LETTER OF AMENDMENT #01 TO:

MTN-033

An Open Label Randomized Phase 1 Pharmacokinetic Study of Dapivirine Gel Administered Rectally to HIV-1 Seronegative Adults

Version 2.0, dated 8 December 2017

DAIDS Protocol #12065
IND #136,320

Date of Letter of Amendment: 26 July 2018

Site Instruction

The following information impacts the MTN-033 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation. Your IRB/EC will be responsible for determining the process of informing participants of the contents of this Letter of Amendment (LoA).

Implementation

Upon receiving final IRB/EC and any other applicable Regulatory Entity (RE) approval(s) for this LoA, the site should implement the LoA immediately. The site is still required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). The site will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. An LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

Summary of Revisions

This LoA does not impact the overall design or the study visit schedule for MTN-033. The primary purpose of this LoA is to clarify data management and documentation storage information for the in-depth interview (IDI) source data. Other changes include clarifying the use of CYP3A inducer(s) and/or inhibitor(s), adding hormone-replacement therapy in the form of a patch as exclusionary, clarifying an exploratory endpoint, and updating Appendix II, Algorithm for HIV Testing for Screening And Follow-up and the Protocol Team Roster.

Text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

Detailed Listing of Revisions

The following revisions (#1-3) have been made to identify IDI source data and clarify source data storage:

1. Section 7.8, *Behavioral Assessments*, second paragraph, after the last sentence:

   An IDI is planned after the application of each single dose (Visit 3 and Visit 5). The IDIs will include, among other topics, questions on user acceptability of the product, user-centered suggestions for product design and delivery, and experiences with the direct application method. **The interview notes, recording and transcript from the in-depth interview will be considered as source documentation.**

2. Section 11.1, *Data Management Responsibilities*, second paragraph:

   Transcriptions of interviews will be generated using the audio files recorded at University of Pennsylvania. Both the audio files and the transcripts will be uploaded and managed using a qualitative software package. Interview notes will be kept at UPenn in the participant files.

3. Appendix III, Sample Informed Consent Form:

   Dosing Visit (Visit 3) section, 4th bullet point:

   - Have a computer-administered interview. This interview may take approximately 45-60 minutes and will occur over video chat, e.g., Google Hangout, Skype, FaceTime, etc. This conversation will be recorded, but your responses will be kept private and confidential~~, and the audio-recording will be destroyed after it has been transcribed and checked~~. You will be asked questions about your thoughts on the study product, what might make the product more appealing to use and your experience with administering the gel in the clinic. **[*Site to modify with its site-specific source documentation storage duration requirements if longer than what is stated here*: The audio recording, notes, and analyses from these materials will be kept for at least two years after the gel is approved for marketing or two years after all developmental research on the gel is stopped.]**

   Dosing Visit (Visit 5) section, 4th bullet point:

   - Have a computer-administered interview. This interview may take approximately 45-60 minutes and will occur over video chat. You will be asked questions about your thoughts on the study product, what might make the product more appealing to use and your experience with administering the gel in the clinic. **[*Site to modify with its site-specific source documentation storage duration requirements if longer than what is stated here*: The audio recording, notes, and analyses from these materials will be kept for at least two years after the gel is approved for marketing or two years after all developmental research on the gel is stopped.]**

The following revisions (#4-7) have been made to clarify the use of CYP3A inducer(s) and/or inhibitor(s) and hormone-replacement therapy in the form of a patch:

4. Section 5.3, *Exclusion Criteria*, criterion #3:

   Anticipated use of and/or unwillingness to abstain from the following medications during study participation:

   g) Hormone-replacement therapy in tablet, **patch**, injectable or gel form

5. Section 6.8.1, *Prohibited and Discouraged Medications and Practices*, first paragraph:

   Use of anticoagulants, aspirin (greater than 81 mg/day), non-steroidal anti-inflammatory drugs (NSAIDS), other drugs that are associated with increased likelihood of bleeding other drugs that are associated with increased likelihood of bleeding, **specified** CYP3A inducer(s) and/or inhibitor(s) **(as per the SSP)**, immunomodulatory medications, and hormone-replacement therapy in tablet, **patch,** injectable or gel form are prohibited.

6. Section 9.3, *General Criteria for Permanent Discontinuation of Study Product*, under Permanent Discontinuation section, 4th bullet:

   <u>Permanent Discontinuation</u>
   A participant will be permanently discontinued from product use by the IoR/designee for any of the following reasons:
   - Reported use of **specified** CYP3A inducers and inhibitors **(as per the SSP)**
   - Reported use of hormone-replacement therapy in tablet, **patch**, injectable or gel form

7. Appendix III, Sample Informed Consent, *Screening Visit*, 5th bullet:

   - You will be asked to abstain from some medications during your participation in the study:
     <u>Medication:</u>
     - **Specified** CYP3A inducer(s) and/or inhibitor(s) (drugs that activate or deactivate an enzyme called CYP3A) **as per the SSP**. Clinic staff can provide you with specific information as to what these drugs are.
     - Hormone-replacement therapy (in pill, **patch**, needle-injected or gel forms)

The following revisions (#8, 9) have been made to update the website address of the Study Specific Procedures (SSP)Manual:

8. Section 7, *Study Procedures*, first paragraph, last sentence:

   Detailed instructions to guide and standardize procedures as well as information regarding the study visit windows are provided in the MTN-033 SSP Manual available at http://www.mtnstopshiv.org~~/studies~~.

9. Section 7.11, *Specimen Management*, first paragraph, first sentence:

   The study site will adhere to the standards of good clinical laboratory practice (https://www.niaid.nih.gov/sites/default/files/gclp.pdf), in accordance with current DAIDS Laboratory Requirements, MTN-033 SSP Manual (http://www.mtnstopshiv.org~~/studies~~) and site SOPs for proper collection, processing, labeling, transport, and storage of specimens to standardize procedures.

Other revisions:

10. An Exploratory Endpoint has been modified throughout the protocol to better reflect planned analyses

    - Changes in laboratory-applied HIV-1 replication ~~as measured by p24~~ levels in colorectal explant supernatant obtained from biopsies collected after dapivirine 0.05% *gel application*

11. Protocol Team Roster:

    Removal: Jennifer Schille

    Additions:

    Nicole Macagna, MA
    Prevention Research Specialist
    FHI 360
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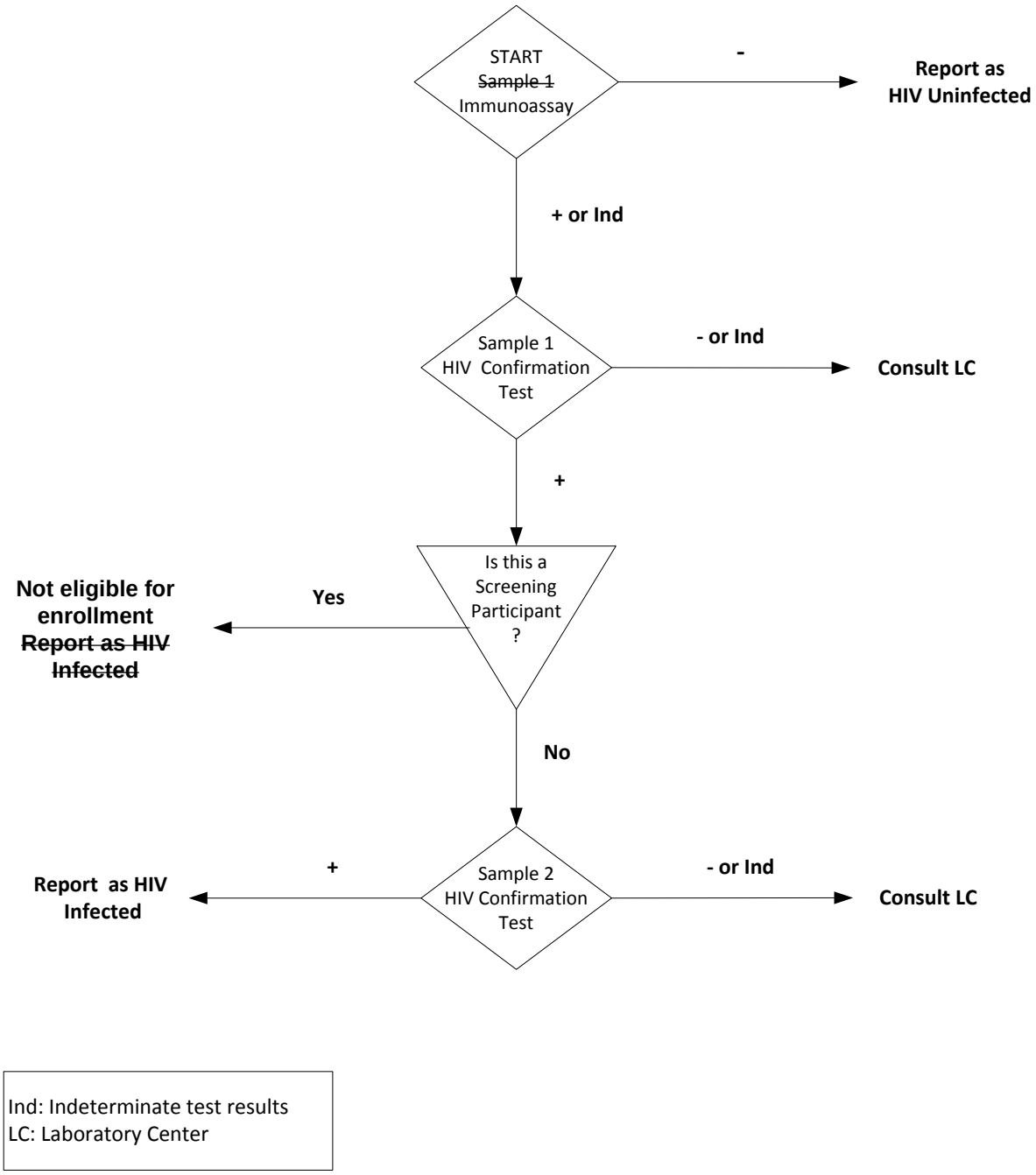
    Email: jhngo@scharp.org

12. In Appendix II, the HIV testing algorithm, as shown in the Algorithm for HIV Testing for Screening And Follow-u,p has been updated:



13. Protocol Signature Page was updated to include Letter of Amendment #1; it is appended to the end of this document.

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

MTN-033

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INVESTIGATOR SIGNATURE FORM
Version 2.0; December 8, 2017
Letter of Amendment #01, July 26, 2018
A Study of the Microbicide Trials Network

Funded by:
Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases
US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
US National Institute of Mental Health
US National Institutes of Health (NIH)

IND Holder:
DAIDS (DAIDS Protocol ID: 35122)

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference for Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., NIH, DAIDS) and institutional policies.

I agree to maintain all study documentation for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. DAIDS will inform the investigator/institution as to when these documents no longer need to be retained.

I have read and understand the information in the Investigator's Brochure(s), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Investigator of Record (print)

_____ _____
Signature of Investigator of Record Date