LETTER OF AMENDMENT #02 TO:

MTN-042

Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy

Version 2.0, dated May 20, 2021

DAIDS Protocol #38544
IND #139598

Date of Letter of Amendment: 14 October 2022

Site Instruction

The following information impacts the MTN-042 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. The following information impacts the sample informed consent. 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, sites should implement the LoA immediately. Sites are still required to submit a LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites 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. A *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-042. The purpose of this LoA is to add Population Council to locations throughout the protocol where the International Partnership for Microbicides (IPM) is mentioned due to the acquisition of IPM by Population Council. This LoA also modifies the protocol and consent form language regarding the regulatory status of the Dapivirine Vaginal Ring-004 (25 mg) (DPV VR) and updates the Protocol Team Roster.

Unless otherwise noted below, text to be deleted is noted by ~~strikethrough~~, text to be added is noted in **bold**, and text in ***bold italics*** is not to be added, but to serve as a clarification of the implementation item in question.

Detailed Listing of Revisions

The following revisions (1-7) were made to add "/Population Council" to IPM throughout the protocol to make it "IPM/Population Council" for any activities that will continue after the IPM's acquisition by Population Council is finalized.

1. Under "Pharmaceutical Company Collaborators" on the cover page:

   Pharmaceutical Company Collaborators:
   Gilead Sciences, Inc.

International Partnership for Microbicides/**Population Council**

2. Under "Pharmaceutical Company Collaborators" in Section 1.2, *Sponsor and Monitor Identification*

   International Partnership for Microbicides (IPM) **(until September 30, 2022)**
   8401 Colesville Road, Suite 200
   Silver Spring, MD 20910 USA

   Population Council (starting October 1, 2022)
   One Dag Hammarskjold Plaza
   New York, NY 10017 USA

3. In the following locations, "IPM" is replaced with "IPM/Population Council."

   - Second sentence in Section 8.1, *Safety Monitoring*:
   - Third sentence in Section 9.7, *Criteria for Early Termination of Study Participation*
   - Second sentence of the third paragraph in Section 12, *Clinical Site Monitoring*
   - Fourth sentence in Section 13.1, *Institutional Review Board/Ethics Committee*
   - Second bullet of the third paragraph in Section 13.6, *Participant Confidentiality*
   - First sentence in Section 13.11, *Study Discontinuation*:

4. Second sentence of the first paragraph in Section 13.3. *Study Coordination*

   Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trial Agreement (CTA) executed by NIAID, IPM, and Gilead Sciences, Inc. **Responsibilities agreed upon by IPM in the CTA were transferred to Population Council on October 1, 2022.**

5. First and Second sentence in Section 14, Publication Policy:

   DAIDS/NIAID and MTN policies and a CTA between IPM **(responsibilities transferred to the Population Council on October 1, 2022)**, Gilead Sciences, Inc., and NIAID, will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to the MTN Manuscript Review Committee, DAIDS/NIAID, NICHD, National Institute of Mental Health (NIMH), IPM/**Population Council**, and Gilead for review prior to submission.

6. First bullet of the "WHY YOU MAY STOP TAKING THE STUDY DRUG EARLY OR BE ASKED TO LEAVE THE STUDY" section in Appendix VII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORTS 3,* and the "WHY YOUR BABY MAY BE ASKED TO LEAVE THE STUDY " section of Appendix VIII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography), INFANT*:

   - The study is cancelled by the US FDA, US NIH, IPM/**Population Council**, Gilead Sciences, Inc., the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB)/Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of study participants

7. The third bullet of the fifth paragraph of the "Confidentiality" section in Appendices VII and VIII

    - IPM**/Population Council**, the organization that supplies the ring

The following revisions (8-10) were made to update the status of regulatory review of the DPV VR in African countries, in addition to adding Population Council to the protocol.

8. Sixth and seventh sentences of the third paragraph in Section 2.2.1, *DPV VR*:

    IPM**/Population Council** is currently seeking regulatory approval of the ring's use in several African countries through a collaborative process led by the WHO that accelerates country regulatory reviews for products that have received a positive opinion from the EMA or other stringent regulatory authority. **The ring has been approved for its use in HIV prevention by cisgender women ages 18 and older in several countries in Africa**. ~~The first of these decisions could occur by mid-2021. The ring is also under review by the US Food and Drug Administration.~~

9. Fourth sentence in "Justification for design change: Merging Cohorts3 and 4 and 4:1 randomization in merged Cohort 3" of Section 2.9, *Rationale for Study Design*:

    IPM**/Population Council** is seeking regulatory approval of the ring in several African countries through WHO's Stringent Regulatory Authorities Collaborative Review process, and the **ring has been approved for its use in HIV prevention by cisgender women ages 18 and older in several countries in Africa.** ~~first in-country decisions are likely to be issued as early as mid-2021~~.

10. Fifth sentence of the first paragraph of "Study Details - Study Products" section in Appendices VII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORTS 3* and Appendix VIII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography) - INFANT*:

    It **has been approved for its use in HIV prevention by cisgender women ages 18 and older by several countries in Africa and** remains under review by regulatory authorities in ~~the United States and~~ several **other** African countries. Study staff can keep you informed on progress being made towards approvals.

11. Protocol Team Roster – Deletion: Cheryl Blanchette

12. Protocol Team Roster – Additions:

    Rhonda White
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13. Protocol Signature Page was updated to include Letter of Amendment #2; 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-042

Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy

INVESTIGATOR SIGNATURE FORM
Version 2.0; May 20, 2021
Letter of Amendment #01; October 1, 2021
Letter of Amendment #02; October 14, 2022

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: 38544)

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