

Section 14. Data Communiqués

NOTE: Effective with Version 2.0 of this section, prior references to the HIV Prevention Trials Network (HPTN) have been replaced where applicable with references to the Microbicide Trials Network (MTN).

For HPTN 035, the MTN Statistical and Data Management Center (SDMC) uses "Data Communiqués" to document and communicate data decisions and procedures that are made or revised during the study. By using Data Communiqués, the SDMC avoids having to distribute a revised version of Section 13 of this manual every time a form completion clarification or revision is made.

Data Communiqués #1 - #11 were issued based on Version 1.0 of Section 13, and have been incorporated into Version 2.0 of Section 13.

Data Communiqués are considered official study documentation. As such, each time a Data Communiqué is sent (via email), please circulate it among relevant staff for their review, print the Data Communiqué, and place it in this section of each 035 SSP binder in your possession. Consider each Data Communiqué an official part of the SSP.

Each Data Communiqué sent will consist of three sections: a Reminders section, used to remind sites of specific data collection or forms completion procedures; a Clarification section, used to clarify data collection or form completion procedures; and an Updates section, used to communicate when an updated version of a form is being issued or to notify the sites that an updated version of the forms instructions is about to be distributed (for example).

Note that a "Data Communiqué" does not request specific actions or corrections to a particular participant's data - it is just a listing of general items to keep in mind when performing data collection for the study.

HPTN 035 Data Communique #1

1 February 2005

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

There are no updates at this time.

CLARIFICATIONS

1. Form revisions which require reissuing of previously distributed forms

The Philadelphia, USA and Durban, South Africa sites have received their initial forms shipments. The following forms contain updates/corrections that require distribution and replacement of revised forms. As such, revised forms will be sent directly to these two sites for manual replacement. All other sites will receive the correct (revised) forms in their initial form shipments. For all sites, all future shipments will include the revised forms.

Screening Part 1 Eligibility (non-DataFax form).

Form revision date: 12-Jan-05.

- The skip rule on item 3 was corrected from “If yes, participant is ineligible” to “**If yes, participant may be ineligible at this time.**” The skip rule on item 4 was corrected from “If yes, participant may be ineligible” to “**If yes, participant is ineligible.**” Please note this change when reviewing eligibility criteria.

Baseline Medical History (non-DataFax form), page 2.

Form revision date: 25-Jan-05.

- A field to record the age of menarche was added in the Menstrual History section. An instruction for this item was also added to the back of the form which reads “Record the participant’s age of first menstrual period.”
- At the bottom of the form, “Current method of contraception/family planning” was changed to “**History of contraception/family planning use.**” The instructions on the back of the form were revised to read, “Record the method(s) of contraception/family planning the participant reports using in the **past and currently.**”

HPTN 035 Specimen Tracking Sheet, PTID format and Visit Code instruction (non-DataFax).

Form revision date: 25-Jan-05.

- The PTID field of the original version of this form has an incorrect PTID format. The revised form has the correct HPTN 035 PTID format.
- The revised form has an added instruction for the Visit Code. The new instruction reads “For specimens collected at Screening Part 2 and/or Enrollment visits, use the visit code “02.0.”

2. Form revisions which do not require reissuing of forms

The following forms/forms instructions have been revised. The revisions are minor enough that they do not require reissuing the forms. For all sites, all future shipments will include the revised forms.

Screening Part 2 Laboratory Results, page 2 (ELR-2), items 4a, 4b.

Form revision date: 12-Jan-05.

- The specific syphilis tests listed in parentheses were printed in error. They are not relevant to the HPTN 035 protocol and therefore syphilis test results should be documented on this form regardless of testing method. This listing will NOT appear on any future versions of this form.

Baseline Medical History, (non-DataFax form), Instructions page 1.

Form revision date: 25-Jan-05.

- This instructions for the “yes/no” field were updated to match the SSP. The instructions originally asked for any medical problems ever experienced by a participant. We have now clarified that **only problems that have occurred since the participant became sexually active should be documented** here. The instruction now reads, “For each organ system/disease listed, mark the “yes” box if there is evidence (either by participant report or by medical records) that the participant has ever experienced any medical problem involving that organ system/disease **since becoming sexually active**. Mark the “no” box for conditions not reported or documented in medical records.”
- The instructions for the reproductive history item were updated to match the SSP. The instructions now read, “Record the total number, **date**, and outcome (for example, full-term live birth, premature live birth, spontaneous abortion, etc.) of each of the participant’s pregnancies. **This should include any gynecologic and obstetrical procedures/surgeries.**”

3. Form completion clarifications

Clinical Eligibility (non-DataFax form), Item 2.

- Per the Enrollment visit checklist, this form should be reviewed when enrollment does not occur on the same day as Screening Part 2. In this case, if a pelvic exam was not performed on the day of enrollment, item 2 (“At this visit, does this participant have a clinically apparent pelvic exam finding involving deep epithelial disruption?”) is not applicable. To document that this item was reviewed on the day of enrollment but was not applicable, write “Not applicable - no pelvic exam done at enrollment” in the white space below item 2, and initial and date.

Adverse Experience Log (AE-1), Date Reported to Site

- For AEs that are determined by laboratory test results, the specimen collection date should be recorded in the “Date Reported to Site” field.

Acceptability Assessment (AA-1), Items 3, 4, and 5

- This form is to be completed only at the Month 3 Visit. If at that visit participant randomized to study gel reports that she has not yet used the gel mark the responses in the following way:
 - draw a single vertical line through all the response boxes
 - initial and date the item (may use a bracket) in the white space near the item
 - *optional*: write “N/A” in the white space near the item
- If the participant responds “Nothing” to these items, mark the “other, specify” box and record “Nothing” on the lines provided.

Note: this applies to the Study Exit Acceptability Assessment (SAA-1, SAA-2) as well.

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REMINDERS

1. Follow-up Behavior Assessment (FBA-1), Item 1 instruction

- The instructions state that if the response to Item 1 is “00” pages 2 and 3 of this form will be skipped. In cases that these pages are skipped, please remember to record the Visit Code, PTID, and **staff initial and date** on each of these pages.

UPCOMING ISSUES

There are no upcoming issues at this time.

HPTN 035 Data Communique #2

4 March 2005

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

1. PTID Labels

SCHARP has become aware that the specimen collection container PTID labels that have been provided to the Philadelphia, South Africa, and Lilongwe, Malawi sites are too large to fit completely on the underside of gram stain slides. As such, SCHARP will begin providing all sites with small PTID labels for use on gram stain slides, wet mount slides, and if the site prefers, genital ulcer (GUD) swab cryovials.

CLARIFICATIONS

1. Demographics (DM-1, DM-2) form

a. Item 3c

Item 3c has been revised to read "Does your partner have any other sexual partners?". The form revision date is 08-Feb-05. The Philadelphia and South Africa sites have been shipped revised copies for replacement in their existing Screening Part 1 form visit packets. All other sites will automatically receive the new version in their form shipments.

b. Completion of items 2d1 and 3d1

When completing these items (average monthly income) for husbands or male partners who are **not employed**, record '0000000' as the husband's/partner's average monthly income.

2. Lilongwe site only - Screening Pelvic Exam (SPE-1) form item 5

Because the Lilongwe site is not performing pap smears, it is not necessary for the Lilongwe site to record a comment when item 5 (was a pap smear collected) is marked "no."

3. Screening Part 2 Laboratory Results (ELR-1, ELR-2)

In the situation where a participant reports for her Screening Part 2 visit, has a pregnancy test performed but is unable to complete the screening pelvic exam due to menses, record the pregnancy test result on the ELR-1 form (initial collection date = date of pregnancy test collection). When the participant returns on a different day and completes her screening pelvic exam, record the screening pelvic exam wet mount results on the ELR-1 form previously completed (with the previous visit's pregnancy test result), making sure to record the date of the wet mount specimen collection in the "Specimen Collection Date" field of item 3. Document the pregnancy test result from this second Screening Part 2 visit in the participant's chart notes or on the visit checklist. **DO NOT** complete a second ELR form for the wet mount results - only one ELR form must be completed for each participant for each screening attempt.

4. Screening Safety Lab Results (SSL-1) and Safety Lab Results (SL-1) items 3f and 3g

As of February 15, 2005, the protocol team has determined that bands and atypical lymphocytes are not required assays for 035. The “not reported” box should be marked for these items (3f and 3g) when completing the Screening Safety Lab Results and Safety Lab Results forms.

5. Pre-existing Conditions (PRE-1) form

The purpose of the Pre-existing Conditions form is to document **all** medical conditions (both self-reported and observed conditions) that are ongoing at the time of study randomization/enrollment. When completing the Pre-existing Conditions form, site staff should review the participant’s Baseline Medical History, Physical Exam, Clinical Eligibility, Screening Pelvic Exam, and all screening lab forms and transcribe all ongoing conditions/abnormal findings/diagnoses onto the Pre-existing Conditions form. The goal is to have **all** of the participant’s ongoing medical conditions captured on one form - the PRE form. Be sure to record detailed information on the severity and frequency of each condition in the “Comments” field of each entry.

6. Pelvic Exam Diagrams form

The team has confirmed with PPD that use of different colored pens (in addition to blue and black) is allowable on the Pelvic Exam Diagrams (non-DataFax) form.

7. Data additions/corrections - what to do when there is no white space available?

When making corrections or additions to case report forms, sometimes it is necessary to write corrected or new information in white space on the form that is not directly adjacent to the original entry. In such cases, it is allowable to use arrows to link the corrected/new information to the original entry.

REMINDERS

1. Recording pregnancy test results when Enrollment and Screening Part 2 are not on the same day

For those sites where Screening Part 2 and Enrollment visits **are not** performed on the same day, remember to record the Enrollment visit pregnancy test result on the Enrollment visit checklist (or in Enrollment visit chart notes) - in these cases **do not** record the Enrollment visit pregnancy test result on the Screening Part 2 Lab Results form.

UPCOMING ISSUES

None

HPTN 035 Data Communique #3

15 April 2005

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

1. Phase II Months 1 and 2 form packet

The HPTN 035 LDMS Tracking Sheet was added to the Phase II - Months 1 and 2 form visit packets on 23-March-2005. For those sites that already had Phase II - Months 1 and 2 form visit packets on-site, additional copies of the LDMS Specimen Tracking Sheet were sent so that they could be manually added to these packets. The LDMS Specimen Tracking Sheet is used at Months 1 and 2 for Phase II participants to document gram stain collection.

CLARIFICATIONS

1. Completion of Menstrual History section of Baseline Medical History (non-DataFax) form for participants who are currently amenorrheic

Step 1: Complete all fields in the Menstrual History section except for "First day of last menstrual period" and "Last day of last menstrual period". For these items, line through the boxes, write "N/A", and initial and date. Complete all other fields under Menstrual History based on participant's description of her periods before she became amenorrheic.

Step 2: Write a note in the "Additional Notes" section of the form similar to "Ppt currently amenorrheic due to _____ (provide reason; example - hormonal contraception use). Details recorded under Menstrual History describe the ppt's periods before she became amenorrheic."

2. Severity grading of STDs/STIs and Reproductive Tract Infections (RTIs)

All STDs/STIs and RTIs, including vaginal candidiasis and bacterial vaginosis, should be assigned severity grades according to the "Infections (any other than HIV infection)" row of the current DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events - Publish Date December, 2004. Note that according to this row, if systemic antimicrobial treatment is given for the STD/STI or RTI, the condition cannot be assigned a severity grade of 1 (the grade must be 2 or higher).

3. Genital Bleeding Assessment (non-DataFax) form and report of multiple genital bleeding events

If a participant reports more than one episode of genital bleeding since her last visit, complete one Genital Bleeding Assessment form for each genital bleeding episode reported.

4. Pelvic Exam Diagrams (non-DataFax) form and documentation of vaginal discharge, cervical discharge, and blood in vagina

To document vaginal discharge, cervical discharge, or blood in vagina on the Pelvic Exam Diagrams form, record "vag discharge", "cerv discharge", or "blood in vag" (or equivalent term) on/near the appropriate diagram. For example, when documenting vaginal discharge, write "vag discharge" near the "vagina" diagram.

5. What to do when rounding of lab values appears to affect the severity grade (Screening Safety Laboratory Results and Safety Laboratory Results forms)

When laboratory reported values need to be rounded in order to be recorded on DataFax forms, and the rounded value appears to be a higher severity grade than the laboratory reported value, please note this in the Comments section of the form page. For example, the lab reports a PT INR value of 1.35. This value is recorded as 1.4 on the CRF. The range for severity grade 1 is 1.375 to 1.875. Technically this participant's INR value is below the grade 1 severity grade cutoff. To document this on the CRF, please add a note in the Comments section to the effect "PT INR value reported by the lab is 1.35 which is below severity grade 1 cutoff."

REMINDERS

1. Enrollment and Follow-up Behavior Assessment item 10 (family planning methods)

Note that the response options for this question are **not** read aloud. Rather, read item 10 as it appears on the form and mark the box to the left of the family planning method(s) the participant reports currently using.

HPTN 035 Data Communique #4

9 June 2005

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

None.

CLARIFICATIONS

1. Termination form item 3a

It has been decided that when study termination is associated with more than one adverse experience (AE), only one AE Log page number should be recorded in item 3a. Record the page number of the AE that most strongly influenced the decision to terminate. Draw a horizontal line through the remaining page number boxes and initial and date to indicate no data will be recorded in those boxes.

2. Pre-existing Conditions form and Abnormal Pap Test Results at Screening Part 2

If a participant's Screening Part 2 pap test result is abnormal, this abnormality needs to be added to her Pre-existing Conditions form since the pap specimen was collected prior to enrollment/randomization.

3. Monthly or Quarterly Visit (MQV) form, item 3

At those visits where safety lab specimens are collected, please mark the "Safety Laboratory Results" box of MQV item 3 before faxing the MQV even though the Safety Laboratory Results forms will be faxed later (once all results are available).

4. Severity grading of seasonal allergies

When assigning a severity grade to seasonal allergies, use the "Estimating severity grade" row of the DAIDS Tox Table (not the "Acute systemic allergic reaction" row).

5. Screening Safety Laboratory Results forms - How to record laboratory tests that are repeated within a screening attempt

When screening safety labs are repeated within a Screening Attempt, please update the originally-completed Screening Safety Laboratory Results form so that it records the results from the latter specimen collection (the specimen collected closest to the enrollment/randomization date). Be sure to complete the "Specimen Collection Date" field when recording additional results. For example, a participant originally has safety labs drawn on 25-Jun-05. The participant's AST value is a grade 4. A liver function specimen is drawn again on 28-Jun-05 (still within the screening attempt window) and the result is now a grade 2. The participant is now eligible to enroll. The participant's Screening Safety Laboratory Results form should be updated so that the results of the 28-Jun-05 specimen are recorded in item 4 (new results in the white space, previous results will be lined-through), and the "Specimen Collection Date" fields should be completed as 28-Jun-05.

REMINDERS

None.

HPTN 035 Data Communiqué #5

16 August 2005

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiqués. This document is considered part of the SSP manual.

UPDATES

1. AE Log form

Items 8 and 9 of the Adverse Experience (AE) Log form have had minor text revisions made to them. The intent of these questions is still the same as the original version of the form, but the question text has been changed so that these items are more clear. The revised form has a date of 13-JUL-05 in the bottom left corner of the form page. The form instructions have also been updated to include instructions on how to complete “Date Reported to Site” field. The instructions also have a revised date of 13-JUL-05. Please continue to use the current version (dated 09-NOV-04) of this form until your supply runs out. The next time you order AE Log forms, SCHARP will fill this order with the revised form. No further action is needed from the sites - this is just to let you know that the form has changed, but the changes do not require you to replace or destroy any unused forms.

CLARIFICATIONS

1. Severity grading of hemoglobin value decreases

The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (“Tox Table”) lists “any decrease” within a specified range as one criteria for assessing hemoglobin severity grade. DAIDS has recently clarified that when determining whether a decreased hemoglobin value meets the grading criteria per the “Adult and Pediatric > 57 days (HIV negative only)” hemoglobin row of the Tox Table, the decrease refers to a decrease from the **participant’s baseline** hemoglobin value only, NOT decreases between sequential hemoglobin tests.

2. Screening Pelvic Exam and Pelvic Exam forms - cervical ectopy assessment questions

When cervical ectopy is not able to be assessed, draw a single horizontal line through **all** response boxes for both “Cervical Ectopy: Percentage of cervical surface area” and “Cervical ectopy assessed by.” In addition write “Not assessed” or “N/A” in the white space near the item, and initial and date. In the “Comments” field, record the reason cervical ectopy was not assessed. On the Screening Pelvic Exam (SPE-1), these are items 6 and 6a. On the Pelvic Exam (PE-1), these are items 7 and 7a.

3. Concomitant Medications Log form, “Taken for a reported AE?” field

If a medication recorded on the Concomitant Medications (Con Meds) Log at baseline is later taken for a reported adverse event, please go back and update the medication’s entry on the Con Meds Log so that the “Taken for a reported AE?” item is marked “yes”. Record the page number of the AE Log form documenting the AE, and initial and date (use a bracket to indicate the initial and date is for all added responses). Make sure that the medication is being taken at the same dosage and frequency as reported at baseline. If the medication is being taken at a different dosage and/or frequency for the AE, report the medication as a new entry on the Con Meds Log form and add a “Date Stopped” to the medication’s entry recorded at baseline.

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4. Monthly or Quarterly Visit - Completion of items 4 and 5 for participants on product hold

When a participant is on product hold, completing MQV item 4 (“How many unused applicators is the participant estimated to have at this time?”) based on the number estimated at the time of the product hold. Decrease this number if needed based on participant reports of unused applicator loss and/or damage since the start of the product hold. Complete MQV item 5 or IV item 4 (“At this visit, how many cartons of study gel were ordered or dispensed by clinic staff”) with a “0” so that this field documents no applicators were ordered or dispensed at this visit.

5. Demographics form, Item 1

PLEASE NOTE: This applies to the Zimbabwe site ONLY.

In Zimbabwe the legal age for participating in research is 18 years. However, local regulations allow women under 18 years to participate if they are considered ‘adult’ based on other criteria (e.g. single parent). In cases where a participant is **under 18 years** of age, please record the participant’s age in item 1, and in the white space near item 1, record “ppt. legal based on local regulations.” Please also initial and date the note.

REMINDERS

1. AE Log form, item 1 - anatomical location

When reporting AEs that are known to occur in more than one anatomical location (for example, candidiasis, itching, burning), please be sure to include the anatomical location of the AE in item 1.

HPTN 035 Data Communique #6

1 December 2005

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

1. Revised Product Hold/Discontinuation form - revised version dated 04-Oct-05

A revised version of the Product Hold/Discontinuation form (version dated 04-Oct-05) has been created. The revised form has a new response box option for item 4. The form instructions have also been revised (Version 2.0, date of 04-Oct-05). All unused copies of the previous version of this form (dated 11-Nov-04) must be destroyed, as DataFax will not accept new submissions of the 09-Nov-04 form. DataFax will continue to accept refaxes (with data corrections and/or additions) of previously-completed Product Hold/Discontinuation forms.

2. Revised HPTN 035 LDMS Specimen Tracking Sheet (non-DataFax) - revised version dated 27-Sep-05

A revised version of the non-DataFax HPTN 035 LDMS Specimen Tracking Sheet has been created. The revised form is Version 3.0, dated 27-Sep-05. The form instructions have not been modified and remain Version 2.0, date of 25-Jan-05. The revised form has plasma aliquot instructions listed, along with boxes to indicate the blood specimen collection time point (enrollment or follow-up). All unused copies of the previous version of this form (Version 2.0, date of 25-Jan-05) must be destroyed.

3. Revised HPTN 035 CRF Request Form - revised version dated 07-Nov-05

A revised version of the HPTN 035 CRF Request Form (version dated 07-Nov-05) has been created. The revised version has items added to page 2 which allow sites to order blank specimen label sheets for printing resupplies of PTID labels. Please remember to complete and fax page 2 of this form even if none of the items listed on page 2 are being ordered.

CLARIFICATIONS

1. AE Log form item 5 and documentation of product holds

When documenting study product holds, note that the "held" box of AE Log form item 5 ("Study Product Administration") should only be marked when product use is held (or would be held, if on product hold already) due to the AE recorded on the AE Log form page. When the "held" box is marked, we look to make sure there is a Product Hold/Discontinuation (PH-1) form corresponding to that particular AE Log page.

If one or more AEs **not** requiring product hold are reported at the same visit that a product hold is initiated, mark "No change" for AE Log form item 5. For example, if two new AEs are reported at one visit, but a product hold is due to only one of those AEs, only the AE responsible for the hold should have the "held" box marked in AE Log form item 5. The other AE Log form completed at the visit should have the "No change" box marked.

Another example: a participant has a (newly) positive pregnancy test at visit 07.0, and also has three new AEs reported at that visit. None of the AEs require the product to be held. Mark "No change" for

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item 5 on the three AE Log forms completed at visit 07.0, and complete a Product Hold/Discontinuation form documenting pregnancy as the reason for the product hold

2. Pre-existing Conditions (PRE-1) form and documentation of STDs/RTIs diagnosed during screening

None of the STIs/RTIs listed on the Clinical Eligibility (non-DataFax) form should be documented on the Pre-existing Conditions form, even if the participant tested positive for one or more of these STIs/RTIs during screening. Because a participant is not eligible for enrollment if she is currently diagnosed with any of these STIs/RTIs, and because the Pre-existing Conditions form only documents ongoing conditions at the time of enrollment, none of the STIs/RTIs should be recorded on this form.

3. Concomitant Medications Log (CM-1) and route for medications administered via patches

For medications administered via a skin patch, mark the “other, specify” box for the route on the Concomitant Medications form and record “transdermal” on the specify line.

REMINDERS

1. Enrollment Behavior Assessment, items 1 and 2

If the participant reports having had no sex partners in the past 3 months (item 1 = “00”), but responds something other than “00” for item 2 (“In the past week, how many times did you have vaginal sex?”), please explain the discrepancy to the participant and ask her items 1 and 2 again. Explain to her that if she has had sex at least once in the past week, then she must have had at least one sex partner in the past 3 months. Update the data recorded in items 1 and 2 as needed. It is important to review participant responses for consistency while the participant is still present at the clinic.

HPTN 035 Data Communique #7

16 February 2006

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

None.

CLARIFICATIONS

1. Assignment of severity grade to lab values when the severity grade range is calculated

For lab assays that have severity grade ranges calculated using a local normal range per the DAIDS Toxicity Table, there will be times when the calculated severity grade range will have more significant digits than the reported lab value. This can lead to uncertainty in determining what severity grade to assign to the reported lab value.

The calculated grade ranges based on the December 2004 DAIDS Toxicity Table and site lab upper limit of normal (ULN) should not be rounded when determining the severity grade. The examples below provide instruction on how to assign severity grades using grading calculations.

Example 1: Total bilirubin. The Grade 1 range per the DAIDS Toxicity Table is 1.1-1.5 x ULN, and the Grade 2 range is 1.6-2.5 x ULN. The site upper limit of normal is 1.3 mg/dL. The calculated Grade 1 range for this site is 1.43 - 1.95 mg/dL and for Grade 2 it is 2.08 - 3.25 mg/dL. A lab reported value of 1.4 mg/dL should **NOT** be assigned a severity grade (and not reported as an AE), as it does not fall within the calculated Grade 1 range. A lab reported value of 2.0 mg/dL is assigned severity Grade 2, because, according to the DAIDS Toxicity Table General Instructions (page 1), when severity falls between two grades, the higher severity grade should be assigned.

Example 2: ALT. The Grade 1 range per the Toxicity Table is 1.25-2.5 x ULN, and the Grade 2 range is 2.6-5.0 x ULN. Based on the site ULN of 49 U/L, the calculated Grade 1 range is 61.25-122.5 U/L, and the calculated Grade 2 range is 127.4-245 U/L. A lab reported value of 61 U/L should not be assigned a severity grade (and should not be reported as an AE). A lab reported value of 123, 124, 125, 126, or 127 U/L should be assigned severity Grade 2, as these values fall “between” the calculated Grade 1 and 2 ranges.

In general, all significant digits beyond those reported in the lab value should be treated as zeroes and assignments of severity grade for values that fall between severity ranges should follow the instructions included in the DAIDS Toxicity Table.

REMINDERS

1. Product Hold/Discontinuation Form, item 3b

Note that this item (“How many unused product applicators were returned”) needs to be obtained from pharmacy staff, not clinic staff (as clinic staff should not be accessing/counting unused product applicators).

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2. Genital ulcer swab collection

Note that a genital ulcer swab for LDMS storage and later analysis by the Central Lab is required to be collected each time a genital ulceration is observed during study follow-up. Collection of a swab is required even if the source of the ulceration is known or suspected to be something other than an STI.

3. Text field completion

To help reduce the number of QC notes generated, please make every effort to print clearly when completing text fields and Comments fields of DataFax forms.

HPTN 035 Data Communique #8

24 March 2006

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

1. Revised Genital Bleeding Assessment (non-DataFax) form - revised version dated 13-Feb-06

A revised version of the Genital Bleeding Assessment non-DataFax form has been created. The revised form contains changes to pages 1 and 3 and revised form instructions. The form instructions are Version 2.0, date of 13-Feb-06.

CLARIFICATIONS

1. Severity grading of Hemoglobin (Hg) lab values for participants who become HIV positive

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Publish Date: December, 2004), also referred to as the Tox Table, contains separate Hg severity grading criteria for HIV negative adults and HIV positive adults (see p. 16 of the Tox Table under "Hemoglobin"). DAIDS has clarified that for participants with confirmed HIV infection, the starting timepoint for using the adult HIV positive Hg grading criteria is the **collection date of the sample confirming the participant's HIV infection**. That is, the collection date of "sample 2" in the follow-up HIV testing algorithm. For those participant's whose HIV infection is not confirmed until "sample 3", the sample 3 specimen collection date is the starting timepoint for using the adult HIV positive Hg grading criteria.

For example, if a participant's HIV sample 1 is collected on 15-Mar-06 and her sample 2 is collected on 22-Mar-06, and sample 2 confirms the participant is HIV infected, all Hg lab values from specimens collected on 22-Mar-06 forwards are graded using the HIV positive Hg severity grading criteria. All Hg values from specimens collected prior to 22-Mar-06 are graded using the HIV negative criteria.

2. Missed visits and phone contacts - how to document phone contacts within the visit window when the participant misses the visit

If a participant does not present to the study clinic within the visit window, the visit is a missed visit and a Missed Visit form is completed. If any phone contacts were made during the participant's missed visit window and DataFax data is collected during the phone call (for example, the participant reports a new AE), the phone call is documented as an interim visit using an Interim Visit form. Phone calls alone are not documented using the Monthly or Quarterly Visit form - only an Interim Visit form.

Please contact SCHARP if you have any questions about which forms to complete or which visit code to assign to phone contacts with a participant.

REMINDERS

None.

HPTN 035 Data Communique #9

31 July 2006

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

1. Faxing in HTR forms when the HIV testing algorithm can not be completed

The current forms instructions for the HTR read “Record specimen test results on this form as they become available from the local lab. Fax this form to SCHARP DataFax once results for all required specimens are available and recorded and item 5 has been completed.”

While HIV testing, as well as proper and timely completion of the follow-up HIV testing algorithm are critical aspects of HPTN 035, there may be occasions when the testing algorithm is incomplete or delayed. For example, it may not be possible to collect Sample #2 if the participant refuses to return to the study clinic for blood collection. There may also be cases when additional Western Blot testing is required in order to determine the participant’s final HIV status. For cases when the required sample(s) (after Sample #1) can not be collected readily (that is within 2 months of the positive HIV rapid test(s)), please complete and fax the HTR form with all available results and specimen collection dates. For item 5 mark the “other” response box and record “algorithm incomplete.” In the comments section of the form, record a brief explanation such as, “ppt. refuses to return to clinic,” “ppt. scheduled for Sample 2 blood draw on ddMMMyy,” etc. If and when, additional results are available, please update the form and refax it to SCHARP.

CLARIFICATIONS

1. Monthly or Quarterly Visit (MQV-1) and Interim Visit (IV-1) forms, item 3a

When counting how many new AE Log forms were completed for a given visit, AE Log forms that have been faxed to SCHARP but then marked for delete must be included in the count. For example, if three AE Log forms are completed at visit 05.0, but one is later marked for delete, the total recorded in item 3a remains ‘03,’ and does not get changed to ‘02.’

2. Monthly or Quarterly Visit (MQV-1) form, item 2 and completion of Genital Bleeding Assessment form

If, based on SSP Figure 10-2a, the participant-reported episode of genital bleeding/spotting does NOT require completion of the Genital Bleeding Assessment form, do not follow the instruction off the “yes” box to item 2. Do document in the Comments field at the bottom of the MQV or in a chart note that a Genital Bleeding Assessment form was not completed as it was not required per SSP Table 10-2a.

3. Follow-up Behavior Assessment (FBA-1 and FBA-2), item 2 and 3

When a participant reports having had vaginal sex in the past week (i.e. item 2 is greater than ‘00’) the date recorded for item 3 should be within one week prior to the visit date. As with all participant-reported data, please remember to review these items before the interview is complete so discrepancies can be addressed.

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4. Grading of lymphocyte counts for HIV positive participants

The DAIDS Toxicity Table contains a row for “absolute lymphocyte count” (p.16), but it is for HIV-negative participants only. There is no row for HIV-positive participants.

For HIV-positive participants, do not assess lymphocyte values for severity, as it is generally felt that the lymphocyte count is of little clinical value for HIV-infected participants. It is recognized that many participants with HIV will have chronically decreased lymphocyte counts, usually with no detrimental clinical effect. As such, lymphocyte counts for HIV-positive participants are not assessed for severity.

REMINDERS

1. Follow-up Behavior Assessment (FBA-5), item 10

When completing the FBA form item 10, please remember to review family planning methods the participant reported using on previous Enrollment and Follow-up Behavior Assessment forms for consistency. For example, if a participant reports surgical sterilization at enrollment, and family planning pills during the Month 3 visit, please review the responses *with the participant* and make the appropriate corrections.

HPTN 035 Data Communique #10

6 October 2006

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

There are no updates at this time.

CLARIFICATIONS

1. Follow-up Behavior Assessment form, page 7 (FBA-7)

Page 7 of the FBA is only completed when a participant reports during the Follow-up Behavior Assessment experiencing a social harm. That is, page 7 is completed only if at least one item of 11a-11h is "yes." If FBA items 11a-11h are **all** "no," end the form per the skip pattern and **DO NOT** complete or fax FBA page 7. Page 7, however, must be kept with the completed FBA pages, even if page 7 is not completed (just remember to not fax unused page 7).

2. HIV Test Results form (HTR-1), how to complete the form when Sample 2 results are anything other than "positive" and Sample 3 and/or 4 are not collected.

In cases when the Sample 2 result is "negative" or "indeterminate," but Sample 3 and/or 4 are not collected (i.e. the testing algorithm is not followed) please mark the "not done/not collected" box corresponding to each applicable sample. The Specimen Collection Dates for these items should be left blank. Also, please record the reason Sample(s) 3 and/or 4 were not collected (e.g. "Sample 3 not collected per Central Lab instruction").

REMINDERS

1. Lab values that are out of "normal" range, but per the DAIDS table for Grading Severity are below a Grade 1.

Please note that lab results that are out of range per your local clinical standards may not necessarily meet the criteria of a Grade 1 event. In these situations, please do not report these values as Pre-existing Conditions or AEs, unless clinical judgement determines otherwise.

HPTN 035 Data Communique #11

20 December 2006

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

There are no updates at this time.

CLARIFICATIONS

1. Rounding laboratory values

For some lab results the values received from the testing lab have more digits than what is provided on the CRFs. In these cases one must “round” the lab values in order to record them on the CRFs. For example, the lab may report a value of 1.82, but the form only allows one to record X.X. When recording laboratory results on CRFs, the rule for rounding is as follows:

- If the number ends in 0 through 4 then you round down.
- If the number ends in 5 through 9 then you round up.

For example, if the lab value is 1.80, 1.81, 1.82, 1.83, or 1.84 the recorded value will be 1.8. However, if the lab value is 1.85, 1.86, 1.87, 1.88, or 1.89 the recorded value will be 1.9.

2. Con Meds - how to record medications taken for more than one indication

If a medication of the *exact same* dose, frequency, and duration is being taken at the same time for more than one indication, record the medication as a single item. Do not record the medication separately for each indication.

3. AE Log form and “severity/frequency increased” Status/Outcome box

When the status/outcome of an AE is marked as “severity/frequency increased” (item 6), the same AE text should be used to describe the increased in severity/frequency AE. If the AE text is not the same on the two forms, review the status/outcome of the original AE and determine if it should be marked as “resolved” rather than “severity/frequency increased.”

Examples:

1. Participant reports a headache, grade 1, that increases in severity to grade 3 at her next visit. Make sure that the text of both AE Log forms is “headache” - do not report the increased in severity/frequency AE as “migraine” or some other version of “headache.”
2. Participant reports vaginal itching, grade 1, and all of her wet mount/pelvic exam tests are negative. At her next visit on 14Dec06, the itching is continuing, but vaginal yeast is observed and treated. Complete a new AE Log form for the grade 2 vaginal candidiasis, onset date of 14Dec06. Since the vaginal itching is continuing, do not make any updates to the “status/outcome” field of this AE - do not mark the vaginal itching AE as “severity/frequency increased” since the AE text of the two forms is different. Once the participant reports no longer experiencing the vaginal itching, mark this AE as “resolved.”

HPTN 035 Data Communique #11

4. Completion of AE Log forms involving genital signs, symptoms, and diagnoses

- Adverse Event (AE) Log case report form completion for genital signs, symptoms, and diagnoses can be quite complicated and may differ depending on the situation. As with all form completion questions, please email Corey and Missy with any questions you have regarding AE Log form completion.
- When reporting abnormal vaginal discharge as an AE, in the Comments field of the AE Log form, please specify what makes the vaginal discharge abnormal. For example, is it an increase in the amount of discharge, the color (grey/white/yellow/greenish) or smell (foul/fishy) of the discharge, or the appearance of the discharge (curd-like).
- A vaginal sign or symptom is not reported as an AE if the sign/symptom is determined to be associated with a diagnosed vaginal infection. For example, participant-reported abnormal (homogenous) vaginal discharge is not reported as an AE if the discharge is determined to be associated with a diagnosis of symptomatic BV. Note, however, that start and stop dates of the associated sign/symptom should be considered when determining onset and outcome dates for the vaginal infection AE - see scenario #3 below.
- If abnormal vaginal discharge occurs and no vaginal infection is identified, report the abnormal vaginal discharge as an AE. If a vaginal infection is later identified, and abnormal vaginal discharge is still present, report the vaginal infection as an AE and keep the abnormal vaginal discharge AE status as “continuing.” Continue to follow-up and resolve each AE (abnormal vaginal discharge and the vaginal infection) separately.

Examples:

1. Ppt comes for Month 3 visit on 15Oct06. No genital symptoms are reported. On wet mount, abnormal vaginal discharge (white, curd-like) is observed, BV negative, Trich negative, no yeast present. At Month 6 on 10Jan07, no genital symptoms are reported. Abnormal vaginal discharge (white, curd-like) is again observed, BV negative, Trich negative, yeast is present.

At Month 3:

- report “abnormal vaginal discharge” as AE, onset date is 15Oct06. In the Comments field of AE Log form, record “white, curd-like discharge.”

At Month 6:

- “abnormal vaginal discharge” AE reported at Month 3 is ongoing (no updates needed to AE Log form). Resolve when white, curd-like discharge is no longer observed on pelvic exam.

- report “asymptomatic vaginal candidiasis” as AE, onset date is 10Jan07. This AE continues until yeast is no longer observed on pelvic exam.

2. Ppt comes in for Month 6 visit on 06Nov06. She reports vaginal itching since 03Nov06. Pelvic exam/wet mount is negative for BV, Trich, and yeast. The vaginal itching is continuing at Months 7 and 8, but no abnormal pelvic exam findings are observed and all pelvic lab tests are negative at both visits. At Month 9 on 07Feb07, vaginal itching is again reported, and the wet mount is negative for BV, negative for Trich, and positive for yeast. Vaginal itching continues at Month 10 on 09Mar07, the wet mount is negative for BV and Trich, and no yeast present.

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At Month 6:

- report “vaginal itching” as AE, onset date is 03Nov06, status is “continuing.”

At Months 7 and 8:

- no change to “vaginal itching” AE

At Month 9:

- no change to “vaginal itching” AE

- report “symptomatic candidiasis” as AE, onset date is 07Feb07, status is “continuing”

At Month 10:

- no change to “vaginal itching” AE; resolve once participant reports no longer experiencing the vaginal itching

- update “symptomatic candidiasis” AE outcome to “resolved,” outcome date is 09Mar07.

3. Ppt comes for Month 3 visit on 23Oct06. Vaginal discharge (large amounts of thin, greyish discharge) is reported by the ppt, starting on 22Oct06, and is also observed on pelvic exam. Wet mount is positive for BV, negative for Trich and yeast. Ppt is treated for symptomatic BV. At Month 4 on 21Nov07, vaginal discharge is still reported by the ppt (again, reported as large amounts of thin, greyish discharge), but discharge is not observed on pelvic exam, Ppt tests negative for BV, and Trich, and no yeast present.

At Month 3:

- report “symptomatic BV” as AE, onset date is 22Oct06, status is “ongoing,” treatment is “Medications.”

At Month 4:

- the “symptomatic BV” AE reported at Month 3 is updated to “resolved,” outcome date is 21Nov07.

- report “abnormal vaginal discharge” as AE, onset date is 21Nov07, status is “continuing,” and in the “Comments” field, note that discharge was reported by ppt as thin, greyish discharge in large amounts.

4. Ppt comes for Month 3 pelvic on 23Oct06. No genital symptoms are reported. Abnormal vaginal discharge (thin, whitish, large amounts) is observed. Wet mount is negative for BV and Trich, yeast is present. At Month 6 on 21Jan07, no genital symptoms reported, but vaginal discharge is again observed (large amounts of thin, whitish discharge), BV negative, Trich negative, and no yeast present.

At Month 3:

- report “asymptomatic vaginal candidiasis” as AE, onset date is 22Oct06, status is “ongoing” (per clinician judgment, the observed discharge is considered part of the candidiasis diagnosis)

At Month 6:

- the “asymptomatic vaginal candidiasis” AE reported at Month 3 is updated to “resolved,” outcome date is 21Jan07.

- report “abnormal vaginal discharge” as AE, onset date is 21Jan07, status is “continuing,” and in the Comments field, note that discharge was clinically observed as thin, whitish discharge in large amounts.

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REMINDERS

1. Onset and Outcome Dates for AEs that increase in severity/frequency

Please remember that when an AE increases in severity or frequency, and a second AE Log form is being completed to document this the following instructions must be followed with regard to dates. The Outcome Date of the preceding (lower grade) AE must be the same as the Onset Date of the subsequent (higher grade) AE. For example, a participant reports a mild headache on 15 December 2006 and it is determined to be severity grade 1, and then on 16 December 2006 she calls the clinic to report that the headache has increased in pain and she is now taking aspirin and can't sleep (Grade 2). The *Outcome Date* for the original headache (Grade 1) will be 16 December 2006 and the *Onset Date* for the Grade 2 headache will also be 16 December 2006.

HPTN 035 Data Communique #12

21 June 2007

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

1. Completion of the Interim visit form (IV-1), item 1 under protocol version 3.0

Because version 3.0 changes the AE reporting requirements, Item 1 will be completed per this change once your site begins operating under version 3.0. this change specifically applies to the instruction off of the “in-person visit to report new symptoms” box. AE Log forms will only be completed if the symptom (or sign/diagnosis) meets the AE CRF reporting criteria in version 3.0.

2. Gaps in log page numbers (e.g. AE Log and Concomitant Medications Log forms)

Beginning July 1, 2007, when gaps are identified in log page numbers (for example, AE Log page 01, 02, and 04 are present, but page 03 is not), you will be notified by an “overdue notice” on your QC Report.

As an example, if AE Log page 01, 02, and 04 are received for PTID 999-99999-9, the overdue QC notice would appear on the QC Report as:

999-99999-9 Overdue Visit: AE Log page #03

This overdue notice should prompt you to review the AE Log pages completed and faxed for the participant. To remove the overdue notice, please fax AE Log page 03 (if already completed) or use page 03 for the next AE Log page completed for the participant.

Please do **not** renumber log page CRFs in response to this overdue notice. You should not renumber log page CRFs unless specifically instructed to do so by SCHARP staff.

CLARIFICATIONS

1. Follow-up Behavior Assessment, page 7, item 13c - BEMBA VERSION ONLY

The skip rule for this item is incorrect and should read “If no, got to item 13d.” All other language versions of this forms are correct.

REMINDERS

None.

HPTN 035 Data Communique #13

13 July 2007

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

1. Disposal of unused Screening and Enrollment forms when accrual is complete

First of all...CONGRATULATIONS on completing accrual if you already have...and CONGRATULATIONS when you do finish - you are almost there!

One month after your site's **last enrollment** please do the following:

- Put aside two unused copies of each Screening and Enrollment packet/form (including languages if applicable). Store these just in case they are needed for any reason, including as references for PPD monitors.
- All other unused Screening and Enrollment forms and packets can be discarded.

2. Return of unassigned randomization envelopes (CLINIC and PHARMACY)

One month after your site's **last randomization** please do the following:

- Return all unassigned randomization envelopes to SCHARP. Please include a cover letter with each shipment stating the envelope numbers in each shipment.
- The clinic is responsible for sending the clinic randomization envelopes and the pharmacy is responsible for sending the pharmacy randomization envelopes. These need to be separate shipments.
- Clinic staff: please share this Communique item with your pharmacy staff.
- Email Missy (missy@scharp.org) and Corey (corey@scharp.org) with the courier name and shipment tracking information so we can follow the progress of each shipment.
- Send shipments to the following address:

SCHARP
1616 Eastlake Avenue East, Suite 400
Seattle, WA 98102
ATTN: Missy Cianciola

CLARIFICATIONS

1. Return of unused applicators

If a participant returns applicators without the carton (i.e. simply in the individual wrappers), clinic staff should place the applicators in a bag or container (without inspecting the applicators), and deliver them to the pharmacist. You may not know if these applicators are in fact those which were assigned to that particular participant, but you must document that product was returned. In addition, please complete the (Product Hold/Discontinuation form) PH-1, item 3b with the number returned.

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2. Clinical follow-up on safety labs

Per protocol, complete blood counts and coagulation testing is required at all Screening Part 1 (if applicable to your site at this time), Month 3, Month 12, Month 24, and Study Exit visits for all participants. In addition, abnormal lab results may be repeated at subsequent visits for clinical management. SCHARP requires that results for the **required** safety laboratory tests (i.e. Screening Part 1, Month 3, Month 12, Month 24, and Study Exit) be recorded on the Screening Safety Laboratory or Safety Laboratory Results forms and faxed to SCHARP. Results from **clinically indicated** testing (e.g. Months 1, 2, ..., 13, 14, ..., 25, 26, 27, 28, 29) should **not** be sent to SCHARP but must be kept in the participant notebook.

Please follow this Clarification starting on 18 July 2007.

REMINDERS

1. AE Reporting Reminder

There may be cases when site staff are informed of an AE that occurred some time ago in the past. For example, this may happen if a participant forgets to report an AE during a visit, but recalls and reports the AE to site staff at a later date. If the *onset date* (**not** the date reported to site) of the AE was during the period that your site was operating under HPTN 035 Protocol Version 2.0, but you are now operating under Version 3.0, you must document and report the AE following the Version 2.0 requirements. If the onset date is within the Version 3.0 period, follow the documentation and reporting requirements for Version 3.0.

HPTN 035 Data Communique #14

7 November 2007

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

1. New forms issued

SCHARP has issued two new DataFax forms and one updated non-DataFax form in order to address data collection changes reflected in HPTN 035 Protocol Version 3.0, Letter of Amendment 1.

The 2 new forms are the:

- **Protocol V3 LOA 1 Consent form (LOA-1):** designed to capture informed consent for collection, storage, and future research testing of vaginal swabs, as well as completion of ACASI interviews. This form must be completed one time for each currently enrolled participant once your site has approval to implement Version 3.0, LOA 1.
- **Vaginal Swab Collection form (VSC-1):** designed to document collection of vaginal swabs from consented participants. this site must be completed for each participant *who has consented* to collection, storage, and future research testing of vaginal swabs. This form is to completed at each quarterly visit (similar to the Pelvic Exam form), and at any other visit when a pelvic exam is completed.

The updated form is the:

- **LDMS Specimen Tracking Sheet (non-DataFax)** - updated to include the vaginal swab specimen collection outlined in Version 3.0. Letter of Amendment 1. This form must be used once your site has received approval to implement Version 3.0, LOA 1.

These forms have been sent to each site in preparation for their use. In addition, the updated LDMS Specimen Tracking Sheet and the new VSC-1 forms have been incorporated into the Quarterly Visit form packets.

CLARIFICATIONS

1. Completion of Month 30 visits and visit codes

Please note that HPTN 035 SSP Section 6.3.2 has been updated to clarify the completion of Month 30 visits. The SSP now states “Regardless of when the Month 30 visit is completed (as long as the window has opened and the study is still running), the visit is considered the Month 30 visit and visit code 32.0 is used. In cases when the visit happens after the typical +2 week window passes, “Overdue Visit” QCs will appear on QC reports. These QCs do NOT count against site performance and will serve only as reminders for outstanding visits.”

2. Completion of Interim Visit form for non-reportable AEs (per HPTN 035 Protocol Version 3.0)

Interim Visit form, Item 1 is used to document the reason for the interim visit. Two option responses for this item direct the site to complete a new Adverse Experience Log form; they are “In-person visit to report new symptoms,” and “Phone call from participant to report new symptoms.” However, with the modified AE reporting requirements under Version 3.0 of the protocol not all reported symptoms require completion

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of a new AE Log form. Only mark these response boxes if the symptom(s) reported require completion of an AE Log form. In cases where a participant reports new symptoms that do not require AE reporting, mark the “other, specify” box for item 1 and specify that the participant reported to/phoned the clinic to report new symptoms which do not meet AE reporting requirements. SCHARP uses these items to track that required safety data has been received from the sites and marking this box without completing an AE Log form will result in a QC.

REMINDERS

None.

HPTN 035 Data Communique #15

9 January 2008

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

1. Pap Test Results form (PTR-1) when the required pap test is not done

In cases when the required pap test can not be completed (e.g., due to late stage pregnancy) please do the following with regards to form completion:

- Complete the Pelvic Exam form and record the reason the pap test was not done in the comments section of the form, and
- do NOT complete a Pap Test Results form (PTR-1).

CLARIFICATIONS

1. Pregnancy Outcome form (PO-1) completion when outcome unavailable

There may be cases when it is not possible to obtain a pregnant participant's pregnancy outcome, for example, if a participant withdraws her consent and refuses further contact, or is lost to follow-up. In these cases please do the following:

- Complete a PO-1 form using the visit code of the corresponding Pregnancy Report and History form,
- draw a single line through the response boxes for items 1, 2a, 2b, and 2c, initial and date,
- leave items 3a, 3b, and 3c blank, and
- record the reason the outcome is unavailable in the comments section. For example, "Pregnancy outcome unavailable, ppt. withdrew consent from study."

2. Pregnancy Outcome form (PO-1), items 2c and 3c, congenital anomalies

If any fetal/infant congenital anomalies are identified for a given pregnancy outcome (i.e. item 2c and/or 3c is marked "yes") then record what the anomaly is in the comments section of the form.

REMINDERS

None.

HPTN 035 Data Communique #16

21 March 2008

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

1. Follow-up Partner Status form (FPS-1 - FPS-3)

This is a new interviewer-administered form which will be completed for each participant during her Study Exit visit. Please review the form instructions carefully with your staff as there are some differences from current HPTN 035 forms. Also, this form should NOT be administered before 1 April 2008.

CLARIFICATIONS

1. Scheduling and completing Study Exit visits (please review the Plan for Exiting Participants from HPTN 035)

Scenario: A participant was enrolled in HPTN 035 on 27 April 2007. Her Month 12 (visit 14.0) target date will be 27 April 2008. She is scheduled to come to the clinic on 20 April 2008. Should the visit proceed as a Quarterly Visit or Study Exit visit?

Two criteria can be used to determine if a Study Exit visit can be completed for this scenario.

The participant:

- has been in the study for 12 months minimum,
- and is due for a quarterly visit ON or AFTER 27 April 2008 (target date).

In this case a Study Exit visit will be completed on 20 April 2008 as the criteria above have been met, and this is within the visit window.

2. CRF Data Collection and Study Termination

Note that once a participant has terminated from the study, **no*** data or information collected from the participant is reported on study CRFs. Data/information collected after the participant's study termination date should be documented in her chart notes, but none of these data are recorded on study CRFs.

**NOTE: The only data collected on a CRF after Study Exit are pregnancy outcomes. For each pregnancy which is ongoing at the time of Study Exit, the site is required to follow-up and make all reasonable attempts to determine the outcome of the pregnancy.*

Example: A participant completes her Study Exit visit on 30 April 2008. The Termination CRF is completed, date of termination is 30 April 2008. No new AEs are identified at the visit on that date, but you will not have the gonorrhea and chlamydia results back until 02 May 2008. When you receive the results, the result for gonorrhea is positive. On 02 May 2008, complete an AE Log form for the gonorrhea with a "Date Reported to Site" of 30 April 2008 (the date the specimen was collected) and record the Study Exit visit code for item 10. For item 7, "Treatment," mark "None" as the participant was not treated for this AE on 30 April 2008. Do not record any medications prescribed or given to this participant after 30 April 2008 on the Concomitant Medications form, as only data collected up through 30 April 2008 is captured on

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study CRFs. Prescribed medications and any other treatments given at this time must, however, be recorded in the participant's chart notes.

REMINDERS

1. Updating AE Log forms at Study Exit visits

Please remember to update all AE Log forms at Study Exit. Specifically, item 6. If still continuing when the participant exits it must be marked as "continuing at end of study participation." In addition, please be sure that ONLY one response box is marked here. And finally, be sure to initial and date all changes.

2. Updating Concomitant Medication forms at Study Exit visits

Remember to update the Concomitant Medication forms. For each medication recorded you either need to record a "stop date" or mark the box for "continuing at end of study."

3. Study Exit Acceptability Assessment, item 7

For gel-participants completing the Study Exit Acceptability Assessment item 7 should have a response box marked (BufferGel, Pro 2000 Gel, placebo). Some participants may be hesitant to answer or say "I do not know" as they are not supposed to have any idea about which product they have been using. However, these data are to help us measure that participants were truly blinded to their product assignments. Some will guess correctly, and some won't - it's OK. No one will be penalized for their answer. Please do your best to get a solid response for this item.

HPTN 035 Data Communique #17

2 June 2008

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

None.

CLARIFICATIONS

1. Updating and Completing Product Hold/Discontinuation forms at Study Exit

We would like to clarify the completion of the Product Hold form (gel participants only) for a couple situations which have recently come up.

Scenario 1: If a participant was put on a product hold during follow-up that resulted in permanent discontinuation of study gel (PH-1 form item 4 is “no - permanently discontinued”), you WILL NOT complete another Product Hold/Discontinuation (PH-1) form at Study Exit. The reason you should not complete another PH-1 form is that there is already a PH-1 form in the database documenting the participant’s permanent discontinuation of study gel. These cases should be relatively rare.

Scenario 2: If a participant was put on product hold during follow-up but prior to the Study Exit visit, and the reason for the hold is still continuing at the Study Exit visit (for example, the participant is exiting at Month 27, and at Month 26 she was put on hold due to pregnancy, and she is still pregnant at Month 27), please do the following:

- update the PH-1 form documenting the ongoing hold (in this case, the PH-1 form completed at Month 26 with item 2 = pregnancy). Complete item 4 as “no (hold continuing for another reason).’ For item 4a, you do not have a date to record, so line through the date boxes, and write “N/A ppt. exited study”, and date and initial. Please refax the updated form.
- complete a new PH-1 form to document permanent discontinuation of study gel due to study exit. On this form, use the visit code of the Study Exit visit, item 1 = date of the Study Exit visit, item 2 = “study termination”, and item 4 should be marked ‘no (permanently discontinued).’

Scenario 3: If, in the very rare case that at her Study Exit visit, the participant is found to be newly pregnant or has a new AE that requires a product hold, DO NOT complete a PH-1 form to document the hold. Since the participant is exiting the study and is no longer receiving study gel, the only new PH-1 forms that are completed at Study Exit visits are completed to document permanent discontinuations of study gel due to study exit/termination.

2. CRF Completion for Participants Who Do Not Complete a Study Exit Visit on or before September 14, 2008

Per the HPTN 035 Study Close-out Plan contained in SSP Section 6.12, the window for the last expected study exit visit closes on September 14, 2008. This means that all 035 participants who miss their scheduled study exit visit should be actively traced and followed (per your site’s Retention SOP) up

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through September 14, 2008, with the goal being completion of the study exit visit. Starting on September 15, 2008, please complete the following CRFs for those participants who missed their Study Exit visit:

- Termination (TM-1) form, item 1= 15-SEP-08, item 2 = 2g (unable to contact participant), item 3 = no.
- End of Study Inventory (ESI-1) form
- Any applicable Missed Visit forms (as indicated by your QC Report)

If, after September 14, 2008, a participant who did not complete the Study Exit visit presents to the study clinic and is willing to have an HIV test, please perform the following Study Exit visit evaluations:

- HIV testing (please perform this testing even if pelvic exam is not done)
- Pelvic Exam and pelvic lab evaluations/specimen collection

If such a situation occurs, please contact Corey Leburg, Missy Cianciola, Kaila Gomez, and Anne Coletti as soon as possible and we will provide instructions on how to document this visit, including case report form completion.

Prior to the HPTN 035 Results Meeting, SCHARP will issue a database freeze date for the HPTN 035 data. Once the freeze date is set, absolutely no HPTN 035 study evaluations should be performed after this date (no HIV testing, no pelvic exams), as these data will not make it into the data used for analyses. SCHARP will inform the study sites of the database freeze date as soon as it is available.

3. Partially-completed Study Exit Visits

In cases where a participant completes some, but not all, of the Study Exit visit evaluations, note that the participant only has up through her Study Exit visit window to complete any remaining exit visit procedures. For example, a participant comes in for her scheduled Study Exit visit (Month 18) on June 15 and completes all procedures except the pelvic exam. Her Month 18 window closes on July 3. If the participant is unable to complete the pelvic by or on July 3, these pelvic is considered “missed”. Complete the PE-1 and PLR-1 forms, visit code of 20.0, marked as “not done”, and terminate the participant from the study.

Note that HIV testing and pelvic exams, especially HIV testing, should be prioritized for completion at participant’s Study Exit visits.

4. Termination (TM-1) form, Reason for Termination

For those participants who are exited before their scheduled exit visit date due to retention concerns, please mark “Scheduled exit visit/end of study” as the reason for termination (item 2).

REMINDERS

1. Blantyre and Lilongwe Sites Only - ACASI Completion

Please note that the ACASI questionnaire should NOT be completed at Study Exit visits, even if the Exit Visit is a quarterly visit.

HPTN 035 Data Communique #18

6 June 2008

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

UPDATES

None.

CLARIFICATIONS

1. This applies ONLY to the Durban, South Africa site: Documentation of CAPRISA 004 and HVTN 503 study medications

For HPTN 035 participants subsequently enrolled in CAPRISA 004, please document this on the participants' HPTN 035 Concomitant Medications Log CRFs as follows:

- **Medication** = “Tenofovir gel/placebo gel (info is from ppt self-report only)”
- **Indication** = CAPRISA 004 investigational study
- **Date Started** = CAPRISA 004 enrollment date
- **Date Stopped** = CAPRISA 004 termination date **OR** HPTN 035 termination date (if the participant's HPTN 035 termination date is *before* her CAPRISA 004 termination date)
- **Dose/Units** = 1 applicator
- **Route** = mark the “other, specify” box and record “vag” on the line provided
- **Frequency** = mark the “other, specify” box and record “with vag sex” on the line provided
- **Taken for a reported AE?** = No

For HPTN 035 participants subsequently enrolled in HVTN 503, please document this on the participants' HPTN 035 Concomitant Medications Log CRFs as follows:

- **Medication** = “ 1.5×10^{10} MerckAd5 HIV-1 gag/pol/nef” for those participants who received vaccine or “HVTN 503 Merck placebo” for those participants who received placebo
- **Indication** = HVTN 503 Investigational study
- **Date Started/Date Stopped** = For each vaccination received, please enter the start and stop date (will be the same date since this is a single-dose vaccination). If a ppt received two vaccinations, then two entries should be made (one for each vaccination received) on the Con Meds Log.
- **Dose/Units** = 1 ml.
- **Route** = IM
- **Frequency** = Once
- **Taken for a reported AE?** = No

CLARIFICATIONS

None.

HPTN 035 Data Communique #19

24 October 2008

This is official study documentation for the HPTN 035 trial. Please circulate it among relevant staff for their review, print it out, and place it in your 035 SSP Manual, Section 14: Data Communiques. This document is considered part of the SSP manual.

1. Form completion for missed Study Exit visits

As we work to clean the final aspects of the HPTN 035 data, we realize that we need to clarify how forms are completed to document missed Study Exit visits. We apologize for not clearly specifying these procedures earlier. Now that we have seen how this has played out, we can offer the clarification below. Many of the QCs you see on your current and future QC reports involve these clarifications, and this guidance will hopefully help you resolve the QC in question.

Important: This clarification pertains *only to cases which are being QCed for correction at this time*. Please **do not** go back to previous cases and change how forms were completed (i.e. cases where the SL-1&2, FLR-1, PE-1, PLR-1 were completed as 'not done') We have accepted these forms and **do not** want you to delete these, and do not want you to complete any additional forms.

For cases where the Study Exit visit was missed (the participant did not complete ANY part of a study exit visit), SCHARP needs the following:

Missed Visit form. A DataFax form is required (usually an MQV-1 or MV-1) for every visit window from the time the participant enrolls until the date of termination. What has been confusing is cases where the participant missed her last visit (especially after a series of many missed visits). In addition to the Termination form (TM-1), we also need a Missed Visit form for visit window in which the termination date falls. For example, PTID 123-45678-9 missed visits 19.0 through 22.0 and MV-1 forms were completed for each of those visits. The participant's termination date on the TM-1 form 15SEP08. The participant's visit 23.0 window is 01SEP08 - 29SEP08. Since the participant's termination date, 15SEP08, falls within the 23.0 visit window, we need a MV-1 form submitted with the 23.0 visit code.

Product Hold/Discontinuation form (gel participants only). If the participant is a gel participant, we require a PH form at Study Exit, even when the Study Exit visit was missed. Continuing the above example, in addition to a Missed Visit form for visit 23.0, we also need you to complete a PH-1 form coded 23.0 (unless the participant had already permanently discontinued study product). For item 1 of the PH-1 form, record the termination date. Mark item 3 as "not applicable". For item 4, mark "no (permanently discontinued)".

Update to End of Study Inventory form. If, per the above, you submit an additional Missed Visit and/or PH-1 form to document the participant missed her last study visit, be sure that item 1 of the End of Study Inventory form (ESI-1) records the same visit code. For the example above, item 1 of the ESI-1 form should be updated to 23.0.

Update to Termination form. In cases where the participant missed her Study Exit visit, the reason for termination (item 2 on the TM-1 form) must **not** be marked as '2a' (scheduled exit visit/end of study). Please review the other options and mark the most appropriate reason.

Thank you. Please do not hesitate to contact the HPTN 035 Data Coordinators and/or Project Managers with any questions regarding these clarifications, and/or how to resolve any current QCs.