CLARIFICATION MEMO #03 TO:

MTN-005
Expanded Safety and Adherence Study of a Non-medicated Intravaginal Ring, Version 2.0, dated 19 October 2010

DAIDS Document ID 10635
Population Council IND #: 109,767

Date of Clarification Memorandum: 26 June 2012

Site Instruction and Summary of Clarification

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 approval of this CM is not required by the sponsor; however, investigators may submit the CM to the IRB overseeing the study at their site for information. This CM is official MTN-005 documentation and is effective immediately. A copy of this CM must be retained in the study site's Essential Documents file for MTN-005. No change in informed consent is necessitated by or included in this CM.

Summary of Revisions

The purpose of this clarification memo is to allow the MTN-005 protocol team to address recommendations of the NARI Ethics Committee (EC). Further details regarding MTN-005 operations can be found within the MTN-005 Operational Guidance, see www.mtnstopshiv.org. In addition, this document clarifies protocol procedures to be completed, if indicated, at interim visits.

Except for changes to Appendix I, *Schedule of Study Visits and Evaluations*, text to be added is noted below in **bold.**

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1. Language has been added to Section 2.7.2, *Rationale*, under the *Study Design* subsection, a new subsection has been added to provide information regarding the changes in appearance of used vaginal rings at the NARI site and corresponding procedures to be followed by the NARI site staff. Of note, enrollment and follow-up visits have completed at the two US sites and the changes in appearance documented at the NARI site were not observed at either US site.

   Additional IVR Information – NARI CRS

   On 4-June 2012 the NARI site informed their Ethics Committee (EC) that spots were noticed on several participants' intravaginal rings (IVRs). An emergency EC meeting was convened on 7-June 2012 and an enrollment pause was initiated. A second EC meeting was held on 16-June 2012. During the follow-up meeting, the EC reviewed the MTN-005 protocol team response to EC concerns and issued additional recommendations. A summary of the NARI EC recommendations is as follows.

- **On the 7-June the NARI EC:**
  - **Required that MTN-005 study enrollment stop at the NARI site.**
  - **Recommended that the IVRs with spots, without spots and unused rings be sent to the sponsor for evaluation and that the IVRs should be subjected to on-site microbiological examinations with a predefined protocol.**
  - **Required that all participants be informed of the new study development**

- **On the 16-June the NARI EC:**
  - **Agreed that the rings may be shipped to MTN Network Laboratory and the study sponsor, Population Council, however the EC suggested that a portion of the rings (10-20%) be retained by the site for evaluation. All regulatory requirements, such as obtaining permission from Drugs Controller General of India (DCGI) and Indian Council of Medical Research (ICMR), should be received prior to shipment.**
  - **Recommended that the study team obtain information on the physical, chemical and surface characteristics of the rings.**
  - **Suggested that the participant information sheet be written using language that is easily understandable.**
  - **Agreed that participants be followed per their original visit schedule, through their week 16 visit, as long as the follow-up period for each participant is not less than one month.**
  - **In an effort to better understand the various factors that may be affecting the IVRs, questions will be asked of participants regarding their vaginal practices. The NARI EC suggested that these questions be limited to the MTN-005 participant and that questions should not be asked regarding vaginal practices in the community.**

As a result of the NARI EC's recommendations and/or agreed upon procedures, the site should perform the following:

- **All participants randomized to the intravaginal ring arm should be asked to return to the study clinic as soon as possible. All other participants are to return to the clinic per their normal study visit schedule.**
- **All participants are to be informed of the EC recommendations, and notified of the planned additional investigations. These investigations are to be carried out both at NARI and USA (MTN and Population Council) in order to determine the cause of the spots on the IVRs.**
- **The IVR will be removed, stored and shipped to the United States for further laboratory evaluations. At least ¾ of each ring will be sent to the United States and up to ¼ of each IVR may be stored at the NARI site for additional laboratory testing.**
- **Participants will be asked a few questions about their vaginal practices by clinicians and/or designees.**
- **Participants will be followed per their original visit schedule, through their week 16 visit, as long as the follow-up of each participant is not less than one month.**

Further details regarding the above information can be found in the MTN-005 Operational Guidance, see www.mtnstopshiv.org.

No additional procedures or specimen collections are to be performed and/or collected, however vaginal specimen collection per protocol Version 2.0, dated October 19, 2010 may assist in determining the source of the IVR spots, such as:

- **Gram stain**
- **Vaginal swabs for vaginal flora assessment.**

Per Section 13.4, *Informed Consent Processes*, the study investigators will keep research participants fully informed of any new information that could affect their willingness to continue study participation.

2. In an effort to maintain consistency with Section 7.6, *Interim Contacts and Visits*, to allow all other study procedures to be performed as indicated, Appendix I, *Schedule of Study Visits and Evaluations*, *Interim* column has been modified:

	SCR	ENR	4W	8W	12W	16W/Study Term	Interim
	Up to and incl. 45 days prior to ENR	Day 0	Must occur within ±7 days of scheduled visit				
Gram Stain	x	x	x	x	x	x	+
Naked Eye Exam	x	x	x	x	x	x	▲

▲ *if clinically indicated* + *if applicable*