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## MTN 001 Data Communiqué #5 - **REVISED**

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September 3, 2009

This is official study documentation for MTN 001. Please circulate it among relevant staff for their review, print it, and place it in your MTN 001 SSP Manual in the Data Communiqués section. This document is considered part of the MTN 001 SSP manual.

### UPDATES

#### 1. New SCHARP Clinical Affairs Safety Associate

Molly Swenson has replaced Donna Robinett as the MTN-001 SCHARP Clinical Affairs Safety Associate. Molly is responsible for identifying and placing clinical QCs, and works closely with the Protocol Safety Monitoring Team (PSRT) to monitor MTN-001 safety data. Molly can be reached by e-mail ([mollys@scharp.org](mailto:mollys@scharp.org)) or by phone (206-667-5410).

#### 2. New Rectal PK form and Updated Page 2 LDMS Specimen Tracking Sheet, Dated 17-AUG-09

On 17-AUG-09, SCHARP issued a new Rectal PK (RPK) form and updated page 2 (version 3.0) of the LDMS Specimen Tracking Sheet (non-DataFax) for use by the Bronx-Lebanon Hospital site only. Both the new form and updated page reflect the addition of optional rectal PK specimen collection at the Bronx site, per Letter of Amendment #1, dated 07-JUL-09. SCHARP will ship hard copies of both the form and the updated LDMS Specimen Tracking Sheet page to the Bronx site.

### CLARIFICATIONS

#### 1. Documenting Genital Bleeding

All cases of participant-reported genital bleeding occurring between usual menstrual periods will be documented on the Baseline Genital Symptoms form (at enrollment) or the Follow-up Genital Symptoms form (at follow-up visits). The non-DataFax Pelvic Exam Diagrams form is used to record all pelvic exam findings, both normal and abnormal. This means that all clinically observed genital blood/bleeding, whether expected, unexpected, menstrual, or non-menstrual, should be documented on the non-DataFax Pelvic Exam Diagrams form. In contrast, the Screening and Enrollment Pelvic Exam form and Follow-up Pelvic Exam form are used to record only abnormal pelvic exam findings. This means that only unexpected menstrual bleeding (excluding early menses) and unexpected non-menstrual bleeding should be recorded on these forms.

Expected non-menstrual bleeding should not be reported as an AE. This may include a small amount of cervical bleeding that can occur with speculum insertion or specimen collection, provided the IoR or designee deems the amount of bleeding to be within the range of normal. If the cervical bleeding observed with speculum insertion or specimen collection exceeds that which is expected, in the opinion of the IoR or designee, then the cervical bleeding should be recorded as an AE of “cervical friability”, and graded according to the “Cervical edema and friability” row of the Female Genital Toxicity Table.

If it is unclear whether a genital bleeding event (during follow-up) is expected or unexpected, complete the non-DataFax Genital Bleeding Assessment form.

## 2. Week 21 In-depth Interviews for Replacement Participants

Participants who are randomized to the Week 21 in-depth interviews should only complete these interviews if they are evaluable participants (i.e., they have been dispensed study product at least once and have returned to report on study product use at least once in *each* of the three study periods). If a participant who is randomized to the Week 21 interview is not evaluable, she will need to be replaced. The replacement participant (who receives the exact same randomization assignments as the woman she is replacing) should complete the Week 21 interview instead, provided that the replacement participant proves to be evaluable.

## 3. Split Visits

Split visits (i.e., procedures for a given visit that are conducted on more than one date) are allowed for all visits except the Enrollment Visit. All Enrollment Visit procedures must be conducted on the same day, with the exception of informed consent for enrollment and specimen storage, which may take place at a prior date within the 30-day screening window. The Screening Visit may occur on multiple dates within the 30-day screening window, and follow-up visit procedures may be conducted over more than one date, provided that all dates are within the allowable visit window.

Note that end-of-study period PK procedures cannot be split across days; the end-of-study period PK procedures must all be completed on the same day (see SSP Manual Section 6-Participant Follow-up for more information on PK procedures). Also, note that the Study Product Adherence and Behavior Assessment must be completed on the same day as the end-of-study period PK procedures.

See Section 13.3.3 of the SSP Manual for information on assigning visit codes to split visits.

## 4. Assigning Interim Visit Codes

A clinic visit is considered an Interim Visit when a participant presents at the site for reasons *other* than to complete required study visit procedures. Interim visits may be performed at any time during the study for reasons that may be administrative (a participant has study-related questions for the staff), product-related (a participant needs additional study product), lab-related (a participant needs a safety lab test repeated for confirmation), or clinical in nature (a participant needs management and/or follow-up of an AE), etc.

A phone call is considered an Interim Visit when it results in the reporting of a new AE. A phone call is also considered an Interim Visit if, on the call, site staff instruct the participant to hold study product, permanently discontinue study product, or resume study product use after a previous hold.

**NOTE:** *not all interim visits are assigned interim visit codes. An interim visit should be assigned an interim visit code only if 1) data collected at the visit warrants completion of a new DataFax form, such as an AE Log or Product Hold/Discontinuation (PH) Log form, or 2) product use was previously held and is now being resumed, resulting in an update to the PH Log form (items 4-4a). An Interim Visit form must be completed for each and every visit that is assigned an interim visit code. See section 13.3.3 of the SSP Manual for instructions on assigning interim visit codes.*

## 5. Recording Returned and Dispensed Study Product Counts At End-of-study Period Visits

The Follow-up Visit (FV) form captures the number of unused study applicators (item 3) and unused study tablets (item 4) that a participant returns at a given regularly scheduled follow-up visit. At the end-of-study period visits (Weeks 6, 13, and 20), if one returned unused applicator and/or tablet is used for the in-clinic observed PK dose, do not include that used applicator and/or tablet in the responses to items 3 and 4. For example, a participant presents

for her Week 6 Visit (dual use period) and returns 7 unused applicators and 9 unused tablets. The participant uses one of these applicators and takes one of these tablets for the in-clinic observed PK doses. Thus, on the FV form completed for the Week 6 Visit, site staff should record “06” as the response for item 3, and “08” as the response for item 4.

If, at the end-of-study period visits, a participant does not return unused product (or the product returned is deemed unsuitable for use), one additional study applicator and/or study tablet may be dispensed for the in-clinic observed PK dose. Do include this dispensation in the responses to items 5 (number of applicators dispensed) and 6 (number of tablets dispensed) on the FV form.

## **6. Recording Urine Dipstick Results**

When urine dipstick testing is required per protocol, only the following analytes are required for study purposes: protein, leukocyte esterase (LE), nitrites, and culture (if positive for LE or nitrites; may be omitted if culture is not a part of a site’s standard of care for UTI diagnosis). These results must be recorded on the Safety Laboratory Results form. If a site’s urine dipstick testing yields additional results, such as glucose or blood, these additional results must be documented in the participant’s study records in the form of a local lab report, chart note, or other participant-specific document developed by the site.

## **7. Early Study Terminations**

If a participant reports that she wishes to discontinue her participation in the study, ask if she would be willing to complete an early Study Exit Visit, or at least a final blood draw (for safety labs and HIV testing) and urine collection (for pregnancy testing). Please document her response in her chart notes. If the participant is willing to complete an early Study Exit Visit, complete all Week 21 Visit procedures and CRFs (except complete the Interim Visit form instead of the Follow-up Visit form). Assign the appropriate interim visit code to the early Study Exit Visit. If the participant is only willing to give blood and urine (for safety labs, HIV, and pregnancy testing), complete the following CRFs: Interim Visit, Safety Laboratory Results, STI Laboratory Results, Termination, and End of Study Inventory. If the participant is unwilling to complete any additional study procedures, complete a Termination form and End of Study Inventory form, and fax these forms to SCHARP.

# **REMINDERS**

## **1. Grading Lab Values According to the DAIDS Toxicity Table**

Depending on a site’s normal reference ranges, it is possible that a participant can have a value that falls within the site’s normal range, but is still gradable per the DAIDS Toxicity Table. Always refer to the DAIDS Toxicity Table to determine whether or not a lab value is gradable. For gradable lab values that occur during follow-up (and are not otherwise associated with a clinical diagnosis), refer to the participant’s previous value for the given assay to determine whether or not there is an increase in severity that warrants reporting of a new AE.

## **2. Completing the Safety Laboratory Results (SL) Form for Gradable Lab Values**

If a lab value is gradable per the DAIDS Toxicity Table, regardless of whether the specimen was collected at screening, enrollment, or during follow-up, record the severity grade in the “Severity Grade” box. Record the “AE Log Page #” if the gradable lab value is reportable as a stand-alone AE (e.g., “proteinuria”), or is part of a clinical AE (e.g., “urinary tract infection”). If a gradable lab value does not meet the criteria for AE reporting (i.e., the specimen was collected at screening or enrollment, or the severity grade represents an ongoing pre-existing condition), mark the “Not Reportable as an AE” box. If a severity grade is recorded in the “Severity Grade” box, either an “AE Log Page #” must be recorded, or the “Not reportable as an AE” box must be marked. The same “AE Log Page #” may be recorded for the same item on SL forms completed at consecutive visits, for example, if a lab value AE persists at the same or lesser severity across study visits.

### 3. Reporting AEs of Gradable Lab Values

When reporting gradable lab value AEs, site staff should first consider whether or not the participant received (or was offered) treatment for the condition. This will determine the text that site staff should record for item 1 on the AE Log form. If the participant did receive (or was offered) treatment for the condition, record a diagnosis for item 1. For example, if a participant has a gradable decreased phosphate value and receives treatment for it, then site staff should record the item 1 text as “hypophosphatemia”. (For purposes of AE reporting, treatment is not limited to the prescribing of medications. In this example, treatment may include a site clinician’s recommendation that the participant supplement her diet with phosphate-rich foods). If the participant is asymptomatic or is not prescribed treatment for the gradable lab value, then site staff should record in item 1 the lab value with the direction of abnormality (increased or decreased). In this example, site staff would record “decreased phosphate” as the text for item 1.

The “Date Reported to Site” on the AE Log form should be the date that site clinic staff first become aware of the gradable lab value. For safety labs, this will be the date the lab report is received at the site clinic. The “Onset Date” (item 2) on the AE Log form should be the date of specimen collection. The “Status/Outcome Date” (item 6a) should be the collection date of the follow-up specimen that yields one of the following: 1) a non-gradable result, 2) a return to baseline severity (if the AE represents the worsening of an ongoing baseline condition), or 3) a result of increased severity (thus requiring completion of a new AE Log). For item 10, record the visit code that is assigned to the specimen collection date; this should be the same visit code that is assigned to the AE “Onset Date”.

### 4. CBC and Differential Testing

Per protocol, CBC testing is required during follow-up for all participants at the Week 7, Week 14, and Week 21 Visits; differential testing is *not* required at these visits. However, for sites conducting flow cytometry, CBC testing with differential is required at each of the end-of-study period visits (Weeks 6, 13, and 20) to obtain the lymphocyte counts needed for flow cytometry calculations and completion of the Flow Cytometry form.

*Note: Differential testing may yield results, such as neutrophils or lymphocytes, that are not recorded on the case report forms. However, if the results during follow-up show a new onset or increase in severity of gradable neutrophil or lymphocyte values (per the DAIDS Toxicity Table), the gradable values must be reported as AEs on the AE Log form.*

### 5. Rounding Lab Values

There may be times when a site must round a given lab value in order to record the result on the appropriate case report form. In these instances, sites must consider *only* the digit to the right of the desired place when rounding. For example, item 3c1 on the Safety Laboratory Results form is used to record calculated creatinine clearance as a 3-digit whole number. If the site calculates the creatinine clearance value as 132.4678 mL/min, then only the tenths digit (the “.4”) is considered when rounding, and the result should be recorded on the form as “132”.

### 6. Calculating Creatinine Clearance

When calculating creatinine clearance, please remember to use the MTN 001 Creatinine Clearance Calculator that is posted on the MTN web site. Remember to enter the participant’s age at the time of specimen collection (for serum creatinine testing), enter the participant’s weight as a whole number in kilograms, and enter the serum creatinine value in mg/dL rounded to the nearest tenths digit (per the above instructions in Reminder #5). The serum creatinine value used in the MTN 001 Creatinine Clearance Calculator should be identical to the serum creatinine value documented on the Safety Laboratory Results form.

*Note: SCHARP is unable to check the accuracy of creatinine clearance calculations at the Screening, Enrollment, Week 7, 14, 21 and Interim Visits, as weight data is not captured on the CRFs or entered into the DataFax database for these visits. Therefore, it is especially important that sites follow the above guidance when calculating creatinine clearance at these visits, in order to ensure that the calculations are correct.*

## **7. Completing Behavioral, Adherence, and Acceptability CRFs**

The MTN 001 Enrollment Behavior Assessment, Study Product Adherence and Behavior Assessment, Product Sharing Assessment, Acceptability Assessment, and Final Acceptability Assessment are interviewer-administered forms. Participant responses are recorded directly onto the forms so that the forms themselves serve as source documents. No changes or updates to the forms should be made once the forms are administered and the interviews in which they are administered are complete. This is especially important since risk reduction and adherence counseling that occurs after the interviews have the potential to bias participant responses.

These forms capture primary and secondary endpoint data. To ensure that this data is complete and accurate, it is crucial that the interviewer review the completed form at the end of the interview, while the participant is still in front of him or her. This way, any missing data or inconsistencies can be resolved with the participant while she is still present with the interviewer. Specifically, the interviewer should make sure that all skip patterns are followed to ensure that all items requiring a response have a response, and all items that should be skipped are left blank.

With the understanding that this data is source, SCHARP will only QC these forms if: 1) a key field, such as a PTID, visit code, or visit date is missing or has an error, 2) an item should have been left blank per the skip pattern, but has a response (the QC will ask for the response to be deleted by lining through it, initialing and dating), and 3) an item should have a response but was left blank (the QC will ask for the response boxes to be lined through, for “missing” to be written next to the lined through boxes, and for the item to be initialed and dated).