MTN-020 (ASPIRE) Operational Guidance #9: Product Use End Visits (PUEVs) and Study Exit/Termination Visits

General Reminders

- **Product Use End Visits (PUEVs)** for ASPIRE will take place over the course of 3 months, March-May 2015. All participants will complete a PUEV, even if the participant is temporarily or permanently off product at the time.
    - When a participant comes for her quarterly or semiannual visit during this time period, her PUEV will be conducted. PTID lists will be provided by SCHARP to facilitate PUEV planning.
    - If a participant misses her scheduled PUEV, conduct the PUEV at the next regularly scheduled visit (or as soon as the participant is able). Efforts to complete the PUEV should continue until **25 June 2015,** after which no further study visits will occur.
- **Study Exit Visits (SEVs)** will occur approximately 4 weeks after the PUEV.
    - If a participant misses her scheduled Study Exit Visit, efforts to complete this visit should continue until **25 June 2015**, after which no further study visits will occur.
    - There should be a minimum of 2 weeks between a participant's PUEV and Study Exit Visit.
    - If a participant seroconverted per the protocol HIV testing algorithm prior to the PUEV, she will not be scheduled for a Study Exit Visit (see protocol section 7.5.1). Rather, the PUEV will serve as her Termination Visit.

Visit Procedures

- PUEV and Study Exit visit procedures are outlined in the ASPIRE protocol sections 7.4.2 and 7.4.3, respectively; further guidance is outlined in SSP section 6.10, Appendix 7-1 (Visit Checklists), and this operational guidance document. It is recommended that all sites review current PUEV/Termination visit checklists to ensure these tools are up to date.
- **PUEV visit procedures** are very similar to procedures completed during a *semiannual* visit, with the following differences:
    - Social Influences CRF is administered at PUEV
    - Pap smear and syphilis testing are completed for all participants
    - Ring Worries CRF and PUEV ACASI are completed at PUEV, if the participant has not previously permanently discontinued from study product
    - No study product is supplied and no adherence counseling is conducted.
    - The ring request slip should be marked "PRODUCT USE PERIOD COMPLETED" for all participants who have not previously permanently discontinued study product use.
    - Note that GC/CT and Trichomonas testing are not required, and are only completed if indicated
- **Study Exit Visit** procedures include standard administrative procedures, HIV and

pregnancy testing, HIV/Risk Reduction counseling, behavioral assessment (Study Exit Assessment CRF), vaginal self-swab, interim medical/menstrual history, AE review, and provision of test results (see protocol/SSP for detailed listing of termination procedures).

- The following procedures are unique to the **Termination Visit** (PUEV for prior seroconverters, or SEV for all others):
    - Completion of the Termination Form and End of Study Inventory Form
    - Review of all AE and CM Log Forms to ensure each is closed or marked as 'continuing at end of study participation'
    - Completion of Study Exit Worksheet to ensure preferences for future contact are documented and locator information is updated. Recommend that 'Permission for future contact' log (or other site specific form) is completed to allow easy contact for HOPE.
    - Participant counseling about anticipated timelines for study results/unblinding, and how these results will be communicated; information about HOPE can also be provided (see script for study exit visits).
    - Follow up referrals for ongoing care post-study should be provided as needed
        - For example, for ongoing medical care (ongoing AEs, pregnancy, or HIV care), continued HIV counseling/testing services, or contraceptive access
- After the Termination visit, a 'final contact' may be needed for some participants to ensure test results are provided and/or AEs are followed up as needed. NO CRFs are completed for these final contacts, but these contacts should be documented in the chart notes.

<u>Study Product Considerations</u>

- It is recommended that a complete review of a participant's study product accountability log be done prior to her PUEV. This will allow for an opportunity at PUEV and Study Exit Visits to reconcile any issues identified with the participant before she is exited from the study.
- Note that if a product hold or discontinuation is warranted at PUEV, study product retrieval guidelines in protocol section 6.4.4 apply.
- It is expected that the majority of participants will return their VRs during the PUEV visit (used and unused). All VRs remaining in the participant's possession should be returned by the Study Exit Visit (at the latest).
- If the participant does not bring her remaining VRs (used or unused) to the Study Exit Visit, study staff must arrange to retrieve the VR within 5 business days (see LoA#2). If the study product(s) are not retrieved within that timeframe, the MTN-020 PSRT must be informed.

<u>Considerations for Seroconverters</u>

- As noted above, participants who have seroconverted prior to their scheduled PUEV will not have a Study Exit Visit scheduled. Instead, termination visit procedures will occur at their PUEV.
- Continue with post-seroconversion testing per the protocol-defined schedule using the MTN 020 Seroconverter Schedule tool until the PUEV.
- If a participant seroconverts at the PUEV or is in the middle of algorithm testing at the

time of the PUEV, schedule her for a Study Exit visit.
    - Even if the participant is able to complete algorithm testing prior to the scheduled Study Exit visit, proceed with completion of the Study Exit visit. HIV testing may be omitted from the Study Exit Visit if the participant completed algorithm testing and was determined to be HIV-infected prior to the visit.
- If the participant has positive rapid(s) at her Study Exit visit, do not terminate her on that day.
    - Complete the algorithm and collect all necessary samples, then terminate the participant.
    - Contact the LC using the Query Form if required by the HIV algorithm (Appendix III) or if guidance is needed to complete the algorithm.
    - This participant is still eligible for MTN-015 after exit from ASPIRE since she seroconverted during participation in the parent protocol. Approach for enrollment once algorithm confirms HIV infection per protocol; recommend as soon as possible to avoid loss to follow-up.

<u>Considerations for Pregnant Participants</u>

- For all pregnancies ongoing at termination, pregnancy outcomes must be obtained.
- The only study data that can be collected after termination is pregnancy outcome data, which is recorded on the Pregnancy Outcome CRF.
- Note that if a participant is confirmed pregnant by her Termination visit (2nd positive pregnancy test or meets other definition(s) for confirmed pregnancy), she is still eligible for MTN-016 enrollment.
- For pregnant participants who have a pregnancy outcome of 'unobtainable', consider if they could be recontacted to try to get this outcome information prior to June 25, 2015.

<u>Considerations for Participants with ongoing AEs at Termination</u>

- For AEs that are ongoing at 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 SCHARP DataFax.
- For serious or expedited AEs (SAEs/EAEs) that are continuing at termination, the IoR/designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the SAE/EAE must be re-assessed by study staff 30 days after the participant's termination visit/date; additional evaluations also may take place at the discretion of the IoR/designee. If the SAE/EAE has not resolved or stabilized at the time of re-assessment, continue to re-assess the participant <u>at least once per month</u> up until **June 25, 2015** (while the study is ongoing).
- For AEs that increase in severity at the SEV), reassess, at minimum, 30 days after the participant's termination visit/date. If the AE has not resolved or stabilized at the time of re-assessment, continue to re-assess the participant <u>at least once per month</u> up until **June 25, 2015** (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 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 termination, 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 CRFs based on the re-assessments (see Protocol Section 8.2.1).

Visit Codes and Visit Scheduling

- Assign the PUEV the visit code that corresponds to the follow-up month in which the PUEV is conducted. For example, if the participant's Month 24 visit is conducted as a PUEV, assign the Month 24 visit code (24.0) to the PUEV.
- It is expected that a participant's PUEV will be conducted in a participant's quarterly or semi-annual visit window; however, a PUEV may be conducted as an interim visit if a participant completes a regularly scheduled visit, then returns to complete the PUEV within the same visit window (e.g., a participant completes her regular Month 23 visit then presents later in the Month 23 window to complete her PUEV). If the participant completes her PUEV as an interim visit, assign the PUEV the appropriate interim visit code (23.1 in this example). Refer to SSP Section 14-Data Collection for a complete list of visit codes.
- A participant may complete her PUEV and then withdraw her consent and terminate early from the study. In this case, the Study Exit Visit will not be completed. Site staff should complete the Termination CRF (marking item 2c) and complete the End of Study Inventory CRF. No other CRFs should be completed for the missing Study Exit Visit.
- The PUEV can be conducted as a split visit over multiple days (e.g., if a participant is on menses and would like to delay the pelvic exam until after menses). HIV testing (for non-seroconverters) must occur during the first part of the visit, if the PUEV is split. Interviewer-administered CRFs and ACASI questionnaires must be completed on the same day. As with other split visits, assign the same visit code to all procedures.
- If the subsequent visit(s) of a split PUEV cannot be conducted within the same visit window, continue to assign the same visit code to all PUEV CRFs completed. For example, if a participant completes the first half of her PUEV at Month 30, but is unable to complete her PUEV procedures until after her Month 30 visit window closes, assign ALL PUEV CRFs visit code 30.0, including the procedures/CRFs completed outside the window.
- If additional visit(s) are needed between the PUEV and SEV to follow-up on AEs, and at least one CRF is newly completed, please assign these visits the appropriate interim visit codes based on the PUEV visit code. For example, if the PUEV is conducted at visit 20.0, the interim visits after this (prior to the SEV) should be coded 20.1, 20.2, etc. An interim visit at which no new CRFs are completed should not be assigned a visit code and a VS-1 should not be completed.
- To ensure that we identify any delayed or masked seroconversions, we ask that sites do their best to schedule the SEV no earlier than 4 weeks after the date of the PUEV. If a participant is unable or unlikely to complete her SEV 4 weeks after the PUEV, sites may use their discretion in conducting the Study Exit Visit earlier in the visit window (as early as two weeks after the PUEV) to ensure the visit is completed (better early than missed).
- The SEV window will remain open until the end of the study. Thus, if a site has difficulty scheduling a participant once 4 weeks have passed after the PUEV, site staff should continue to try and schedule the participant for the SEV until they are successful or the study ends on June 25, 2015, whichever comes first. Missed Visit CRFs should be completed for all monthly visit windows that close prior to completion of the SEV.
- If a participant remains lost to follow-up at the study end date of June 25, 2015,

complete a Termination CRF (marking item 2g) and an end of Study Inventory CRF. Refer to SSP Section 6.9.

CRF Completion

- Refer to SSP Section 14-Data Collection for a complete list of CRFs required to be completed at the PUEV and the Study Exit Visit.
- At the PUEV and the Study Exit Visit, complete item 4 on the Visit Summary CRF by marking 'yes' and mark the visit type in item 4a as either "PUEV" or "scheduled termination". Once item 4a is completed, go to item 6. It is not necessary to complete items 5 or 5a, even if the PUEV/early termination/scheduled termination visit has an interim visit code. "Scheduled termination" should only be marked in item 4a on the VS-1 CRF if the Study Exit Visit is completed. If a participant's final study visit is the PUEV, mark "PUEV" in item 4a on the VS-1.
- If a participant's final study visit is the PUEV (e.g., she is a confirmed seroconverter or refuses to complete the SEV), the SEV and all associated procedures (including administration of the Study Exit Assessment CRF) will be skipped. The participant will be terminated once the PUEV has been conducted and a Termination (TM-1) and End of Study Inventory (ESI-1) CRF should be completed. Mark "scheduled exit visit/end of study" as the reason for participant termination in Item 2 of the TM -1 CRF if the participant is a seroconverter and the PUEV serves as her termination visit. Refer to SSP Section 6.10.
- Do not complete a new Product Hold/Discontinuation Log CRF at the PUEV (it is not needed, since completion of the Product Use End Visit (PEV) CRF tells SCHARP that the participant is expected to permanently discontinue study product use at this visit). This is true, even if a participant develops a new or increased severity AE at the PUEV which warrants product hold/discontinuation per protocol.
- For participants with an ongoing product hold at the time of the PUEV:
    - If product is being permanently discontinued due to the PUEV, and not due to the reason for the hold, mark the "no - hold continuing at scheduled PUEV" box for item 4 on the PH Log. In item 4, record the date of the PUEV. If, prior to the participant's study termination, the reason for the hold resolves sufficiently to meet the protocol criteria for product resumption (and product would have been resumed if not for the PUEV), update item 4 with the date of resolution. If, prior to the participant's study termination, the reason for the hold persists or increases in severity to meet the protocol criteria for permanent discontinuation (and product would have been permanently discontinued if it had not already been discontinued at the PUEV), update item 4 to "no (permanently discontinued)" and update item 4 with the date when the reason met protocol criteria for permanent discontinuation.
    - If the reason for the ongoing hold is a reportable AE, and the AE does not meet protocol criteria for permanent discontinuation of study product, do not change the AE Log item 5 response (it should remain "Held"). If, at the PUEV or prior to the participant's study termination, the same AE meets protocol criteria for permanent discontinuation (and product would have been permanently discontinued if it had not already been discontinued at the PUEV), update the item 5 response to "permanent discontinuation". If, at the PUEV or at any time between the PUEV and the participant's Study Exit Visit,, the AE increases in severity or frequency and

warrants reporting of a new AE that meets criteria for permanent discontinuation, complete a new AE Log CRF and mark item 5 “N/A”. Do not complete a new PH Log CRF.

- Review all AE and CM Log CRF at the participant’s study termination to ensure each is closed or marked as ‘continuing at end of study participation’. Review each completed Social Harm log CRF to ensure that a resolution date is provided in Item 7 or that ‘unresolved at end of study’ is marked.

- At the PUEV, administer the Ring Worries CRF only if the participant is discontinuing study product use at her PUEV. For those participants who previously discontinued study product and completed the Ring Worries CRF at the time of product discontinuation, complete the RW-1 CRF by lining through the items and indicating in the white space of the CRF that this form is not required.

ACASI

- At the PUEV, administer PUEV/Discontinuers questionnaire for all participants unless permanently discontinued from product prior to PUEV. On the Follow-up ACASI Tracking CRF, mark item 1b “scheduled PUEV”.
- If the participant already completed her PUEV/Discontinuers questionnaire at the time of permanent discontinuation (prior to her PUEV), do not complete a second questionnaire. Complete a FAT-1 CRF and note on the form that a PUEV/Discontinuers questionnaire was not completed at the PUEV; provide the reason in the Comments section.

Co-Enrollment in MTN-015 or MTN-016

- Participants enrolled in MTN-015 or MTN-016 will not be terminated from either study. Termination from the parent study (ASPIRE) does not affect participation in MTN-015 or MTN-016.

Reminder Related to AE Documentation

- Additionally, all AEs that meet the protocol safety endpoint definitions (related G2, all G3/G4 AEs, and all SAEs) should be reviewed to confirm they were evaluated by qualified and designated staff, and that the relationship status, AE grade, and outcome are accurately documented in the participant record.

All Operational Guidance documents must be printed and filed with regulatory documentation.