MTN-025 (HOPE) Operational Guidance #3:
Reminders and Guidance about HOPE PUEV and Study Exit Procedures

Procedural requirements for conducting PUEV and Study Exit visits are specified in protocol Sections 7.4.3 and 7.4.4; further procedural guidance is provided in SSP Section 6.10, the PUEV/Early Termination/Termination Visit template checklist, and this operational guidance document. 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.

Product Use End Visits (PUEVs)

- PUEVs for all HOPE participants enrolled on or before 15 September 2017 will take place at the Month 12 (Visit 8) study visit. The visit code of the PUEV is 8.00.
    - Note: If the participant completes her PUEV as an interim visit, the PUEV will be assigned the appropriate interim visit code. Refer to SSP Section 14-Data Collection for a complete list of visit codes.
- Participants enrolled between 16 September 2017 and 25 May 2018 will have abbreviated follow-up schedules ending with a PUEV visit around September/October 2018.
- At the PUEV, complete the Follow-up Visit Summary CRF by selecting 'Yes' for the item "Is this visit a PUEV, scheduled Study Exit Visit, or an early termination?" and select the visit type as "PUEV". This option (PUEV) should be selected even if a participant is terminating at the PUEV (i.e. Seroconverters).
- PUEV procedures include most follow-up visit procedures, with the following modifications:
    - HIV prevention Options counseling will be modified to focus on risk reduction plans without the dapivirine ring. Please note that the "End Visit, Month 12" section of the Options counseling flipchart should be used for these sessions. Counselors are also advised to review the corresponding section in the Options counseling manual (pg 34-41) in advance of completing PUEV Options sessions.
    - A physical and pelvic exam are required
    - Testing for GC/CT, Syphilis, and Trichomonas is completed
    - Blood for serum chemistries and CBC with platelets is collected
    - The Behavioral Assessment CRF is administered, including additional questions specific to PUEV visits. Additionally, the Vaginal Practices and Social Influences Assessment CRFs are administered.
    - PUEV/Discontinuers ACASI is completed, if the participant has not previously permanently discontinued from study product. On the ACASI Tracking CRF, select "scheduled PUEV" for the "Reason PUEV/Discontinuers ACASI questionnaire was completed".
        - Note: 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 an ACASI Tracking Y/N CRF and note on the form that a PUEV/Discontinuers questionnaire was not completed at the PUEV; provide the reason in the text field provided.
    - No vaginal rings are offered
    - For participants who ever accepted a ring: Complete vaginal ring request slip for "Product Use Period Completed" and send to pharmacy at PUEV.
        - Note: Do not complete a new Product Hold/Discontinuation Log CRF at the PUEV; it is not needed, since completion of the PUEV CRFs 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 that warrants product hold/discontinuation per protocol.
        - A complete review of a participant's study product accountability log should be done prior to her PUEV. This will allow for an opportunity at the PUEV and/or Study Exit Visit to reconcile any issues identified with the participant before she is exited from

the study. If a participant does not return all rings in her possession by her PUEV, request that she return these by SEV at the latest.

- 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, select "no - hold continuing at scheduled PUEV" for item "Was the participant instructed to resume study product use?" on the PH Log. 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 the date 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 "Was the participant instructed to resume study product use?" to "No - permanently discontinued" and update 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 "Study Product Administration" (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 "permanently discontinued". 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 select "N/A" for item 5. Do not complete a new PH Log CRF.

- If a participant has a positive rapid HIV test at PUEV and:
  - A final HIV positive status is confirmed at PUEV (based on Geenius completed on that day) then scheduling the SEV is not necessary.
  - However, if the participant is confirmed HIV negative, or if her status is not resolved as of the time of PUEV, then then scheduling of the SEV should proceed. 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.
- 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. All applicable eCRFs should be completed within the same visit folder. If the subsequent visit(s) of a split PUEV cannot be conducted within the same visit window, all PUEV CRFs should be completed within the same folder.
- If additional visit(s) are needed between the PUEV and SEV to follow-up on AEs, and at least one CRF is newly completed, the appropriate interim visit codes will be assigned based on the PUEV visit code. For example, interim visits after the V8 – Month 12 visit will be assigned 8.01, 8.02, etc. An interim visit at which no new CRFs are completed should not be assigned a visit code and a Follow-up Visit Summary eCRF should not be completed.

Study Exit Visits (SEVs)

- SEVs will occur approximately 4 weeks after the PUEV except for those participants who have become HIV infected prior to the PUEV (in this case, the participant will be terminated at her PUEV).
- Sites should utilize the SEV visit calculator to determine scheduling of the SEV. The SEV visit calculator is located on the last tab of the excel visit calendar tool.
- To ensure identification of any delayed or masked seroconversions, sites should do their best to schedule the SEV no earlier than 4 weeks after the date of the PUEV. However, if a participant is

unable or unlikely to complete her SEV 4 weeks after the PUEV, sites may use their discretion to conduct 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 or a participant misses her scheduled SEV visit, site staff should continue to try and schedule the participant for the SEV until they are successful or the study ends, whichever comes first.
    - Note: Teams will be notified of the official end of study date by the management team.
- If a participant remains lost to follow-up at the study end date, complete a Termination CRF (selecting "unable to contact participant" for "Reason for termination").
- SEV procedures include most follow-up visit procedures, with the following modifications:
    - No HIV prevention options counseling is completed, however, participants still receive HIV risk reduction counseling per site SOPs
    - No vaginal rings are routinely offered or collected
        - Note: If the participant has outstanding rings in her possession as of the Study Exit Visit, study staff must arrange to retrieve the VR within 5 business days. If the study product(s) are not retrieved within that timeframe, the MTN-025 PSRT must be informed.
    - The Study Exit Assessment (behavioral CRF) is completed
    - Contraceptive counseling only occurs if indicated (note this is recommended per standard of care)
    - Next visit scheduling only occurs if indicated
- At the SEV, complete the Follow-up Visit Summary CRF by selecting 'Yes' for the item "Is this visit a PUEV, scheduled Study Exit Visit, or an early termination?" and select the visit type as "scheduled termination".
- If the participant has positive rapid(s) at her Study Exit visit, complete algorithm testing and additional required sample collection.
    - If the confirmatory test is positive, refer the participant for treatment and complete termination visit procedures on that same day.
    - If the confirmatory test is negative or indeterminate, query the LC as required by protocol and notify the management team for guidance. Do not complete termination visit procedures until her HIV status is finalized.
    - This participant is still eligible for MTN-015 after exit from HOPE 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.
- 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 (selecting "participant refused further participation" as the reason for termination). No other CRFs should be completed for the missing Study Exit Visit.

Termination Procedures

- The following procedures are unique to the **Termination Visit** (PUEV for Seroconverters, SEV for all other participants):
    - Completion of the Termination Form
        - If a participant's final study visit is the PUEV (e.g., she is a confirmed seroconverter or refuses to complete the SEV), please contact SCHARP in advance of her scheduled PUEV (if possible), and SCHARP will manually add the Termination eCRF to the participant's PUEV folder. Select "scheduled exit visit/end of study" as the reason for participant termination on the Termination CRF if the participant is a seroconverter and the PUEV serves as her termination visit.

- Review of all AE and Concomitant Medications Log CRFs to ensure each is closed or marked as "continuing at end of study participation" or "continuing at end of study", respectively.
- Review each completed Social Impact log CRF to ensure that a resolution date is provided or that 'unresolved at end of study' is selected for the item "Record current status".
- Review all AEs that meet the protocol safety endpoint definitions (related G2, all G3/G4 AEs, and all SAEs) 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.
- Ensure that for every vaginal ring dispensed per the Pharmacy Ring Dispensation, there is an associated log line on the Vaginal Ring Tracking Log with the 'stored/not stored' status for that ring completed.
- Ensure all forms (with exception of the Additional Study Procedures Y/N) are completed within the participant's casebook, including the Adverse Experience Y/N and Concomitant Medications Y/N eCRFs.
- Complete documentation of how best to contact for study results, as well as permission to contact for future research, in particular 032/AHA. Template study exit worksheet and permission to contact logs are available on the MTN website under 'study implementation tools'.
- Follow up referrals for ongoing care post-study should be provided as needed

<u>Considerations for Participants with an Ongoing AE at Termination:</u>

- A subset of AEs must be followed after a participant's termination
    1. Ongoing SAE/EAEs at termination
    2. AEs that are found to have increased in severity at termination
- Frequency of Follow-up on this subset of AEs:
    - IoR/designee must establish a clinically appropriate follow-up plan for AEs requiring follow-up
    - At a minimum, re-assess 30 days after SEV
    - Additional evaluations also may take place at the discretion of the IoR/designee
    - Continue to reassess at least once per month while the study is ongoing until resolution or stabilization
    - If the AE has not resolved by study end (i.e., once all participants are exited), these AEs should be re-assessed at least once more within 30-60 days after the study end date
- For AEs that are continuing at the termination visit but do not meet the criteria above, it is left to the discretion of the IoR/designee as to whether the AE needs to be followed. The PSRT can be consulted as needed.
- 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.

<u>Considerations for Pregnant Participants:</u>

- Participants who are pregnant at the SEV 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)
- Offer enrollment into or continue follow-up for MTN-016, as appropriate
    - Note that if a participant should be confirmed pregnant by her Termination visit (2nd positive pregnancy test or meets other definition(s) for confirmed pregnancy), in order to be eligible for MTN-016 enrollment.
- The only HOPE study data that can be collected after termination is pregnancy outcome data, which is recorded on the Pregnancy Outcome CRF.

<u>Preparing for PUEVs/SEVs</u>

In preparation for the first PUEV/SEV visits, site staff should:

- Familiarize themselves with PUEV/SEV CRFs in Medidata MTN-025 TRAIN database.
- Review current PUEV/Termination visit checklists to ensure these are up to date.
- Start to educate and prepare participants beginning at their Month 9 visits (or between Month 9 and PUEV) about their upcoming study exit. To help facilitate this process, the following materials have been developed:
    - **End of Study Messages Power Point**: This slide set is intended for education in group settings with participants or communities, but concepts can also be reviewed on an individual basis as needed. Sites should modify the presentation to include site-specific information where indicated (red font). The slide deck is intended to be adapted for the audience as needed – e.g. sites may choose to break up the slides and deliver in several, shorter sessions, or only cover certain slides as needed (i.e. if questions are raised by participants). In other words, please adapt the materials as needed to optimize their use at your site.
    - **Internal Q&A document**: This is a word document that covers the concepts outlined in the power point presentation in more detail. This is intended for internal staff use only and is not to be distributed to participants.

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