MTN-020 (ASPIRE) Operational Guidance 5:
Additional Clarifications to SSP

This operational guidance to MTN-020 sites is intended to provide updates to the Study Specific Procedures (SSP) Manual, version 1.1. The SSP will be updated with this information in the next revision (scheduled for July 2013).

SSP Section 4.4.2 - Enrollment Procedures

According to Protocol Section 7.3, if a participant is menstruating on the day of enrollment, her entire visit should be rescheduled for two days after the completion of menses. Genital bleeding on the day of enrollment determined not to be menses (e.g. spotting) does not require rescheduling, as long as the participant is comfortable with continuing. Menstruation on the day of enrollment is not one of the formal exclusion criteria for the study and does not pose a safety concern to participants.

SSP Section 6.5.1 - Modified Procedures for Participants Who Become HIV-infected (Have a Positive Western Blot Result)

If LoA#2 is not approved, the PUEV/Discontinuers ACASI, FAT-1 CRF, and the Ring Worries CRF should be completed at the quarterly visit following the visit in which the participant is informed of her HIV-infection/permanent product discontinuation. At all sites, regardless of LoA#2 status, a FAT-1 CRF is completed at the visit in which the participant is informed of her permanent product discontinuation (even if ACASI is not administered per the above) - see Data Communique #7 for more details.

SSP Section 6.5.2 - Procedures for Participants Who Have an Unclear HIV Status (Have a Negative or Indeterminate Western Blot Result)

Note the following additions (in **bold**) and deletions (strikethrough) during the next round of SSP revisions to section 6.5.2. This is to align this text with guidance in Lab Section 13.7.2.

If the participant has a RNA viral load result above the limit of detection, the participant should be counseled that she is probably HIV-infected (see SSP section 12 for further details regarding counseling messages).Repeat Western Blot in about 1 month (at the next MTN-020 scheduled visit) for endpoint confirmation. **When collecting repeat Western Blots, also collect post seroconversion samples (CD4, RNA and plasma storage). Testing for the RNA and CD4 should proceed immediately.** ~~Follow any additional guidance for sample collection from the Network Lab.~~ Document ~~the Western Blot~~ **all** results on a new HIV Confirmatory Results CRF.

SSP Section 6.7 - Modified Procedures for Visits When Product Is Not Dispensed (Participant is on a Clinical Hold/Discontinuation or Refuses to Accept Study Product)

If a participant permanently discontinues from product use at her *Month 3* visit, the PUEV/Discontinuers ACASI is administered at this visit instead of the Month 3 ACASI. As usual, only one FAT-1 CRF is completed at the Month 3 visit, with the PUEV/Discontinuers survey marked (do not document on the FAT-1 that the Month 3 ACASI was not completed).

SSP Section 6.9 - Voluntary Withdrawal/Early Termination

Section 6.9 was initially developed to address situations whereby a participant withdraws consent and decides to terminate trial participation early. Section 6.9 should now apply to any participant who is terminated early from the trial, either per her request (voluntary withdrawal) or due to IoR discretion. As specified in protocol section 9.8, the IoR may withdraw participants from the study to protect their safety and/or if they are unwilling or

unable to comply with required study procedures, in consultation with the PRST. The following guidance should be taken into consideration with regards to IoR decisions to terminate ASPIRE participants from the study who are unwilling/unable to comply with study procedures.

- It is recommended that site IoRs use their discretion with regards to terminating participants who relocate and cannot transfer to another study site, or can no longer come to the clinic, or consistently refuse to accept or use study product and are unlikely to resume study visits or product use after counseling efforts and discussions with appropriate study staff.
    - If participants exhibit actions such as those listed above that indicate they may no longer be interested in study participation, it is recommended that they be offered a meeting with site leadership to discuss their desire to continue participation.
    - When making termination decisions, study teams should weigh the advantages of keeping a participant in the trial against the negative impacts of a participant's poor retention or adherence on the study outcomes and clinic resources.
    - Participant terminations should be viewed as a last resort and utilized only after other options have been thoroughly explored.
    - Site teams are encouraged to discuss particularly challenging participants and potential terminations as a full group, on the available cross-site listservs, and with the study management team, as needed.
    - All discussions, counseling, and decisions about early termination should be adequately documented in the participant's study records. Consultation with the PSRT regarding early terminations per IoR decision should be printed and filed in the participant chart. PSRT consultation is not required for voluntary withdrawals.
    - Site teams are encouraged to review their Retention SOPs to make sure any site-specific procedures are in line with this guidance (e.g. that site teams may consider early termination as one option for participants who permanently relocate). Updates should be sent to FHI 360 for review before finalization.
- For all participants who are terminated early (regardless of reason) and have not been permanently discontinued from study product by the time of early termination, site staff should complete a Vaginal Ring Request Slip to inform the pharmacy that this has happened. The Vaginal Ring Request Slip should be marked "permanent discontinuation" and the specify reason is that the participant is being terminated early.

Note the following text **will be deleted** during the next round of SSP revisions and no longer applies:

~~Withdrawal of consent is the only reason for early termination from MTN-020. For example, if a participant has relocated but has not withdrawn consent, she should not be terminated early, as it is possible her circumstances may change and she may relocate back to the study site area prior to study end. In cases such as this, and other "chronic defaulters", sites should continue to contact/attempt to contact the participant using a modified contact schedule per site retention SOPs. A Missed Visit CRF should be completed for each visit missed up until the study's end date.~~

SSP Section 10.4.2 - Pelvic Exams Conducted at Follow-up

Note the following additions (in **bold**) and deletions (strikethrough) during the next round of SSP revisions:

Follow-up pelvic exams are required semiannually, at the PUEV visit, and when clinically indicated. Pelvic exams are considered clinically indicated when new genitourinary complaints are present, i.e. new bleeding, vaginal discharge, pelvic pain. ~~Per Section 10.6.6, new~~ **New** adverse events for bleeding should prompt a pelvic exam even if the bleeding has subsided by the time of the report. **The need for a pelvic exam in response to other genitourinary complaints that have resolved at the time of the visit is up to clinician discretion. All new symptoms, regardless of resolution date and whether or not a pelvic exam was**

conducted, should be reported as adverse events per section 11.3 of this manual. Pelvic exams must also be performed before resuming use of VR after product hold due to pregnancy.

SSP Section 10.13 - Clinical and Product Use Management

Participants should be advised to remove the vaginal ring prior to a laparoscopic tubal ligation or IUCD insertion procedure. The participant may reinsert the same vaginal ring after completion of the procedure unless, as a result of the procedure, the participant experiences any complications that would prompt a product hold per protocol section 9. All ring outages should be captured on the Ring Adherence CRF completed during the participant's next scheduled study visit. No product hold CRF or pharmacy documentation is required to document these brief removals for the procedure. However, if a new clinical hold is initiated following the procedure due to complications/AEs, the participant's ring should be returned to the study clinic and study staff should complete a Product Hold CRF, a new AE Log form, and a vaginal ring request slip marked "hold" should be sent to the pharmacy. The IoR/designee should follow relevant guidance in protocol section 9 regarding resumption of product use. If for some reason the participant does not want the ring re-inserted (even though the clinician determines it is okay to do so), this is not a product hold but will be captured as an outage on the RA-1 CRF completed at the participant's next visit.

SSP Section 11.3 - Reportable Adverse Events and Terminology

Any abnormal lab, regardless of where the testing took place, should be reported as an AE and documented on the AE Log CRF. Lab result CRFs should only be used to document lab results from protocol specified tests run at site approved labs. Lab results from outside sources should be filed in participant charts as source documentation, if they are available. Even when source documentation from an outside lab is not immediately available, self-reported lab-based AEs (for example, a participant was told by an outside health care provider that she tested positive for gonorrhea) should be captured on the AE Log (and confirmed by on-site testing as soon as possible).

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