week visit window. In addition, since the procedures for the Two-Week Visit are broader than those for the Three-Week Visit – in particular, the colposcopy, PK, adherence assessment (CRF), acceptability assessment (CRF), and the acceptability and adherence assessment (web-based)– these also must be done to at the Three-Week visit to maintain the integrity of the data collection for study endpoint analysis.</p>												

6-1.5 Suppose Miss X completes her One-Week Clinic visit on September 25 and then presents to the study site complaining of genital pain and irritation on September 28. What do you do?

- Conduct an interim visit on September 28, if the participant is able and willing
- On September 28, complete a urine pregnancy test per protocol section 7.6.8
- Schedule participant for colposcopy, if clinician deems necessary
- Complete a Follow-up Genital Symptoms form (optional, at discretion of site clinic staff)
- Complete a pelvic exam and any clinically indicated testing in response to the participant's symptoms and observed exam findings
- Provide or refer to appropriate medical care
- Complete the Interim Visit, Follow-up Pelvic Exam, and AE Log CRFs
- Schedule participant for follow up as clinically indicated (i.e., schedule an interim visit if necessary); otherwise re-evaluate at Two-Week visit
- Remind participant of Two-Week visit date already scheduled

Why? The participant has presented during an interim time interval to report an adverse event. The Two-Week visit window has not opened yet, so Two-Week visit procedures are not conducted at this visit. A pregnancy test is required, as are any other clinically-indicated tests to evaluate the participant's symptoms.

Section Appendix 6-2
Sample Participant Visit Tracking Sheet for MTN 004

Participant ID Number	
Participant Enrollment Date	

***Instructions:** The Participant Enrollment Date is defined as the date upon which an MTN 004 Clinic Randomization Envelope (or an MTN 004 Replacement Envelope, for replacement participants) is assigned to the participant. Once the enrollment/randomization date is determined, enter target visit dates and visit windows below. File this sheet with the participant's study chart and update it with scheduled and actual visit information at each visit.*

Follow-up Timepoint	Target Visit Date	Visit Window	Scheduled Visit Date	Actual Visit Date	Pelvic Exam Performed?	Colposcopy Performed?	Safety Labs Performed?
Day 2 Phone Assessment							
Week 1							
Week 2							
Week 3							

***Note:** This tracking sheet is not a source document. Information on this sheet is based on other source documents contained in the participant study chart.*

Section Appendix 6-3
Sample Pregnancy Management Worksheet for MTN 004

PARTICIPANT ID:			
BACKGROUND INFORMATION			
First day of last menstrual period			
Date of positive pregnancy test			
Estimated full term pregnancy dates			
PREGNANCY MANAGEMENT INFORMATION		Mark ✓ When Done	Initials/Date/Comments
1	Pregnancy Report and History form completed and faxed to SCHARP		
2	Pharmacy informed of pregnancy		
3	Product supplies retrieved from participant and returned to pharmacy		
4	Product Hold/Discontinuation form completed (items 1-3) and faxed to SCHARP		
5	Pregnancy outcome and outcome date ascertained, based on: <input type="checkbox"/> medical records or other written documentation from a licensed non-study health care practitioner <input type="checkbox"/> verbal report from a licensed non-study health care practitioner <input type="checkbox"/> participant self-report <input type="checkbox"/> negative pregnancy test performed by study staff <i>(medical records should be obtained whenever possible)</i>		
6a	Pregnancy Outcome form completed and faxed to SCHARP		
6b	If applicable, AE Log form completed and faxed to SCHARP		
6c	If applicable, EAE Report completed and faxed to DAIDS Safety Office and Starpharma		
6d	If applicable, SAE Report completed and faxed to Starpharma		