Microbicide Trials Network

CLARIFICATION MEMO #02 TO:

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

DAIDS Protocol #: 11985

IND#: 108,743

Version 2.0 / 16 December 2014
Letter of Amendment #01 / 11 April 2016

Clarification Memo Date: 11 November 2016

Section 1: Summary of Clarifications and Rationale

The procedures clarified in this Clarification Memorandum (CM) have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance. IRB/IEC approval of this CM is not required by the sponsor; however, investigators may submit the CM to the IRB/IEC overseeing the study at their site for information. This CM is official MTN-025 documentation and is effective immediately. A copy of this CM must be retained in each study site's Essential Documents file for MTN-025. No change in informed consent is necessitated by or included in this CM.

This document clarifies the intent of one of the exclusion criteria in the context of an open-label follow-on trial to explicitly allow former MTN-020(ASPIRE) participants who have moved since ASPIRE and/or who plan to move or travel during MTN-025(HOPE) to enroll in HOPE. This document also deletes language related to cervical fluid collection from the sample informed consent, which was left in the informed consent text due to an administrative error, clarifies product dispensation and hair sampling language for consistency, and clarifies that the data management system utilized is compliant with US-EU Safe Harbor, the EU Data Protection Directive 95/46/EC, ICH GCP and CFR requirements. Additionally, this document updates the location of DAIDS policy and guidance documentation, and the Protocol Team Roster.

Section 2: Implementation

With the exception of updates to the protocol team roster, text to be deleted is noted below with a ~~strikethrough~~, text to be added is in **bold**, and text in ***bold italics*** is not to be added, but to serve as a clarification of the implementation item in question. This information will be included in the protocol the next time the protocol is updated.

1.) The following refers to Section 5.3, *Exclusion Criteria,* and clarifies the intent of Exclusion Criteria 2a and 2b in the context of an open-label follow-on trial to explicitly allow enrollment of former ASPIRE participants who have relocated since ASPIRE and/or who plan to relocate or travel during HOPE, but who would otherwise be eligible and willing to participate in HOPE:

The intent of Exclusion Criteria 2a and 2b is to ensure that only study participants who will be able to adhere to their Study Visit schedule are enrolled.

A participant who plans to move away from the MTN-025 study site at which she will be enrolled (i.e., Exclusion Criteria 2a) may still be enrolled if, once she moves, she will have access to another MTN-025 study site and can be transferred to that other site, or if she is willing and able to travel back to her study site to attend study visits.

A participant who plans to travel for more than three months away from the MTN-025 study site at which she will be enrolled (i.e., Exclusion Criteria 2b) may still be enrolled if she is willing and able to travel back to the study site to attend study visits.

Therefore, participants should be excluded from enrollment as per Exclusion Criteria 2a and 2b only if they plan to move away from the study site or they plan to travel away from the study site for more than three months and they are unwilling or unable to travel back to their site to attend study visits and do not have access to any MTN-025 study sites to which they can be transferred for the study.

2.) The following modifications have been made to delete language related to cervical fluid collection that remained in the protocol text due to an administrative error, as there are no cervical fluid samples being collected for research purposes in this study:

a) Appendix V: Sample Informed Consent Document (Enrollment), *What Do I Have to Do if I Decide to Take Part in the MTN-025 Study?*:

- Provide vaginal fluid ~~and cervical fluid~~ samples:
  - To see how the dapivirine vaginal ring protects against HIV and to explore the health of the female genital tract. The vaginal fluid ~~and cervical fluid~~ collected will be used for research purposes only.

b) Appendix V: Sample Informed Consent Document (Enrollment), *Consent for Storage and Future Testing of Specimens*:

There might be a small amount of blood, hair, **and** vaginal fluid ~~and cervical fluid~~ samples left over after we have done all of the study related testing after your study visits. We would like to ask your permission to store your leftover blood, hair, **and** vaginal fluid~~, and cervical fluid~~ samples, and related health information for use in future studies… You can still enroll in this study if you decide not to have leftover blood, hair, **and** vaginal fluid ~~and cervical fluid~~ samples stored for future studies. If you do not want the left-over blood, hair, **and** vaginal fluid ~~and cervical fluid~~ samples stored, we will destroy these left over specimens.

3.) The following modifications have been made to Section 6.4.2, Study Product Dispensing, to clarify that the IoR designee can also use their discretion to provide additional rings to participants unable to attend their next scheduled visit:

If the participant is unable to attend her next scheduled visit an additional ring(s) may be provided at the discretion of the IoR**/designee** as permitted in the SSP…

… If a participant requires an additional ring for any reason, at a time other than when she is scheduled to receive one, additional product may be dispensed at the discretion of the IoR**/designee**.

4.) The following modifications have been made to clarify that hair sampling procedures are optional at each study visit, to be consistent with hair sampling language in the sample informed consent:

a) Tables in Section 7.4.1 – Months 1 and 2, Section 7.4.2 – Quarterly Visits (Months 3, 6, 9), Section 7.4.3 – Product Use End Visit (PUEV), and Section 7.4.4 – Study Exit/Termination Visit, only row under "Hair":

- Collect hair **(required unless participant declines)**

b) Appendix I, Schedule of Study Visits and Evaluations, only row under "Hair":

Hair sample(s) for DPV testing and archive **(required unless participant declines)**

5.) The following modifications have been made to Section 11.1, *Data Management Responsibilities*, to explicitly state that the overall data management system used in this study adheres to the US-EU Safe Harbor requirements and the EU Data Protection Directive 95/46/EC and is both ICH GCP and CFR compliant, along with a note clarifying how paperless data collection is being rolled out in the HOPE study:

Study CRF data are **entered into the MTN-025 database,** transferred **in compliance with the US-EU Safe Harbor Requirements and the EU Data Protection Directive 95/46/EC** to the MTN SDMC, ~~entered,~~ and cleaned using **Medidata Rave, a**~~the~~ data management system **compliant with the International Council on Harmonization (ICH) Good Clinical Practices (GCP) and US CFR guidelines for electronic data capture**.

Screening visit CRFs will first be completed in paper format, with data entered into the electronic format CRFs (eCRFs) in the Medidata Rave study database after an enrollment determination has been made for a given participant. The intent is for all other CRFs to be completed in electronic format (paperless) only.

Sites may continue to complete enrollment and follow-up visit CRFs in paper format first, prior to data entry into the study database, until they have completed their transition to paperless eCRF completion in the study database.

6.) The following modifications have been made to update the URLs where current DAIDS guidance documents can be found:

a) Section 7.13, *Specimen Collection and Processing*:

Each study site will adhere to the standards of good clinical laboratory practice (~~https://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/gclp.pdf~~) **(https://www.niaid.nih.gov/sites/default/files/documents/gclp.pdf)**

b) Section 7.14, *Specimen Handling*, has been modified to update the URL where the current DAIDS Laboratory Policy can be found:

Specimens will be handled in accordance with current requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials. (~~https://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Laboratories.aspx~~) **(https://www.niaid.nih.gov/sites/default/files/documents/laboratorypolicy1.pdf)**

c) Section 8.4.1, *Adverse Event Reporting to DAIDS*, has been modified to update the URL where the current DAIDS EAE Manual can be found:

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at ~~http://rsc.tech-res.com/safetyandpharmacovigilance/~~**http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual**.

d) Section 8.4.1, *Adverse Event Reporting to DAIDS*, has been modified to update the URL where the current DAIDS EAE Form can be found:

In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. This form is available on the RSC website, ~~http://rsc.tech-res.com/safetyandpharmacovigilance/~~**http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting**.

e) Section 8.4.3, *Grading Severity of Events*, has been modified to update the URL where the current DAIDS AE Grading Tables can be found:

The most current DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014 [Dated November 2007]), will be used and is available on the RSC website at ~~http://rsc.tech-res.com/safetyandpharmacovigilance/~~**http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables**.

f) Section 11.2, *Source Documents and Access to Source Data/Documents*, has been modified to update the URL where the current Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials policy and appendices can be found:

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (~~http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocpolicy.pdf~~)**(https://www.niaid.nih.gov/sites/default/files/documents/daids-sourcedocpolicy.pdf)** and the relevant appendix regarding source documentation (~~http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocappndx.pdf~~)**(https://www.niaid.nih.gov/sites/default/files/documents/sourcedocappndx.pdf)**.

g) Section 11.3, *Quality Control and Quality Assurance*, has been modified to update the URL where the current Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites policy can be found:

All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites ~~(http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdfhttp://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdf)~~**(https://www.niaid.nih.gov/sites/default/files/documents/qmppolicy.pdf)**.

h) Section 13.5, *Informed Consent Process*, has been modified to update the URL where the current Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials policy can be found:

Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials ~~(http://rsc.tech-res.com/policiesandregulations/)~~**(https://www.niaid.nih.gov/sites/default/files/documents/daids-sourcedocpolicy.pdf)**.

7.) Protocol Team Roster- Removals: Ken Ho, Ian McGowan.

The above information will be incorporated into the next version of the protocol at a later time if it is amended.