

MTN-003 (VOICE) Data Communiqué #3

April 16, 2010

This communiqué is official study documentation for MTN-003. It is considered part of the MTN-003 Study-Specific Procedures (SSP) Manual. Please circulate this communiqué among relevant staff for their review, and print and file a copy in Section 15 of each MTN-003 SSP Manual maintained at your site.

UPDATES

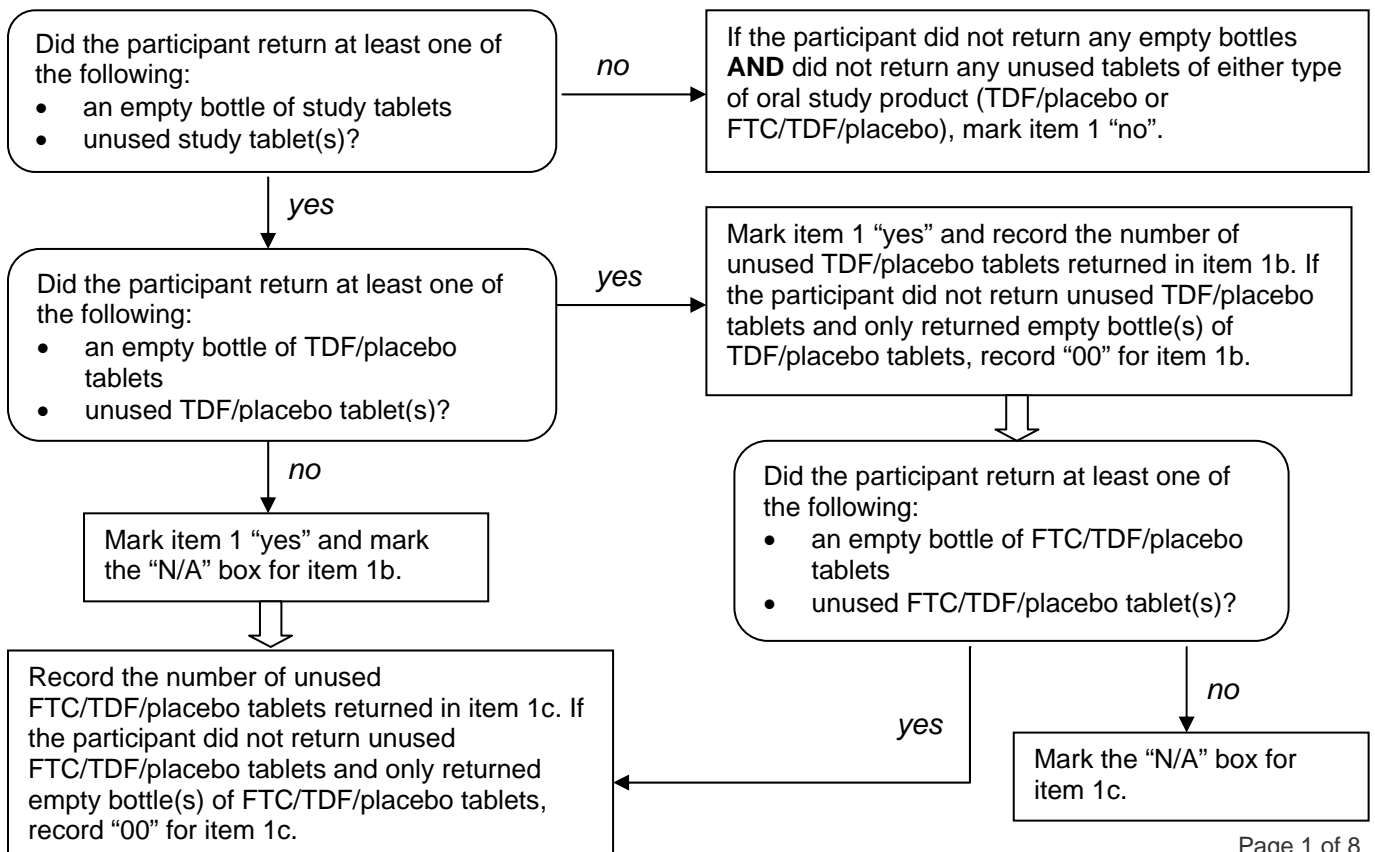
1. SCHARP Staffing Update

Karen Patterson has assumed responsibility as sole SCHARP Project Manager on MTN-003. Please contact Karen (karen@scharp.org or karenp@scharp.org) regarding any questions related to data collection or data management in MTN-003.

2. Documenting Empty Bottle Returns on the Product Returns and Dispensations (PRD) CRF

In response to the recommendation from the Study Monitoring Committee, site staff will now consistently counsel participants randomized to oral product to return previously dispensed **bottles** of study tablets to the site clinic, including any empty bottles (in the event that a participant has used all of the study tablets in a given bottle prior to her next study visit).

To document oral study product returns, complete the Product Returns and Dispensations CRF per the diagram below.



For purposes of consistency in reporting study product counts, SCHARP asks that each site reviews its previously completed Product Returns and Dispensations (PRD) CRFs for participants randomized to oral study product. If item 1 is marked “no”, sites are asked to review available source documentation to determine, if possible, whether or not empty bottle(s) of study tablets were returned at the visit. For cases in which such documentation is available, sites are asked to update responses to the PRD CRF if appropriate, per the above guidance. To facilitate this process, SCHARP will provide each site with a site-specific list of PRD CRFs with item 1 marked “no” for participants randomized to oral study product.

3. Documenting Race/Ethnicity on the Demographics CRF

a. Mixed Race/Ethnicity

Item 17 of the Demographics CRF asks about participants’ ethnic group or tribe. If a participant self-identifies with more than one ethnic group or tribe, record “90”, which is the new SCHARP-designated code for “mixed”. Ask the participant to specify each ethnic group or tribe to which she belongs, and record the participant’s verbatim (word-for-word) response on the “Local Language” line. If the participant responds in a language other than English, provide the English translation of the response on the “English” line. This documentation allows SCHARP to report on participant race/ethnicity according to NIH guidelines.

b. Race/Ethnicity Associated with Another Site Country

If a participant reports an ethnic group or tribe that is associated with another site country (as listed in the item 17 form instructions), please use the appropriate code as listed for the other site country.

For example, a participant screens at one of the Zimbabwe sites. During administration of the Demographics CRF, she states that she is originally from Zambia and that her ethnic group/tribe is “Chewa”. There is no code listed for “Chewa” under the Zimbabwe code list in the form instructions. However, there is the code “13-Chewa” listed under the Zambia code list. Although this participant is screening in Zimbabwe, please record the Zambian code “13-Chewa” for her, as this is the code that best fits her reported ethnic group/tribe.

CLARIFICATIONS

1. Screening Part 2 Medical Eligibility CRF (non-DataFax) – Items 4 and 4a

The intent in item 4 is to ask about Pap tests done in the past 12 months, INCLUDING Pap tests done as part of the Screening Part 2 Visit (SP2). This means that item 4 is marked “yes” if the participant has a normal SP2 Pap result, or documentation of a normal Pap result from an outside provider in the past 12 months. By “normal”, we mean a Pap result that is negative for intraepithelial lesion or cancer (malignancy). Item 4 is only marked “no” if the participant has an abnormal Pap result from a Pap done at SP2 or in the prior 12 months. For participants who undergo Pap testing at SP2, site staff will need to leave items 4-4a blank until they receive the results, at which time they can record responses to these items and initial/date the updates.

If your site has not consistently followed the guidance above, please review all previously completed Screening Part 2 Medical Eligibility CRFs to date. Update the responses to items 4 and 4a as appropriate, to ensure that the forms are completed consistently in accordance with the above guidance. Initial and date all form changes.

2. Assessing and Documenting Post-Exposure Prophylaxis (PEP) for HIV Infection at Screening and Enrollment

Per protocol section 5.3, exclusion criterion 1e, sites must assess whether a participant has used PEP for HIV infection within the 6 months prior to enrollment. It is expected that PEP use will be rare, and identified in the context of the baseline medical and menstrual history assessment.

Site staff must consistently source document this required assessment of PEP use in a designated location, such as in:

- the “History of any other obstetric, gynecologic, or reproductive problems, and/or procedures not recorded elsewhere on this form” section of the non-DataFax Participant-reported Baseline Medical and Menstrual History form
- a designated section on the site local baseline medical and menstrual history form (if used instead of the SCHARP-provided non-DataFax Participant-reported Baseline Medical and Menstrual History form)
- the participant chart notes.

This source documentation is then used to provide a response to item 2b on the non-DataFax Screening Part 2 Medical Eligibility form.

3. Documenting Dates of Last Menstrual Period for Participants Currently On Menses

The first and last dates of a participant’s last menstrual period are source documented on the baseline and follow-up medical and menstrual history forms (that is, the SCHARP-provided non-DataFax forms or other local forms, if used per site SOPs). These dates are then transcribed onto the Screening and Enrollment Pelvic Exam CRF (items 5-6) and the Follow-up Family Planning CRF (items 3-4), respectively.

The “last menstrual period” includes menstrual periods that are ongoing at the time of the study visit. If a participant is menstruating at the time of a given visit, please document the first day (start date) of the participant’s current menstrual period. For the last day (end date) of the participant’s current menstrual period, please line through the “dd-MMM-yy” boxes, write “participant currently menstruating” in the adjacent white space, then initial and date the note. After the visit, please do not update any of the above-mentioned forms with an end date once the participant has completed the menstrual period. These CRFs should only reflect data through the visit in which they are completed, in order to reflect the stage of menstrual cycle the participant is in at the time of the visit.

4. Documenting New AEs on the Follow-up Visit and Interim Visit CRFs

Items 2-2a on the Follow-up Visit CRF and items 2f-2f1 on the Interim Visit CRF ask if any new AEs were reported at the current visit, and if yes, how many new AEs were reported. Please note that the term “new AEs” refers to new *reportable* AEs that meet the criteria for reporting on an AE Log CRF to SCHARP, per protocol section 8.2. When documenting a response to these form items, do not include non-reportable AEs; that is, AEs that do not meet protocol reporting requirements. In addition, do not update these form items if an AE Log completed at the visit is subsequently marked for deletion (as deleted AE Logs remain in the study database). These form items should reflect all AE Logs completed at the visit, including any AE Logs that are subsequently marked for deletion.

For example, a participant has two new AEs identified at the Month 5 Visit. One of the AEs is reportable, and the other is not. On the Follow-up Visit form completed at Month 5, mark item 2 “yes” and record “01” for item 2a. If the reportable AE is later marked for deletion, do not update the item 2 and 2a responses.

5. Requirements for Collection of Vaginal and Endocervical Swabs

Collection of vaginal and endocervical swabs for biomarker analyses is required once prior to randomization. If a participant undergoes more than one pelvic exam during screening and enrollment, collect the vaginal and endocervical swabs at the Screening Part 2 Visit only.

Collection of vaginal and endocervical swabs for biomarker analyses is required at *every study follow-up* visit (scheduled or interim) when a pelvic exam is conducted.

6. Documenting Repeat Laboratory Tests and Examinations During Screening and Enrollment

a. Documenting Repeat Laboratory Tests During Screening and Enrollment

If a laboratory test is repeated between the Screening Part 1 and Screening Part 2 Visits (i.e., to confirm a participant's study eligibility), update the appropriate laboratory CRF, completed at Screening Part 1, to document the repeat test result.

For example, a participant is tested for serum phosphate at her Screening Part 1 Visit, and the result is less than the site laboratory lower limit of normal. The site completes a Safety Laboratory Results CRF, assigns it visit code 1.0, and records the phosphate result in item 3e. Before proceeding with the Screening Part 2 Visit, site staff decide to repeat phosphate testing in order to confirm the participant's study eligibility (per protocol section 5.3, exclusion criterion 2f). The repeat test result falls within the site's normal reference range. To document the repeat test result, site staff should line through the original result recorded in item 3e, record the repeat test result in the adjacent white space, and record the specimen collection date of the repeat test in the "Alternate Collection Date" boxes. In addition, site staff should update the response in the "Severity Grade" box as appropriate. All form updates require staff initials and date.

If a laboratory test is repeated as part of the Screening Part 2 Visit, complete a new laboratory CRF to document the repeat test result, and assign the CRF visit code 2.0.

If a laboratory test is repeated as part of the Enrollment Visit, complete a new laboratory CRF to document the repeat test result, and assign the CRF visit code 3.0.

b. Documenting Repeat Examinations During Screening and Enrollment

If a pelvic exam is repeated between the Screening Part 2 and Enrollment Visits (i.e., to confirm a participant's study eligibility), update Screening and Enrollment Pelvic Exam CRF completed at Screening Part 2 to document the repeat examination and findings, if any. Be sure to update the Exam Date, and to initial and date all updates to the CRF. If a pelvic exam is repeated as part of the Enrollment Visit, complete a new Screening and Enrollment Pelvic Exam CRF document the repeat pelvic exam, and assign the CRF visit code 3.0.

If a physical examination is repeated between the Screening Part 2 and Enrollment Visits (i.e., to confirm a participant's study eligibility), document the repeat exam and all findings in the participant's chart notes only. The Physical Exam form completed at the Screening Part 2 Visit does not need to be updated, as it is a non-DataFax form; the data is not sent to SCHARP or entered into the study database.

7. Defining Social Harms

On the Oral Product Adherence and Behavior Assessment CRF (OPA), and the Vaginal Product Adherence and Behavior Assessment CRF (VPA), social harms are defined as "any emotional, physical, social, or other difficulties" with other people as a result of study participation. Please include economic or financial difficulties in this definition, and document any economic or financial social harms on the CRFs (OPA items 18, 19c, and 20; VPA items 15, 16c, and 17).

8. When to Complete the Product Hold/Discontinuation Log CRF

Complete the Product Hold/Discontinuation Log CRF only for instances in which *site staff* initiate a new product hold or discontinuation at an unscheduled time point. Do not complete this CRF for participants who voluntarily choose to hold or discontinue study product use, as this represents participant non-adherence. Also, do not complete this CRF at the Product Use End Visit (scheduled or early termination), as all participants are expected to permanently discontinue study product use at the PUEV.

9. Calculating Serum Creatinine Changes from Baseline

Per protocol section 9.5.3, any increase in serum creatinine that is greater than or equal to 1.5 times the participant's baseline value warrants a hold of oral study product. The site Investigator of Record (IoR) or designee may resume oral study product use, unless other contraindications exist, once the creatinine level improves to 1.3 times baseline or less.

When calculating serum creatinine changes from baseline, use the serum creatinine values as they appear on the Safety Laboratory Results forms (rounded to the tenths place and in units of mg/dL). Round the change to one decimal place, and use this rounded value to determine whether or not the change has met the protocol-specified criteria for a temporary hold of oral study product. (FHI has provided an optional creatinine safety flow sheet for the purpose of tracking serum creatinine changes across study visits).

For example, a site local lab reports a participant's baseline serum creatinine value as 0.64 mg/dL (Screening Part 1 Visit). Site clinic staff round this value to one decimal place (0.6 mg/dL) for recording on the Safety Laboratory Results CRF. At her Month 6 Visit, the site local lab reports this participant's serum creatinine value as 0.95 mg/dL. Site clinic staff round this value to one decimal place (1.0 mg/dL) for recording on the Safety Laboratory Results CRF. As done for every follow-up visit in which serum creatinine is tested, site clinic staff should calculate the change in serum creatinine from baseline. In this example, the change from baseline to Month 6 is calculated as follows: $1.0 \text{ mg/dL} \div 0.6 \text{ mg/dL} = 1.6666667$. Round the change to one decimal place; in this example, 1.6666667 rounds to 1.7. If the participant in this example was randomized to oral study product, hold study product per protocol section 9.5.3.

For detailed information on rounding laboratory values in VOICE, refer to the rounding presentation sent to each site for internal review prior to study-specific training.

10. Documenting Positive Urine Leukocyte Esterase (LE) and Nitrites During Follow-up

Urine dipstick LE and nitrite tests are performed during follow up to help assess the presence of a urinary tract infection. Per Section 11.3 of the Study Specific Procedures Manual (SSP), urinary tract infections (UTIs) are diagnosed in VOICE based on the presence of symptoms and positive findings for both nitrites and leukocyte esterase on dipstick urinalysis. If a site clinician suspects that a participant may have a UTI, but the participant does not have both a positive urine LE and positive nitrites on dipstick urinalysis, the clinician may choose to provide treatment for the UTI. However, the site should not report an AE using the term "Urinary Tract Infection". Instead, each symptom should be reported as its own AE on a separate AE Log form. A positive urine LE or positive nitrites result on dipstick urinalysis should not be reported separately as its own AE on its own AE Log form. Rather, the positive dipstick results will be captured on the Safety Laboratory Results CRF completed for the visit.

11. Accounting for Vomited Doses of Oral Study Product

If a participant vomits after taking her daily dose of study tablets, and is able to determine that she threw up both study tablets (i.e., she can see both tablets in the vomit), do not count these doses as having been taken when assessing product adherence via the CRFs. Also, instruct participants not to

count these doses as having been taken when responding to product adherence questions via ACASI. If, after waiting 30 minutes, the participant is able to take another of each study tablet and does not vomit again, count the second set of tablets as having been taken on the CRFs and in ACASI. If, however, the participant vomits the second set of tablets as well, do not count these tablets as having been taken.

If a participant vomits after taking her daily dose of study tablets and cannot see both tablets in the vomit, these doses *should* be counted as having been taken on the CRFs and via ACASI.

12. Completing Behavioral CRFs During Periods of Product Hold/Discontinuation

When completing the Monthly Product Adherence and Behavior Assessment CRF (MBA), site staff should *not* administer the questions on study product adherence (items 3-4b) for participants who have had product held continuously for 7 or more days prior to the current visit. When completing the Oral/Vaginal Product Adherence and Behavior Assessment CRFs (OPA and VPA), site staff should *not* administer the questions on study product adherence (OPA items 4-17; VPA items 4-14) for participants who have had product held continuously for 4 or more weeks prior to the current visit. This guidance applies to site-initiated product holds only. Participants who have voluntarily chosen to temporarily hold study product should still be administered the adherence questions.

If a participant permanently discontinued study product use 7 or more days prior to the current visit (for the MBA), or 4 or more weeks prior to the current visit (for the OPA and VPA), site staff should not administer the questions on study product adherence. This applies to both site-initiated product discontinuations, and discontinuations based on participant choice.

13. Audio Computer Assisted Self Interview (ACASI) Administration Schedule

Below are tables that outline which ACASI questionnaire to administer at the following visits: quarterly, semi-annual, annual, Product Use End Visit (PUEV), and Study Exit Visit (SEV). The first table lists the ACASI questionnaire schedule for participants randomized to oral study product; the second table lists the ACASI questionnaire schedule for participants randomized to vaginal study product.

Refer to Table 14-2 of the SSP for the complete list of visit codes assigned to each protocol-specified study visit.

Note: In addition to the questions contained in the Regular Quarterly ACASI questionnaires (oral and vaginal), the First Quarterly ACASI questionnaires (oral and vaginal) contain questions on partner reaction to study product use and study product sharing. In order to maximize collection of this additional data, please follow the guidance listed in the bullet points below.

- *If a participant does not complete the First Quarterly ACASI questionnaire at her Month 3 Visit (i.e., she misses her Month 3 Visit or is administered the Product Hold/Discontinuers/SEV ACASI questionnaire at her Month 3 Visit), administer the appropriate First Quarterly ACASI questionnaire (oral or vaginal) at her Month 6 Visit (unless the Product Hold/Discontinuers/SEV ACASI questionnaire is indicated at the Month 6 Visit, per the tables below).*
- *If a participant does not complete the First Quarterly ACASI questionnaire at her Month 3 or Month 6 Visit (i.e., she misses a visit and/or is administered the Product Hold/Discontinuers/SEV ACASI questionnaire at a visit), administer the appropriate First Quarterly ACASI questionnaire (oral or vaginal) at her Month 9 Visit (unless the Product Hold/Discontinuers/SEV ACASI questionnaire is indicated at the Month 9 Visit, per the tables below).*
- *If a participant does not complete the First Quarterly ACASI questionnaire at her Month 3, Month 6, or Month 9 Visit, refrain from further attempts to administer this questionnaire. Instead, administer the appropriate ACASI questionnaire, per the schedule below, at the next visit at which completion of an ACASI questionnaire is required.*

ACASI Questionnaire Schedule - Oral

Visit	Visit Code	ACASI Questionnaire to administer	Administer to:
Enrollment	3.0	Enrollment	All participants enrolled
Month 3*	6.0	First Quarterly Oral	All participants randomized to oral arm (unless product continuously held/discontinued past 4 weeks)
Months 6, 9, 15, 18, 21, 27, 30	9.0, 12.0, 18.0, 21.0, 24.0, 30.0, 33.0	Regular Quarterly Oral	All participants randomized to oral arm (unless product continuously held/discontinued past 4 weeks)
Months 12, 24, and PUEV/Early Termination	15.0, 27.0, visit code associated with study month when PUEV/Early Termination occurs**	Annual/PUEV Oral	All participants randomized to oral arm who are completing an annual visit, scheduled PUEV, or early termination visit (unless product continuously held/discontinued past 4 weeks)
Study Exit (SEV) or any quarterly or semiannual visit where participant has been on continuous product hold/discontinuation for the past 4 weeks	89.0, visit code associated with study month when quarterly or semiannual visit occurs**	Product Hold/Discontinuers/SEV	Participants randomized to oral arm who are completing a scheduled SEV, who have had product continuously held by site staff for 4 weeks or more, or who have permanently discontinued study product (site or participant choice) 4 or more weeks ago

ACASI Questionnaire Schedule - Vaginal

Visit	Visit Code	ACASI Questionnaire to administer	Administer to:
Enrollment	3.0	Enrollment	All participants enrolled
Month 3*	6.0	First Quarterly Vaginal	All participants randomized to vaginal arm (unless product continuously held/discontinued past 4 weeks)
Months 6, 9, 15, 18, 21, 27, 30	9.0, 12.0, 18.0, 21.0, 24.0, 30.0, 33.0	Regular Quarterly Vaginal	All participants randomized to vaginal arm (unless product continuously held/discontinued past 4 weeks)
Months 12, 24, and PUEV/Early Termination	15.0, 27.0, visit code associated with study month when PUEV/Early Termination occurs**	Annual/PUEV Vaginal	All participants randomized to vaginal arm who are completing an annual visit, scheduled PUEV, or early termination visit (unless product continuously held/discontinued past 4 weeks)
Study Exit (SEV) or any quarterly or semiannual visit where participant has been on continuous product hold/discontinuation for the past 4 weeks	89.0, visit code associated with study month when quarterly or semiannual visit occurs**	Product Hold/Discontinuers/SEV	Participants randomized to vaginal arm who are completing a scheduled SEV, who have had product continuously held by site staff for 4 weeks or more, or who have permanently discontinued study product (site or participant choice) 4 or more weeks ago

REMINDERS

1. Documenting Pre-existing Conditions on the Pre-existing Conditions (PRE) CRF

The Pre-existing Conditions CRF (PRE) used in VOICE is the standard SCHARP PRE form used in other studies for which SCHARP is the SDMC. The form includes the question “Is condition ongoing?”, and sites are instructed to mark “yes” if the condition is ongoing at the time of enrollment. Since pre-existing conditions are defined in VOICE as only those conditions that are ongoing at the time of the Enrollment Visit, the response to this question should always be “yes”. If a condition has resolved prior to enrollment, and is not present at the time of the Enrollment Visit, do not record it on the PRE CRF.

2. Documenting Early Termination Visits

If a participant chooses to withdraw consent from the study and terminate early (during her expected study product use period), site staff should ask the participant if she would be willing to complete one final study visit. If she is willing, site staff should conduct all required Product Use End Visit (PUEV) procedures at this final visit and complete all required CRFs for the PUEV, as listed in SSP Table 14-3. In addition, site staff should complete the Termination CRF and the End of Study Inventory CRF for this participant. If the participant is not willing to complete one final study visit, site staff should complete the following CRFs: Perceived Product Assessment, Product Use End Visit, Termination, and End of Study Inventory.

Note: Participants who terminate early from the study will not complete a protocol-specified Termination Visit. Rather, the participant’s last completed visit will be considered her PUEV.

3. Reporting Pelvic Exam Findings as AEs

Per SSP Figure 11-4, report AEs of pelvic exam findings using the terminology corresponding to either the DAIDS *Female Genital Grading Table for Use in Microbicide Studies* (FGGT), or the Follow-Up Pelvic Exam CRF, whichever is more specific. Specify the anatomical location of the finding (e.g., cervical, vaginal, vulval). When possible, avoid using generic terms.

For example, if an ulcer is observed on the participant’s vaginal wall during a follow-up pelvic exam, do not report the AE as “genital lesion”; instead, report the AE on the AE Log CRF using the term “vaginal ulcer”.