

**SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:**

MTN-005

DAIDS Protocol #:10635

**Expanded Safety and Adherence Study of a Non-medicated Intravaginal Ring
Version 1.0/03 April 2008**

**THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 2.0/October 19, 2010**

Population Council IND#: 109,767

Information/Instructions to Study Sites

The information contained in this protocol amendment impacts the MTN-005 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. IRB approval is required before implementation of the modifications contained in this amendment. All IRB requirements must be followed.

Please file this Summary of Changes, Version 2.0 of the protocol and all associated IRB correspondence in your essential documents files for MTN-005.

Summary of Revisions

This amendment incorporates a previously issued Clarification Memo in addition to the revisions listed below.

- The Protocol Team Roster is updated to reflect current members. The roster format is also modified to list members by affiliation
- The study sponsor is changed from the International Partnership for Microbicides to the Population Council throughout the protocol document
- The study objectives and endpoints are modified to reflect an increased focus on adherence as well as to reflect current methods of describing vaginal microflora and biomarkers. Adherence is now a primary objective while acceptability is a secondary objective. Additionally, the assessment of biofilms and biomarkers are now exploratory aims of the study.
- The background section is updated to include additional information regarding clinical studies of intravaginal rings (IVR) and to indicate that a new study IVR is selected for this study. Section 6, *Study Product* and the Sample Informed Consent documents are updated accordingly

- The eligibility criteria are updated to reflect language standardized across recent MTN protocols
- The study procedures are updated to reflect the revised objectives and endpoints. The study procedures are now comprehensively listed in table format. Appendix I, *Schedule of Study Visits and Evaluations* and the Sample Informed Consent documents are updated accordingly
- The listing of laboratory evaluations is updated to reflect the revised study endpoints
- References to the DAIDS AE Grading Table are updated to indicate that a clarification to the tables was issued in August 2009
- The adverse event reporting requirements are modified to reflect recent updates to requirements for Expedited Adverse Event Reporting to the US NIH Division of AIDS
- Clinical management guidelines are updated to treatment based on local guidelines/standards and to instruct clinicians to consult with the Protocol Safety Review Team (PSRT) regarding permanent discontinuation of study IVR use
- Section 10, *Statistical Considerations*, is modified to reflect the revised study objectives and endpoints
- Section 13, *Human Subjects Protection*, is updated to reflect new DAIDS Protocol Registration template language
- Language regarding the possible provision of test results has been removed from the Sample Informed Consent document (Storage and Future Testing of Specimens)
- The Signature Page in the Sample Informed Consent document (Storage and Future Testing of Specimens) is revised to include checkboxes for participants to indicate whether or not they agree to long-term specimen storage.
- The HIV-1 algorithm is updated to distinguish between rapid and non-rapid EIA tests and combines the algorithms for testing during screening and follow-up
- References to the Regulatory Compliance Center are changed to the Regulatory Support Center throughout the protocol document
- Other minor updates, corrections, and clarifications are incorporated

Rationale

The primary rationale for the modifications included in this protocol amendment is to update the protocol to reflect information regarding the new study intravaginal ring (IVR) provided by the Population Council. Due to regulatory and drug supply issues, the study product selected in MTN-005 Version 1.0 (non medicated cured silicone elastomer ring) is no longer available. Three rings are currently anticipated to move forward as possible vehicles for ARV-based prevention (CONRAD, IPM and Population Council rings); of these three, only one has completed preclinical testing. This ring is being tested in MTN-005.

In addition, the study objectives and endpoints are updated to reflect the revised endpoints as well as current methods of describing vaginal flora and biomarkers, which require changes to the study procedures and list of laboratory evaluations. Adherence, a new primary objective, plays a critical role in the effectiveness of a potential drug-delivery system. Acceptability is considered a one component of adherence, however many other factors also contribute to ring adherence. For example, if a ring is expelled in a location where there is no access to running water, it may not be immediately reinserted. The protocol team will assess intravaginal ring adherence as a primary endpoint and evaluate acceptability secondarily.

This amendment also includes recent updates to requirements for Expedited Adverse Event Reporting to the US NIH Division of AIDS, updates to the Protocol Registration template language, and indicates a clarification to the DAIDS AE Grading Table. Finally, discussions of study implementation, and changes to standard language across recent MTN protocols have resulted in minor updates, corrections, and clarifications to the protocol.

Implementation

This amendment is now official MTN-005 protocol documentation. Prior to implementing the revisions listed below, MTN-005 study sites will submit this Summary of Changes and protocol Version 2.0 to all relevant regulatory authorities and IRBs/ECs.

Upon receipt of all regulatory and IRB approvals and completion of protocol registration procedures, the protocol modifications listed below will be implemented. With exceptions to modifications to the Protocol Team Roster, detailed modifications of the protocol text are indicated by ~~strike through~~ (for deletions) and **bold** (for additions).

Detailed Listing of Revisions Included in Clarification Memo #01, dated April 22, 2008

1. The Protocol Team Roster has been updated.

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2. Section 1.4 Site Investigators has been updated.

Site Investigator: ~~Mallika Alexander, MBBS, DGO~~ **Sanjay Mehendale, MBBS, MD, MPH**
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Detailed Listing of Revisions New to Version 2.0

1. The Protocol Title is updated throughout the protocol to reflect the current primary objectives of the protocol:

Expanded Safety and ~~Acceptability~~ **Adherence** Study of a Non-medicated Intravaginal Ring

2. The *List of Abbreviations and Acronyms* is updated:

ASCCP	American Society for Colposcopy and Cervical Pathology
CLIA	Clinical Laboratory Improvement Amendment
CT	<i>Chlamydia trachomatis</i> , chlamydia
CONRAD	Contraceptive Research and Development Organization
DAIDS PRO	Division of AIDS Protocol Registration Office
EE	ethinyl estradiol
FHI	Family Health Interational
FHCRC	Fred Hutchinson Cancer Research Center
GC	<i>Neisseria gonorrhoeae</i> , gonorrhea
H₂O₂	hydrogen peroxide
ICH	International Conference on Harmonisation
MO	Medical Officer
NES	Nestorone
NET-Ac	norethindrone acetate
PVR	progesterone-releasing vaginal ring
RE	regulatory entity
RH	relative humidity
RGSC	Regulatory Compliance Support Center
SDA	strand displacement assay amplification
T-Cu	Copper T 380 A
UNAIDS	Joint United Nations Programme on HIV/AIDS

3. The Protocol Team Roster is updated to reflect current Protocol Team members and contact information:

The following individuals are added to the Protocol Team Roster:

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The following individuals are removed from the protocol: Grace Chow, Nancy Connolly, Bryna Harwood, Sherri Johnson, Corey Kelly, Benoît Mâsse, Karen Patterson, Jeanna Piper, Joseph Romano, Mala Shah, and Morenike Ukpung

4. Investigator Signature Form, first paragraph:

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. **I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed.** I agree to maintain all study documentation for a ~~minimum of three~~ **at least two** years ~~after submission of the site's final Financial Status Report to the US Division of Acquired Immunodeficiency Syndrome (DAIDS), unless otherwise specified by DAIDS or the Microbicide Trials Network (MTN) Coordinating and Operations Center.~~ **following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US Food and Drug Administration is notified.** Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be made available by the investigators to the MTN Manuscript Review Committee, DAIDS, and ~~IPM~~ **the Population Council** for review prior to submission.

5. Protocol Summary, modified section only:

Short Title: Safety and ~~Acceptability~~ **Adherence** of a Non-medicated Intravaginal Ring (IVR)

Sample Size: Total: 252 (168 and 84 in the IVR and No IVR arms, respectively)
India: 150 (100 and 50 in the IVR and No IVR arms, respectively)
US: ~~with competitive enrollment for two US sites~~ 102 (68 and 34 in the IVR and No IVR arms, respectively)

Study Design: ~~Three~~ **Multi**-site, open-label, two-arm, randomized controlled trial comparing study IVR to no IVR with randomization of 2:1 (IVR: No IVR)

Study Regimen: Participants will be randomized to study IVR or no IVR. The study IVR will be used for a 12-week period. Participants will be followed every 4 weeks until the **16-Week/s**~~Study t~~Termination ~~v~~Visit

Primary Objectives

- Evaluate the safety of the study IVR in HIV-uninfected women over 12 weeks of use
- Evaluate the ~~acceptability of~~ **adherence to** the study IVR in HIV-uninfected women over 12 weeks of use

Primary Endpoints

- Evidence of Grade 2 or higher genitourinary events as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (**Clarification dated August 2009**), Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies)
- ~~For women randomized to the study IVR arm, participant report on acceptability including genitourinary discomfort, ring insertion/removal issues, expulsions (including context of expulsion), and changes in sexual function~~
- **For women randomized to the study IVR arm, participant report of frequency of study IVR removal (voluntary and involuntary) and duration without IVR inserted in vagina over 12 weeks of use**

Secondary Objectives

- ~~Evaluate the study IVR after 12 weeks of use for the presence of biofilms~~
- **Describe changes in sexual behavior and changes in vaginal hygiene practices in the study IVR vs. no IVR group over 12 weeks of use/non-use**
- Evaluate the ~~adherence to~~ **acceptability of** the study IVR in HIV-uninfected women over 12 weeks of use
- Measure vaginal flora characteristics, and ~~to~~ descriptively examine changes in these characteristics over the course of study IVR use

Secondary Endpoints

- **Per participant report, changes in sexual behavior and vaginal hygiene practices**
- ~~For women randomized to the study IVR arm, participant report of frequency of study IVR removal and duration of time without IVR inserted in vagina over 12~~

~~weeks of use~~ **acceptability including genitourinary discomfort, ring insertion/removal issues, expulsions (including context of expulsion), and changes in participant and/or partner sexual feeling**

- ~~Changes in vaginal flora from enrollment to week 12 in vaginal flora as measured by Gram stain, Nugent score and quantitative culture [1] as measured by count of Lactobacillus (H2O2 positive and negative strains), anaerobic gram negative rods, Gardnerella vaginalis, Escherichia coli, Staphylococcus aureus, Candida species, Group B Streptococcus, and Enterococcus species. (Note that these quantitative vaginal cultures will only be available from the US sites, therefore reducing the available sample size for this objective)~~
- ~~Assessment of vaginal symptoms and signs suggestive of bacterial vaginosis (BV) or vulvovaginal candidiasis~~
- ~~Changes in vaginal pH and vaginal wet mount microscopy~~

Exploratory Objective

- **Test candidate biomarkers in the cervicovaginal environment before and after the use of study IVR (US sites only)**
- **Evaluate the study IVR after 12 weeks of use for the presence of biofilms (US sites only)**

Exploratory Endpoint

- **Changes in vaginal biomarkers (US sites only)**
- **Presence of biofilms on study IVR surface (US sites only)**

6. Section 1.1, *Protocol Identification* has been updated to include the new Protocol Title and Date.

7. Section 1.2, *Sponsor and Monitor Identification*:

Sponsor ~~International Partnership for Microbicides (IPM)~~
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Co-Sponsor **US National Institute of Mental Health (NIMH)**
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8. Section 1.3, *Medical Officer*:

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9. Section 1.4, *Site Investigators*:

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Site Investigator: ~~Mallika Alexander, MBBS, DGO~~
~~National AIDS Research Institute~~
~~Pune, India~~

Site Investigator: Jessica Justman, MD
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Site Investigator: Sanjay Mehendale, MBBS, MD, MPH
National AIDS Research Institute
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10. Section 1.5, *Network Laboratory*:

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11. Section 1.6, *Data Center*:

Section(s) not modified.

12. Section 1.7, *Study Operations*:

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13. Section 2.1, *New Proposed Modalities in HIV Prevention*:

While the male condom is effective in preventing sexual transmission of HIV, its use is hampered by deeply rooted cultural and social barriers. About half of all HIV infections worldwide are among women, yet the only available female-controlled method of HIV prevention is the female condom. The fact ¶that half of all HIV infections worldwide are among women indicates the pressing need for alternative prevention methods to stem the spread of heterosexual HIV infection. Research continues on many different strategies targeted at the prevention of HIV transmission, including topical microbicides, oral pre-exposure prophylaxis, prevention case management, vaccines, treatment of sexually

transmitted infection, and others.^{1, 2} ~~Recent~~ **Some** studies have provided strong evidence that male circumcision can ~~prevent~~ **reduce** female to male transmission of HIV² but there remains a critical need for female controlled methods of prevention. Use of an intravaginal ring (IVR) to deliver microbicide products is a novel investigational method for prevention of heterosexual transmission of HIV, and one that may circumvent potential difficulties related to adherence to daily or coitally dependent regimens of microbicide use. Evaluating the ~~acceptability and safety~~ of this delivery method **as well as adherence**, are therefore necessary first steps ~~before~~ **prior to** evaluating the efficacy of vaginal rings for the prevention of HIV.

14. Section 2.2, *Intravaginal Rings* (Note: The order of the section has been changed.):

There are currently three IVRs (**NuvaRing[®], Estring[®] and Femring[®]**) that have received US Food and Drug Administration (US FDA) approval.³⁻⁵ NuvaRing[®] (Organon) is approved for use as a vaginal contraceptive, it releases etonogestrel and ethinyl estradiol and must be replaced every month. **It was also approved for use in India in November 2009.** Estring[®] (Pfizer) is a hormone replacement ~~therapy~~ **system** that releases a low dose of estradiol and must be replaced every three months. **Like Estring[®], Femring[®] (Warner Chilcott) must be replaced every three months and** is another hormone replacement therapy that releases estradiol (available in two different dosing options) ~~and must be replaced every three months.~~

~~Several different rings have been investigated for contraceptive effectiveness. The Population Council has developed and carried out numerous safety and effectiveness studies on a progesterone ring for lactating women[7, 8] While not an effective contraceptive method for cycling women, it can be used by nursing women to extend the contraceptive effectiveness of lactation. The method was well accepted and effectively protected women from pregnancy. A Chilean company is currently manufacturing and distributing this ring in Chile and Peru. This ring may also be used for hormone therapy in women who require a progestin. Phase III studies are currently in progress for a 1-year contraceptive ring developed by the Population Council that releases Nestorone, a synthetic progestin and a low dose of ethinyl estradiol[9].~~

Safety studies have been conducted for all three rings currently approved by the US FDA. Published safety data from these studies include results from physical, pelvic, and colposcopic exams. In general, the adverse events (AE) reported in these studies were mild and only a small percentage ~~was~~ **were found to be** related to the device. No clinically relevant changes or abnormalities were found upon examination in study participants.⁷⁻¹⁰ Nonetheless, as with any vaginal device, there is consensus that such products are not appropriate for women who are prone to vaginal irritation or ulceration.^{3, 4}

The Population Council has been instrumental in developing vaginal rings for contraceptive effectiveness. They have developed and carried out numerous safety and effectiveness studies on Progering[®], a platinum-catalyzed, silicone elastomer progesterone vaginal ring (PVR) for lactating women.¹¹⁻¹⁵ While not an effective contraceptive method for cycling women, Progering[®] can be used by nursing women to extend the contraceptive effectiveness of lactation. The method was well accepted and has effectively protected women from pregnancy in several research studies.^{12, 14-16} A Chilean company is currently manufacturing Progering[®] which is licensed for distribution in Bolivia, Chile, Ecuador, and Peru.¹⁷ The Population Council recently completed Phase 3 studies for a 1-year contraceptive ring made of platinum-catalyzed

silicone elastomer that releases Nestorone (NES), a synthetic progestin and a low dose of ethinyl estradiol (EE).¹⁷ While the two rings are composed of the same material, the Progering[®] has a matrix delivery system while the NES/EE ring has a two-core delivery system. The Population Council has a well-established record of product development in the reproductive health field and an interest in pursuing the IVR as a platform for candidate microbicide delivery. Based on their experience with this ring and the available data on the commercially available product, the non-medicated version of Progering[®] will be used in MTN-005.

Limited studies have also been conducted to determine the effect of IVR use on vaginal microflora **and pathogenic organisms**. A study evaluating changes in the quantities of vaginal cells, aerobic and anaerobic bacteria, *Chlamydia trachomatis*, *Gardnerella vaginalis*, yeast, and *Trichomonas vaginalis* was conducted in 59 women using a combined contraceptive vaginal ring **made of Silastic[®] with an ethylene vinyl acetate (EVA) core** for either a 21, 28, 42, or 56 day cycle.¹⁸ No increases in pathogenic bacteria were found upon examination of vaginal cultures. Another study conducted with a Silastic[®] ring **with a polyethylene vinyl acetate core and** containing a combined hormonal contraceptive, evaluated the effect of the ring on bacterial flora over 20 cycles of use among 76 women.¹⁹ The investigators found no significant changes in bacterial flora over the course of the study. Two studies conducted among 92 women with NuvaRing[®] showed no adverse effects on vaginal flora as measured by Nugent score.^{20, 21} Interestingly, a NuvaRing[®] study conducted by Veres et al.²⁰ found an increase in **hydrogen peroxide (H₂O₂) producing *Lactobacillus* colonies as measured by Nugent score and colony morphology quantitative culture**. Presence of H₂O₂-producing lactobacilli is beneficial to vaginal health and it has been suggested that further studies be conducted to confirm these findings.

~~Acceptability is one of the key drivers of product uptake. Acceptability of NuvaRing[®], Estring[®], and Femring[®] has been measured through patient reporting; often through questionnaires, diary cards, and interviews[18]. In general, participants are asked about the ease of ring insertion and removal, whether or not she or her partner felt the ring during intercourse, if the partner objects to the ring, whether or not the ring is comfortable, if they are satisfied with the ring, and whether or not the ring is deemed to be effective as either a contraceptive method or hormone replacement therapy.~~

The success of IVRs in delivering effective contraceptive and hormone- replacement methods has spurred an interest in developing IVRs expressly for the prevention of HIV. Phase III ½ safety studies have been conducted **by the International Partnership for Microbicides (IPM) for the an IVR containing TMC120dapivirine**, a nonnucleoside reverse transcriptase inhibitor (NNRTI). The IVRs used in these studies (both active and placebo) ~~are silicone elastomer rings with the same design as the Femring[®], and have been well tolerated by most study participants. The nonmedicated version of the Femring[®] will be the study product investigated in MTN-005.~~ **have been well tolerated by most study participants.**

15. Section 2.3, *Silicone Elastomer*

Section(s) not modified.

16. Section 2.4, *Preclinical Studies*, first paragraph added:

Preclinical studies for NuSil are provided below. The ring planned for MTN-005 is made from the same silicone elastomer material as NuSil.

17. Section 2.4, *Preclinical Studies*, third paragraph, final sentence:

In an Ames test, a saline extract of the NuSil silicone material was considered ~~not~~ to be non- mutagenic.

18. Section 2.5, *Clinical Studies*, has been divided into two subsections-2.5.1, *Progering*[®] and 2.5.2, *Other Clinical IVR Studies* (Note: References to paragraph numbers refer to the current structure):

Section 2.5.1, *Progering*[®]:

Progering[®] is a silicone elastomer progesterone-releasing ring, a non-medicated version of this ring will be studied in MTN-005.

Sivin and colleagues²⁸ compared the efficacy of Progering[®] to the T-Cu IUD among lactating women across nine clinics in Asia, Latin America, North Africa, and the US. Participants chose either the PVR (n=802) or the Copper T 380 A (T-Cu) intrauterine device (IUD, n=734). Women in this study inserted the PVR 4-9 weeks postpartum and were asked to replace the ring every three months, and continue use up to one year or until weaning. Follow-up visits were conducted at 1, 3, 6, 9, and 12 months and once again at two months following PVR discontinuation. Participants in the PVR group reported problems with expulsion and unexpected bleeding during the first month of PVR use. Importantly, Progering[®] use was not associated with macroscopic lesions, although the majority of participants reported discharge, leukorrhea, or vaginitis. Overall, Progering[®] was found to be a well-accepted method of contraception during lactation.

The safety and efficacy study that ultimately led to the registration of the PVR in Chile was conducted by Massai et al., among 547 lactating women at three different clinics.¹⁴ Participants chose either the PVR (n=285) or the T-Cu IUD (n=262). Women inserted the PVR 5-9 weeks postpartum. Women in the PVR arm were asked to use a PVR for three months at a time for either one year or until weaning, whichever came first. Follow-up visits were conducted every three months. Colposcopic examinations were conducted in 45 participants using the PVR and 280 participants were included in the PVR safety analysis. Changes to the vaginal epithelium were found in 8 participants. Two participants presented with vaginal abrasion (one required no follow-up and the other resolved after three months), and the remaining 6 presented with minor changes. No serious adverse events (SAE) were found in women using the PVR. Results from this study were used as the reference group for the study below.

Massai and colleagues also conducted a Phase 2 safety and efficacy study of extended use of the PVR among 220 lactating women.¹⁵ Women in this study inserted the PVR 8-9 weeks postpartum and were asked to replace the ring after every four months of use, and to continue use for one year or until weaning. Follow-up visits were conducted every month. Women who completed ring use the first four months were included in the safety analysis (n=192). Although no SAEs were reported in this study, the rate of overall events was higher in this study than in the reference group (32.3/100 vs. 12.4/100 women-months). This frequency of follow-up

visits likely explains the higher rate of overall events. Nonetheless, study results also demonstrated the safety and efficacy of the PVR over an extended period of time.

The Massai and Sivin studies evaluated the IVR proposed for use in MTN-005 in a total of approximately 1,307 women, for safety and contraceptive efficacy study. The study populations are different from MTN-005: the former is in Chilean nursing women, the latter is in lactating women in Asia, Latin America, North Africa, and the US. The IVRs used in smaller studies, e.g., IPM 013 (n=48) and IPM 024 (n=16), are also made from platinum-catalyzed silicone elastomer, but are not the same IVR proposed for use in MTN-005. While several IVR studies have been performed or are currently in progress, MTN-005 is the first of its kind as an expanded safety and adherence study, specifically for use as a potential platform for HIV prevention agents. The targeted sample size (252) allows us to investigate the comprehensive profile of safety, tolerability, and adherence to the silicone elastomer study IVR in sexually active younger women, contributing to the body of data regarding IVR use in this population.

Section 2.5.2, *Other Clinical IVR Studies:*

Contraceptive Intravaginal Silicone Elastomer Rings

The Population Council conducted a series of Phase 1 safety studies of various contraceptive rings at four study sites in California, Australia, the Dominican Republic, and Finland.²⁸ These studies were designed to assess changes in the vaginal epithelial surface of women using four types of contraceptive rings for up to one year. Women used IVRs containing NES (50, 75, or 100 µg), NES/EE (100/30 and 150/15 µg, or norethindrone acetate (NET-Ac, 1000 µg)/EE (20 µg). Two NET-Ac/EE IVRs were included in these studies—one to be used for 4 months and another, for one year. Detailed vaginal inspections including colposcopy were conducted prior to ring insertion and every two months until study exit.

Two NET-Ac/EE IVRs were included in these studies—one to be used for 4 months and another, for one year. Detailed vaginal inspections including colposcopy were conducted prior to ring insertion and every two months until study exit.

Data from these studies were compared with a historical control group (non ring users, N=107).²⁹ Although study results showed some differences in findings among the different clinics, there were no marked differences in vaginal lesions by ring type.²⁸ Eighty-eight cases of atypical or abnormal vaginal epithelial surface findings were detected out of a total of 507 colposcopic examinations over the course of the study. Petechiae and aceto-petechiae were the most common findings (16 and 9 occurrences respectively in ring users as compared to 18 and 16 occurrences among non ring users coupled with pretreatment findings). It is important to note that the bulk of these findings were subtle and similar to the historical control group. Overall findings suggest that the rings contributed little, if at all, to clinically significant lesions or overall lesion incidence.

A 13-week, Phase 3 double-blinded, randomized, controlled clinical trial of the estrogen-containing Femring[®] was conducted with postmenopausal women.³¹ Of the 333 women in the study, 108 were randomized to the placebo ring group, 113 to the Estradiol vaginal ring group delivering 0.05 mg/day, and 112 to the Estradiol vaginal ring group delivering 0.10 mg/day. The non-medicated ring treatment group showed

a higher incidence of vaginal discharge (8.3% vs. 1.8% and 2.7%), genital disorders (8.3% vs. 2.7% and 2.7%), vulvovaginitis (6.5% vs. 5.3% and 0.9%) and vaginal irritation (3.7% vs. 0.9% and 1.8%).⁴ These findings were consistent for women who received estrogen replacement therapy vs. those who did not.

Dapivirine-Releasing Intravaginal Silicone Elastomer Rings

The International Partnership for Microbicides (IPM) conducted a Phase 1 crossover safety study of a reservoir-type silicone elastomer IVR (IPM 001).³² All 12 participants initially used the placebo IVR for 7 consecutive days followed by 7-day use of a 200 mg dapivirine-containing IVR. Safety and tolerability were assessed via pelvic exams, colposcopy, and clinical laboratory measurements. Most (11/12) participants experienced at least 1 AE while on study, the most common being mild bleeding (50%), although judged to be doubtfully related to IVR use. No specific trends between vaginal bleeding and IVR insert/removal for tissue biopsy (for PK) were observed. Three treatment-emergent laboratory abnormalities were also reported in the placebo IVR group and 1 in the dapivirine IVR group. None, however, were reported as AEs by study investigators. IPM 001 results demonstrate that IVR use was generally safe and well-tolerated among study participants.

The safety of ~~the another reservoir-type silicone elastomer~~ non-medicated IVR ~~that will be used in this study~~ was recently also evaluated in IPM 008, ~~a pharmacokinetics and safety study of the TMC 120 ring.~~^{20-23, 28} IPM 008 was a randomized, double-blinded, placebo controlled, safety and pharmacokinetics trial in thirteen sexually abstinent healthy women. Ten women were randomized to the dapivirine (25mg) IVR group and 3 women to the placebo IVR group. The women in both the treatment and placebo groups ~~were used the study rings for 7 days.~~ **Safety and tolerability were assessed via pelvic exams, colposcopy, and clinical laboratory measurements. Participants in both IVR groups (n=6) experienced mild vaginal bleeding which was likely unrelated to IVR use. Some participants also experienced fatigue, abdominal discomfort, genital pruritus, and urinary incontinence (all were grade 1). One participant in the placebo IVR group was also diagnosed with grade 1 hypokalemia. Overall, the study results showed that there were no clinically relevant changes over time with regards to physical examinations, vital signs, vaginal pH, Nugent scores, laboratory parameters, and urinalysis. Furthermore, no SAEs were reported during this study, and of the AEs that were reported, none appeared were deemed to be related to the study products.**

IPM 018, an exploratory safety and pharmacokinetic study of matrix and reservoir tin-catalyzed silicone elastomer IVRs, was completed among 24 healthy, HIV-negative women at a single site in Belgium. Women were randomized to a matrix-type IVR containing 25 mg of dapivirine, a reservoir-type IVR containing 25 mg of dapivirine or a placebo matrix IVR in a 1:1:1 ratio.^{31, 32} Women used the IVR for 28 consecutive days and follow-up visits were conducted over a 33-day period. Safety was assessed via pelvic exams, colposcopy, and clinical laboratory tests, with pelvic exams performed at screening, days 0-3, 5, 7, 14, 21, 28, and 33. Colposcopy was done on days 0, 28, and 33 and treatment-emergent AEs were captured at all follow-up visits. Some participants in the placebo IVR (63%) and in the dapivirine IVR (50% and 63%) groups were diagnosed with headache, abdominal pain, fatigue, vaginal/genital discharge, and nausea that were considered to be possibly related to study product. However, all events resolved within two days. One participant in the matrix-type IVR group had mild vaginal epithelial peeling and one in the placebo group had mild vaginal discharge—both of which were judged to be possibly related to the IVR.

Additional IVR Safety Studies for HIV Prevention or Contraception

Several other safety studies assessing the safety of IVRs as possible platforms for HIV prevention agent delivery or contraception are summarized in the table below. These studies are either planned, ongoing, or in analysis.

Table 2: Summary of Other IVR Studies

Location	Study Number	Study IVR	Composition of Study IVR	Population	Design
Belgium	IPM 013 ³³	Dapivirine (25 mg) matrix IVR Placebo IVR	Silicone elastomer	Sexually active women	Double-blinded, randomized, placebo-controlled, safety and pharmacokinetic study of dapivirine for a duration of 56 or 58 days
South Africa Kenya, Malawi, Rwanda, Tanzania, Zambia	IPM 015 ³³	Dapivirine (25 mg) IVR Placebo IVR	Silicone elastomer	Sexually active women	Phase 1/2 randomized, placebo-controlled, expanded safety, of dapivirine for a duration of 28 days
Belgium	IPM 024 ³³	Dapivirine (25 mg) matrix IVR Placebo IVR	Silicone elastomer	Sexually abstinent women	Double-blinded, randomized, placebo-controlled safety and pharmacokinetic study of dapivirine for a duration of 12 weeks
Multi-center	Population Council ³⁷	NES (150 µg)/EE (15 µg) IVR	Silicone elastomer	Sexually active women	Open-label study on the efficacy, cycle control, and safety of a contraceptive vaginal ring delivering a daily dose of 150 µg of NES and 15 µg of EE

Non-medicated Intravaginal Silicone Elastomer Rings

Limited studies have been performed solely in non-medicated IVRs as most often use non-medicated IVRs as the placebo control in contraceptive, hormone, or candidate microbicide-releasing IVR studies. IPM 011 is a safety and acceptability study of the same—a non-medicated tin catalyzed, silicone elastomer vaginal ring that will be used in MTN-005.³¹ **This study is a recently completed, randomized, open-label crossover study currently enrolling participants in among 200–170 healthy, sexually active women at four sites in Kenya, South Africa and Tanzania.³² The participants are either in the Vaginal Ring group or Observational Study (no ring). The participants were randomized to the IVR group or no ring group for the first twelve weeks, and if asymptomatic for genital infections and negative for findings on the pelvic examination after the first twelve week period is was completed, participants then crossed over into the opposite group for an additional twelve weeks. In addition to the enrollment visit, the participants have had follow-up visits at 2, 4, 8, and 12 weeks prior to the crossover, and again at 2, 4, 8, and 12 weeks post-crossover. Participants also undergo underwent a colposcopy examination at enrollment, crossover, and at the last study visit. Participants also underwent pelvic examinations at the screening, enrollment, 2 and 8 weeks, crossover, 2 and 8 weeks post-crossover, and at the last study visit. Study staff will conducted AE assessments, including evaluating for vaginal complaints, at all of the follow-up visits. Preliminary data suggest that IVR use is safe and well-tolerated. Twenty-two women reported possibly/probably related AEs. Only 1 colposcopic finding (moderate) was detected among the women who completed the study (n=144). No ring-related SAEs were reported.**

In 2002, Warner Chilcott conducted an acceptability study of a non-medicated silicone elastomer IVR in nearly 6000 women throughout the United States.³⁵ Overall, the non-medicated IVR was well tolerated by subjects-participants. The most frequently reported

AE was vaginal discharge (1.4%) and no other AEs were reported with a frequency of >1%. A 13-week long, Phase 3 double-blind, randomized, controlled clinical trial of the estrogen-containing Femring[®] was conducted with postmenopausal women.³⁶ Of the 333 women in the study, 108 were randomized to the placebo ring group, 113 to the Estradiol 0.05mg/day group, and 112 to the Estradiol 0.10mg/day group. The non-medicated ring treatment group showed a higher incidence of vaginal discharge (8.3% vs. 1.8% and 2.7%), genital disorders (8.3% vs. 2.7% and 2.7%), vulvovaginitis (6.5% vs. 5.3% and 0.9%) and vaginal irritation (3.7% vs. 0.9% and 1.8%).⁴ These findings were not unexpected because they demonstrated the effect of the non-medicated IVR in an estrogen-deprived atrophic vagina. Furthermore, the medical opinion was that it is not uncommon to find vaginal mucosa defects or lacerations in the postmenopausal vagina.

19. Section 2.6, *Marketing Experience*:

~~Warner Chilcott's IVR has been approved as the delivery method for a hormone replacement drug Menoring[®] in the United Kingdom (2001) and Femring[®] in the United States (2003). Organon's IVR has been approved as the delivery method for the combined contraceptive, NuvaRing[®] (2001).~~

~~The US FDA recently placed a black box warning on Femring[®]; however, this warning is a result of data associating oral conjugated estrogens with an increased risk of certain serious medical complications in postmenopausal women. The additional warning stems from The Women's Health Initiative study that reported an increased risk of cardiovascular events in postmenopausal women during five years of treatment with oral conjugated estrogens combined with medroxyprogesterone acetate and the Women's Health Initiative Memory Study, that reported an increased risk of developing probable dementia in postmenopausal women over four years of treatment with oral conjugated estrogens combined with medroxyprogesterone acetate. Thus, this black box warning does not apply to the study IVR.~~

Laboratorios Andromaco's IVR Progering[®] has been approved as the delivery method for contraception in Peru and Chile (1999) and is licensed for distribution in Bolivia, Chile, Ecuador, and Peru. Progering[®] is the brand name of one progesterone-only vaginal ring manufactured and supplied by Laboratorios Andromaco S.A. in Chile.

20. Section 2.7.1, *Study Hypothesis*:

MTN-005 hypothesizes that the study IVR will be safe and acceptable for a three month period of use **will be used as directed by US and non-US women over 12 weeks of use.**

21. Section 2.7.2, *Rationale*:

Medicated IVRs have the potential to reduce the heterosexual transmission of HIV if found to be safe, acceptable, and effective against HIV infection. This study will provide data to support the **on the safety of and investigate adherence to acceptability** of a three month period of IVR use in US and Indian populations. Safety of the silicone elastomer ring has primarily been studied in postmenopausal women **although recent studies of candidate microbicide-releasing IVRs have also used the silicone elastomer composition.** While safety and tolerability of NuvaRing[®] **have** been studied in thousands of sexually active younger women, its ethylene-vinyl-acetate copolymer (EVA) composition and smaller

diameter may preclude results from these studies from being extrapolated to the safety and tolerability of the silicone elastomer ring in pre-menopausal women. MTN-005 will investigate the safety and tolerability of the silicone elastomer study IVR in sexually active younger women, contributing to the body of data regarding IVR use in this population.

Second through fifth paragraphs:

Adherence and Acceptability

This study will investigate adherence and acceptability parameters regarding the non-medicated version of Progering[®], in both Indian and US populations. Assessments of IVR adherence and acceptability will include a combination of interviewer-administered questions and audio computer-assisted self-interviewing (ACASI) questionnaire instruments that participants will complete in a private setting. The advantage of ACASI over face-to-face interviews is that neither the investigator nor anyone else in the interview area hears the question or response, thus reducing social desirability bias. Studies in developing countries have increasingly implemented ACASI in Kenya³⁸⁻⁴⁰, Malawi⁴¹; Zimbabwe⁴², Thailand^{43, 44}, India⁴⁵, Vietnam⁴⁶ and Mexico⁴⁷ among very diverse populations, including some in remote rural areas, with varying degrees of literacy and computer exposure. Findings from these studies suggest that even in countries with low literacy or among populations unfamiliar with computers, ACASI is a useful technique for collecting data on sensitive behaviors.

Adherence

As noted in Section 2.2, commercially available IVRs are designed to be replaced every month or every 3 months. An IVR designed to release HIV prevention agents will likely need to be used continuously unless future studies prove otherwise. In clinical trials, participants often indicate that the product is acceptable, but in the end do not use the study product as advised. In CAPRISA 004, for example, a placebo-controlled effectiveness and safety trial of tenofovir 1% gel when used before and after each act of intercourse, a high percentage of participants indicated that the gel was acceptable (97.4%). However, about 41% of the women had less than 50% gel adherence.⁴⁸ The CAPRISA 004 results confirmed the importance of adherence on effectiveness since the greatest incidence reduction was among those who were most likely to use the gel as instructed.

IPM 011, for example, evaluated the safety and acceptability of a silicone elastomer IVR as a potential platform for microbicide delivery among African women for a duration of 3 months.³⁶ Despite the fact that 100% of the women reported that they would be willing to use the IVR designed for HIV prevention if found to be effective, approximately 18% reported either ring expulsion or removal, with the most frequent reason for expulsion or removal being menses. In a preregistration study of Progering[®], Massai and colleagues¹⁴ also found that a significant proportion of ring users discontinued use due to use-related problems (26.8%). The most frequent reasons for IVR discontinuation were ring expulsion (4.9% event rate) and uncomfortable use (6.9% event rate). Other reasons for non-use included delayed insertion of a replacement ring (13.6% event rate) and having the ring out of place for > 48 hours (3.2% event rate). Sivin also presented information regarding IVR adherence in 802 participants who used the Progering[®]. Frequent expulsions occurred in 6.0% of the IVR users and led to a termination rate of 8.1 per 100 at one year. Other problems related to the use of the IVR (one-year gross rate = 25.9 per

100) were removal of the ring for more than 24 hours (9.2% of participants), use considered unpleasant (6.9%), and no new ring available when ring replacement was due (1.9%).¹¹

As the HIV prevention field continues to move forward with novel delivery mechanisms for HIV prevention agents, it is critical to explore the factors that impact adherence. In studies involving active product, the intent-to-treat (ITT) analyses may not demonstrate efficacy if participants are unwilling or unable to use the product. As such, MTN-005 is designed to assess the frequency of ring use and non-use, and the reasons for such.

Sixth paragraph, first sentence:

Acceptability

Product acceptability is a critical factor in determining whether an IVR should be introduced in a particular setting, **but is also a determinant of product adherence.**

Sixth paragraph, last two sentences:

A follow-up study at AIIMS showed that women preferred the vaginal contraceptive ring to any other available contraceptive method. While these data give some idea of tolerability to IVR among Indian women, they are specific to a hormone-IVR, and not necessarily applicable for a non-medicated ring of a different design-IVR as a possible platform for microbicide delivery.

Seventh paragraph:

While data exist on tolerability parameters for NuvaRing[®] among perimenopausal US and European women^{8, 51, 52} and for Progering[®] among the study IVR among perimenopausal women in the US³⁶⁻³⁸ nursing women in Latin America^{12, 29}, acceptability data in perimenopausal Indian and US pre-menopausal women for this particular ring design are currently limited-the non-medicated version of Progering[®] is lacking. As the thickness of the proposed study IVR is nearly twice greater than that of the commonly used NuvaRing[®], it will be important to evaluate whether reproductive age women find this alternate ring design to be acceptable. Furthermore, there are currently ~~no~~ **limited** published data on contraceptive or hormonal vaginal ring use among Indian women even though discussions of vaginal rings have been published in a limited number of Indian medical journals.^{16, 53} Articles published in Indian medical journals tend to focus on vaginal rings as novel contraceptives and do not specifically address IVR acceptability among Indian women.

Eighth paragraph, second through fifth sentences:

The availability of acceptability data in areas where there is a high risk of HIV acquisition is crucial. UNAIDS recently reported that among young people in India, ages 15-24, only 51% of the women as compared to 59% of the men surveyed, reported condom use during their last casual sexual encounter. These data highlight an urgent need for acceptable methods of HIV prevention. Since the study IVR is a new platform for microbicide delivery it is imperative to assess its acceptability prior to proceeding with further studies. Even if a ring were developed that was effective in reducing HIV transmission, if the product has physical or clinical attributes that women and their partners dislike or find distasteful, it is less likely that women will initiate use or use it consistently. Therefore, a primary objective of this

~~study is to assess the acceptability of the study IVR in study participants. Smith and colleagues recently assessed the potential acceptability of an IVR among female sex workers and male clients in Kenya.⁴¹ Findings from focus group discussions underscored the myriad attitudes and concerns that could impact the uptake of an IVR in a high-risk population. These data highlight an urgent need for acceptable methods of HIV prevention. Since the study IVR is a new platform for microbicide delivery it is imperative to assess its acceptability prior to proceeding with further studies. Even if a ring were developed that was effective in reducing HIV transmission, if the product has physical or clinical attributes that women and their partners dislike or find distasteful, it is less likely that women will initiate use or use it consistently. Therefore, a primary objective of this study is to assess the acceptability of the study IVR in study participants.~~

~~Assessments of IVR acceptability will include audio computer assisted self interviewing (ACASI) questionnaire instruments that participants will complete in a private setting. The advantage of ACASI over face-to-face interviews is that neither the investigator nor anyone else in the interview area hears the question or response, thus reducing social desirability bias. In addition, the researcher does not have to be concerned with differences in the characteristics or interviewing styles of the interviewers[32]. Recent studies in developing countries have increasingly implemented ACASI in Kenya[33-35], Malawi[36]; Zimbabwe[37]; Thailand[38, 39], India[40], Vietnam[41] and Mexico[42] among very diverse populations, including some in remote rural areas, with varying degrees of literacy and computer exposure. Findings from these studies suggest that even in countries with low literacy or among populations unfamiliar with computers, ACASI is a useful, and often superior, technique for collecting data on sensitive behaviors.~~

Tenth paragraph, title and last sentence added:

Vaginal Flora

Given the time sensitive nature of specimen collection, the biofilm assessments will only be done at the US sites.

Eleventh paragraph:

The inclusion of a no ring group in MTN-005 will permit the collection of data on AEs (including colposcopic findings) and changes **in** vaginal flora that are likely to be present in the study population in the absence of vaginal ring use. The inclusion of this group will also provide **comparator** data on changes in sexual behavior ~~without ring use~~ **and vaginal hygiene practices** during the study period.

22. Section 3.1, *Primary Objectives*, second bullet:

- Evaluate the acceptability **adherence of to** the study IVR in HIV-uninfected women over 12 weeks of use

23. Section 3.2, *Secondary Objectives*, first and second bullets:

- **Describe changes in sexual behavior and changes in vaginal hygiene practices in study IVR vs. no ring group over 12 weeks of use/non-use**
- Evaluate the adherence **acceptability** ~~to~~ of the study IVR in HIV-uninfected women over 12 weeks of use

24. Section 3.3, *Exploratory Objective*:

- **Test candidate biomarkers in the cervicovaginal environment before and after the use of study IVR**
- **Evaluate the study IVR after 12 weeks of use for the presence of biofilms (US sites only)**

25. Section 4.1, *Identification of Study Design*:

MTN-005 ~~will be~~ **is** a ~~three~~ **multi**-site, open-label, two-arm, randomized controlled trial of a non-medicated IVR.

26. Section 4.2, *Summary of Major Endpoints*:

- Evidence of Grade 2 or higher genitourinary events as defined by the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (**clarification dated August 2009**), Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies)
- For women randomized to the study IVR arm, participant report ~~on acceptability including genitourinary discomfort, ring insertion/removal issues, expulsions (including context of expulsion), and changes in sexual function~~ of **frequency of study IVR removal (voluntary and involuntary) and duration without IVR inserted in vagina over 12 weeks of use**

27. Section 4.3, *Description of Study Population*:

The study population will include 252 ~~evaluable~~ generally healthy 18-45 year-old women who are HIV-uninfected, non-pregnant, sexually active and using adequate contraception, as described in Sections ~~5.2~~ **3 and 5.4**.

28. Section 4.4, *Time to Complete Enrollment*

The approximate time to complete study enrollment is expected to be six months for the US sites and ten months for the India site. The time of total study duration is expected to be a minimum of approximately ~~fourteen~~ **14** months, including the study follow-up period.

29. *Table 2: Study Groups*, in Section 4.5, *Study Groups*, is omitted to eliminate redundancy within the protocol.

30. Section 4.6, *Sequence and Duration of Trial Periods*

The total duration of participation from the Enrollment Visit to the Termination Visit is 16 weeks. Visits ~~may~~ **will ideally** be completed within a specified ± 7 day windows around target dates. Detailed information regarding visit windows will be thoroughly described in the MTN-005 Study-Specific Procedures (SSP) Manual.

31. Section 4.7, *Expected Duration of Participation*; Section 4.8, *Sites*; Section 5.1, *Selection of the Study Population*

Section(s) not modified.

32. Section 5.2, *Recruitment* added:

Participants will be recruited from a variety of sources across sites, including family planning clinics, colleges and universities, and gynecology clinics, as well as community-based locations. Participants also will be referred to the study from other local research projects and other health and social service providers serving the target study population. Recruitment materials will be approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs) prior to use. Site community representatives should advise on these materials before they are submitted to the IRB/EC for review.

33. Section 5.3, *Inclusion Criteria*:

Item 1:

1. Age 18-45 years (inclusive) at ~~screening~~ **Enrollment**, verified per site standard operating procedures (SOP)

Item 2:

2. Willing and able to provide written informed consent **to be screened for screening and enrollment and to take part in the study**

Item 4:

4. HIV-uninfected at ~~s~~ **Screening based on testing performed by study staff at Screening** (per algorithm in Appendix II) **and willing to receive HIV counseling and test results**

Item 6 (*old*):

- ~~6. Per participant report at screening, usual menstrual cycle with at least 21 days between menses and no history of intermenstrual bleeding in the past three months (does not apply to participants who report using a progestin-only method of contraception at screening, e.g., Depo-Provera®, or any type of IUD)~~

Item 6 (*new*):

6. Per participant report at Screening **and Enrollment**, sexually active, defined as having had penile-vaginal intercourse at least once in the past 30 days prior to screening **and enrollment**

Item 7:

7. Per participant report at Screening **and Enrollment**, expecting to continue penile-vaginal intercourse at least monthly for the duration of study participation

Item 8:

8. Per participant report, ~~use of~~ **using** an effective method of contraception at Enrollment, and intending to use ~~same~~ **an effective** method for the duration of study participation ~~and one month thereafter~~. **Effective methods include hormonal methods (except ~~IVR~~ **contraceptive vaginal rings**), IUD inserted at least ~~307~~ days prior to enrollment, study provided male condoms, and/or sterilization (of participant or her sexual partner ~~(s)~~ **or partners** as specified in site SSOPs)**

Item 9:

9. ~~Normal Pap smear result at screening or adequately documented normal Pap smear result per SSP within the 12 calendar months prior to screening (ASCUS with no evidence of HPV included)~~ **Pap result in the 12 calendar months prior to Enrollment consistent with Grade 0 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) or satisfactory evaluation with no treatment required of non-Grade 0 Pap result per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines or per local standard of care, in the 12 calendar months prior to the Enrollment Visit**

Item 11:

- ~~11. Willing to agree not to use any intravaginal product, including douches, creams, lubricants etc. during the course of study participation~~

Item 11:

11. **Able and willing to abstain from the use of non-study vaginal products and/or practices (other than tampons) including but not limited to spermicides, diaphragms, contraceptive vaginal rings, vaginal antibiotic or antifungal medication, sex toys, lubricants or condoms that contain silicone, menstrual cup and douching, within the 14 days prior to Enrollment through study termination**

34. Section 5.4, *Exclusion Criteria*:

Items 1c, 1d, 1e, and 1f:

- b. Adverse reaction to latex (**as** defined per SSP)
- c. **Adverse reaction to titanium dioxide**
- d. Any current male sex partner with known history of adverse reaction to latex or, silicone, **titanium dioxide** or **any components of the study product (as defined per SSP)]**

- e. ~~Gynecologic procedure (e.g., biopsy, tubal ligation, dilation and curettage, piercing) within 90 days~~ **Last pregnancy outcome within 30 days or less** prior to enrollment
- f. **Hysterectomy**

Item 2:

- 2. At Screening or Enrollment, has a clinically apparent Grade 2 or higher pelvic exam finding (observed by study staff) per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), Addendum 1, Female Genital Grading Table for Use in Microbicide Studies

Note: Cervical bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the IoR/designee is considered expected non-menstrual bleeding and is not exclusionary.

Note: Otherwise eligible participants with exclusionary pelvic examination findings may be enrolled/randomized after the findings have improved to a non-exclusionary severity grading or resolved. If improvement to a non-exclusionary grade or resolution is documented within 45 days of providing informed consent for Screening, the participant may be enrolled.

Item 4c (old):

- ~~c. Has any vaginal or cervical warts and external genital warts requiring treatment~~

Item 4c (new):

- c. Is diagnosed with a **symptomatic** urinary tract infection (see additional information below)

Note to Item 4:

Note: RTIs requiring treatment per site specific treatment guidelines, include symptomatic BV, symptomatic vaginal candidiasis, other vaginitis, trichomoniasis, chlamydia (CT), gonorrhea (GC), syphilis, active HSV lesions (HSV-2 seropositive women not excluded except with active lesions), chancroid, pelvic inflammatory disease, genital sores or ulcers, or cervicitis. Otherwise eligible participants diagnosed with RTI and/or UTI during Screening will be offered treatment or a prescription for treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 45 days of obtaining informed consent for screening, the participant may be enrolled.

Item 5 (old):

- ~~5. Per participant report, use of the following at Enrollment, and/or anticipated use during the period of study participation diaphragm, sex toys, douching and other~~

~~intravaginal cleansing practices, female condom, IVR, spermicide, and/or menstrual cup. Tampon use will be permitted.~~

Item 5 (new):

5. At Screening or Enrollment, has any ~~social or medical~~ condition that, in the investigator's opinion, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

Item 6 (old):

- ~~6. Participation in other drug or device research study at and/or during the period of this study participation~~

Item 6 (new):

6. Severe pelvic relaxation such that either the vaginal walls or the uterine cervix descend beyond the vaginal introitus with valsalva maneuver ~~in either the standing or supine position.~~

Item 7:

- 7. Participant report of 3 or more sexual partners in the month prior to Screening**

35. Section 6.1, *Regimen*:

First paragraph, fourth sentence:

The study IVR will be removed by the ~~study physician~~ **clinician/designee** at the 12-Week Visit.

Table 3, Study Regimen, third row:

B	84	No IVR for 12 consecutive weeks
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36. Section 6.2, *Administration*:

Section(s) not modified.

37. Section 6.3.1, *Study IVR*, first paragraph:

The study IVR is made of cured silicone elastomer composed of an elastomer base, normal propylorthosilicate (NPOS), and ~~stannous octoate~~ **titanium dioxide** but will contain no active pharmaceutical ingredient. The ring dimensions are as follows: outer diameter ~~56.8~~ mm, cross-sectional diameter ~~7.68~~ **8.4** mm, core diameter 2 mm.

38. Section 6.4.1, *Study Product Supply*, first paragraph:

The study IVRs will be manufactured by ~~Warner Chilcott (Lame, Northern Ireland)~~ **Laboratorios Andromaco S.A. (Santiago, Chile)** and supplied by the ~~International Partnership for Microbicides (IPM), Inc. (Silver Spring, MD)~~ **Population Council (New York, NY)**.

39. Section 6.4.2, *Storage and Dispensing*, first sentence :

Based on stability studies of Progering[®], the study IVRs have a shelf life of 24 months and must should be stored between 15°C to 30°C (59°F to 86°F) at a controlled room temperature.

40. Section 6.4.3, *Accountability*:

Section(s) not modified.

41. Section 6.5, *Participant Counseling*:

Participants **in Group A** will receive study IVR adherence counseling at the Enrollment, 4-Week, and 8-Week Visits. Site staff will counsel participants to refrain from removing the ring (except as directed) and from using concomitant vaginal products and/or devices as described in Section 6.7.1. Site staff will also provide counseling for re-insertion in case of ~~accidental-ring removal/expulsion~~.

The site staff will counsel participants to remove the IVR immediately and contact study site staff if they experience a rash, **itching**, or other skin trouble, ~~itching~~, joint pain, or difficulty breathing as these may be signs of ~~allergy~~ **an allergic reaction**.

42. Section 6.6, *Assessment of Participant Adherence*;

Participant behaviors regarding ~~condom~~ and study IVR use will be collected via standardized questions developed by the protocol team in conjunction with study site staff and community representatives, to maximize the accuracy of self-reported data. Assessment of participant adherence will be addressed using a quantitative instrument.

43. Section 6.7, *Concomitant Medications*

Enrolled study participants may use concomitant medications during study participation. All concomitant medications, as well as illicit substances reported throughout the course of the study, will be recorded on case report forms designated for that purpose. All prescription medications, over-the-counter preparations, vitamins, ~~and~~ nutritional supplements, and herbal preparations will be recorded on forms for concomitant medications.

44. Section 6.7.1, *Prohibited Products and Devices*, first sentence:

Concomitant use of non-study vaginal products or other devices including **but not limited to diaphragms, menstrual cups, sex toys, douching, and intravaginal cleansing practices, female condoms, diaphragms, contraceptive vaginal ring, cervical caps, lubricants or condoms that contain silicone**, and/or spermicides are prohibited for the duration of the study except for tampons.

45. Section 6.7.2, *Recommended Practices*, first paragraph, first and second sentences:

Study sites will distribute an ~~single~~ **approved** brand of latex male condoms to study participants for use during study participation. Instructions and counseling on use of **study approved** male condoms will be provided throughout study participation. Study ~~provided~~**approved** male condoms will not be impregnated or coated with spermicide. In the event that a participant needs additional male condoms between visits, she may request these from clinic staff at any time.

46. Sections 7.1 through 7.4 are updated to reflect current study procedures. The format of this Section is updated for ease of comprehension. Additionally, procedures that are behavioral in nature were removed from clinical section and inserted into a new behavioral section. An asterisk (*) is added to denote procedures that are clinically indicated, while a double cross (̄) denotes procedures that are done per local standards/guidelines. Study procedures that are modified, added, or omitted are detailed by study visit and updated visit component below:

Section 7.1, *Screening Visit*:

Administrative and Regulatory:

- Assess ~~behavioral~~-eligibility
- **Provide available test results**
- Schedule next study visit, **if applicable**

Clinical:

- **Collect obstetric history**
- **Collect urine sample**
- **Collect blood sample**
- **Perform pelvic exam (see Appendix III)**
- **Perform naked eye exam**
- **Collect pelvic samples**
- Treat **or prescribe treatment** for symptomatic UTI/RTIs/STIs or refer for other findings*

Urine:

- ~~Collect urine sample~~
- ~~Nucleic Acid Amplification Test (NAAT) for chlamydia and gonorrhea (US FDA approved for female urine)~~
- ~~Dipstick urinalysis (UA) (and culture if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis)~~
- **Urine culture***

Blood:

- ~~Collect blood sample~~
- ~~Syphilis serology (with confirmatory tests as needed)~~
- ~~HIV-1 test (with confirmatory tests as needed (US FDA approved HIV test))~~

Pelvic Samples:

- ~~Perform pelvic exam (see Appendix III)~~
- ~~Collect pelvic samples~~

- Vaginal fluid tested for *Trichomonas vaginalis* by rapid test (**Clinical Laboratory Improvement Amendment (CLIA)** waived test)
- **Cervical swab for Nucleic Acid Amplification Test (NAAT) for GC/CT**
- Pap smear, if no documented result of normal (**Grade 0**) Pap smear in the past twelve months
- Vaginal pH* †
- Vaginal fluid for wet mount microscopy (~~saline for BV, Trichomoniasis; KOH for vulvovaginal candidiasis~~) * †
- **Vaginal fluid for wet mount microscopy (saline for BV)* †**

Section 7.2, *Enrollment Visit:*

Administrative and Regulatory:

- Obtain written informed consent for enrollment **and storage and testing of future specimens**
- Confirm ~~behavioral~~ eligibility
- ~~Administer comprehension checklist~~
- Provide **available test** results from screening tests (if not previously provided)
- Schedule next study visit, **if applicable**

Behavioral:

Provide Counseling:

- **HIV testing process***

Clinical:

- Perform **targeted** physical exam (see Appendix III)
- **Collect urine sample**
- **Collect blood sample**
- **Perform pelvic exam (see Appendix III)**
- **Perform naked eye examination and colposcopic examination as described by the CONRAD/WHO Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products (Update 2004) to assess condition of vaginal and/or cervical epithelium or blood vessels. Digital images may be recorded**
- **Collect pelvic samples**
- Treat **or prescribe treatment** for symptomatic UTI/RTIs/STIs or refer for other findings*

Urine:

- ~~Collect urine sample~~
- ~~If clinically indicated, NAAT for chlamydia and gonorrhea (US FDA approved for female urine)~~
- ~~Dipstick urinalysis (UA) (and culture if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis)*~~
- **Urine culture***

Blood:

- ~~Collect blood sample~~
- **Plasma archive**

- Syphilis serology (~~with confirmatory tests as needed~~)
- HIV-1 test (~~with confirmatory tests as needed (US FDA approved HIV test)~~)

Pelvic Samples:

- ~~Perform naked eye examination and colposcopic examination as described by the CONRAD/WHO Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products (Update 2004) to assess condition of vaginal and/or cervical epithelium or blood vessels. Digital images may be recorded~~
- Collect pelvic samples
 - Quantitative ~~v~~Vaginal cultures (~~at US sites only~~) **swabs for vaginal flora assessments**
 - **Cervical swabs for innate factors (US only)**
 - **Vaginal fluid tested for *Trichomonas vaginalis* by rapid test (CLIA waived test) *†**
 - Vaginal pH*†
 - Vaginal fluid for wet mount microscopy (~~saline for BV, Trichomoniasis; KOH for vulvovaginal candidiasis~~) *†
 - **Cervical swab for NAAT for GC/CT***
- ~~Perform pelvic exam (see Appendix III)~~

Study Product Supply:

- For Group A, **provide** participants ~~will receive~~**with** instructions on study IVR insertion, self-insert one study IVR followed by digital exam by clinician to check placement. **Instruct** ~~participants will also be instructed~~ participants to rinse ring in warm water and re-insert in event of ring expulsion, unless ring falls into toilet or other unsanitary surface, in which case participant will be instructed to return used ring to clinic. Due to variations in water quality, participants may also receive a bottle of water with which to rinse the study ring in case of expulsion.

Section 7.3, Follow-up Visits:

First sentence:

~~Note for all follow-up visits:~~ **All** follow-up visits should be scheduled, ideally, on dates (within the ± 7 day visit window) when the participant is not on her menses.

Third sentence:

If indicated, the pelvic exam, colposcopy, and associated specimen collections required for the given visit will be rescheduled for a date as soon as practical (preferably within the ± 7 day visit window) after the end of participant's menses.

Administrative and Regulatory:

- Provide **available test** results ~~from previous visits (if not previously provided)~~

Behavioral:

- Administer follow-up adherence assessment (**Group A only**)
- Administer final acceptability assessment (for Group A participants at 12-Week Visit ~~or in the event that use of the study IVR is permanently discontinued~~)
- Provide counseling (second, fourth and fifth sub-bullet)
 - HIV testing process ~~and results from previous visits (if indicated)*~~

- For Group A, product use/adherence (~~omit at 12-week visit~~ **4-and 8-Week Visit Only**)
- **HIV testing process***

Clinical:

- **Collect urine sample***
- **Collect blood sample***
- **Perform pelvic exam (see Appendix III)**
- **Perform naked eye examination (all study visits) and colposcopic examination (12-Week Visit only, and if indicated at 4-and 8-Week Visits) as described by the CONRAD/WHO Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products (Update 2004) to assess (1) condition of vaginal and/or cervical epithelium or blood vessels and (2) quantity and quality of vaginal discharge. Digital images of abnormal findings may be recorded**
- **Collect pelvic samples**
- **Treat or prescribe treatment** for symptomatic UTI/RTIs/STIs or refer for other findings*

Urine:

- ~~Collect urine sample~~
- ~~If clinically indicated, NAAT for chlamydia and gonorrhea (US FDA approved for female urine)~~
- ~~Dipstick UA (and culture if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis)*~~
- **Urine culture***

Blood:

- ~~Collect blood sample~~
- ~~Syphilis serology* (with confirmatory tests as needed)~~
- ~~HIV-1 test* (with confirmatory tests as needed (US FDA approved HIV test))~~

Pelvic Samples:

- ~~Perform naked eye examination (all study visits) and colposcopic examination (12-Week Visit only, and if indicated at 4-and 8-Week Visits) as described by the CONRAD/WHO Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products (Update 2004) to assess (1) condition of vaginal and/or cervical epithelium or blood vessels and (2) quantity and quality of vaginal discharge. Digital images of abnormal findings may be recorded~~
- ~~Collect pelvic samples~~
- ~~Quantitative vVaginal cultures (at US sites only) swabs for vaginal flora assessments~~
- **Vaginal fluid tested for *Trichomonas vaginalis* by rapid test (CLIA waived test)* †**
- **Vaginal pH* †**
- ~~Vaginal fluid for wet mount microscopy (saline for BV, Trichomoniasis; KOH for vulvovaginal candidiasis) * †~~
- **Vaginal fluid for wet mount microscopy (saline for BV)* †**
- **Cervical swab for NAAT for GC/CT***

- Perform pelvic exam (see Appendix III)
- ~~Physician to remove study IVR from Group A participants at 12-Week Visit, or at visit in which study IVR use is permanently discontinued.~~
- US sites only: a biofilm assessment will be performed on the used ring that is removed at the 12-Week Visit if the ring is removed by a study clinician. In the event that an IVR is removed at an earlier visit, the used ring will have a biofilm assessment if assessment criteria are met, including **IVR** removal by a study clinician/designee.

Study Product Supply:

- ~~Collect Study clinician/designee to removed~~ used study IVR (in case of ring expulsion) **at 12-Week Visit**
- **Provide study IVR at 4-and 8-Week Visits in case of ring removal/expulsion***
- **Collect used study IVR at 4-and 8-Week Visits in case of ring removal/expulsion***
 - In case of ring expulsion **or removal**, participants may also receive a bottle of water with which to rinse the study ring (**4- and 8-Week Visits only**)

Section 7.4, 16-Week/Study Termination Visit:

Administrative:

- Provide **available test** results from previous visits (if not previously provided)
- Schedule next study visit, **if applicable**

Behavioral:

- Provide counseling
 - ~~Protocol adherence~~
 - ~~HIV testing process and results from previous visits (if indicated)~~
- **Administer final acceptability assessment (for Group A- in the event that use of the study IVR is permanently discontinued at an earlier visit)***

Clinical:

- **Collect urine sample**
- **Collect blood sample**
- **Perform pelvic exam (see Appendix III)**
- **Perform naked eye examination and colposcopic examination as described by the CONRAD/WHO Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products (Update 2004) to assess (1) condition of vaginal and/or cervical epithelium or blood vessels and (2) quantity and quality of vaginal discharge. Digital images of abnormal findings may be recorded**
- **Collect pelvic samples**
- **Treat or prescribe treatment** for symptomatic UTI/RTIs/STIs or refer for other findings*

Urine:

- ~~Collect urine sample~~
- ~~Dipstick UA (and culture if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis)*~~

- **Urine culture***

Blood:

- Collect blood sample
- HIV-1 test ~~(with confirmatory tests as needed (US FDA approved HIV test))~~
- Syphilis serology* ~~(with confirmatory tests as needed)~~

Pelvic Samples:

- Perform pelvic exam ~~(see Appendix III)~~
- Perform naked eye examination and colposcopic examination as described by the CONRAD/WHO Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products (Update 2004) to assess (1) condition of vaginal and/or cervical epithelium or blood vessels and (2) quantity and quality of vaginal discharge. Digital images of abnormal findings may be recorded
- Collect pelvic samples
- Quantitative ~~v~~Vaginal cultures ~~(at US sites only)~~ **swabs for vaginal flora assessments**
- **Cervical swabs for innate factors (US sites only)**
- **Vaginal fluid tested for *Trichomonas vaginalis* by rapid test (CLIA waived test)* †**
- Vaginal pH* †
- Vaginal fluid for wet mount microscopy ~~(saline for BV, Trichomoniasis; KOH for vulvovaginal candidiasis) * †~~
- **Vaginal fluid for wet mount microscopy (saline for BV)* †**
- **Cervical swab for NAAT for GC/CT***
- ~~Biofilm Assessment (for Group A if indicated, for participants at US sites only)~~

Study Product Supply, second bullet:

- **Collection of used IVR (for Group A)***

47. Section 7.5.1, *Participants Who Seroconvert to HIV, bullet points:*

Study staff will record information regarding seroconversions that occur during study participation on study case report forms (CRF). Participants in Group A will be ~~advised to discontinue study IVR~~ **permanently discontinued from IVR** use. Protocol-specified procedures will continue except:

- HIV-1 serology ~~test~~
- Further provision of study IVR (for Group A)
- ~~Counseling for HIV/STI risk reduction. Counseling will be modified to address primary and secondary HIV/STI prevention for infected women and prevention for transmission to sex partners.~~

48. Section 7.5.2, *Participants Who Become Pregnant, bullet points and last sentence:*

- Pelvic exam **including colposcopy** (unless clinically indicated)
- **Further provision of study IVR (for Group A)**

49. Section 7.5.3 *Participants Who Voluntarily Discontinue Study IVR* and Section 7.5.4, *Participants Who Discontinue Study IVR Use Permanently (Advised by Study Staff)* we combined to create the following section:

7.5.3 Participants Who Discontinue Study IVR Use Permanently (**Either Voluntarily or as Advised by Study Staff**)

50. Section 7.6, *Interim Contacts and Visits*:

First paragraph, second and third sentences:

Participants will be asked to provide staff with updated locator information, concomitant medications, as well as provide an update on their medical and menstrual history at all interim contacts and visits. All other study procedures will be performed as indicated.

Second paragraph, third sentence:

Other interim contacts and visits may occur in response to AEs or social harms experienced by study participants.

51. Section 7.7, *Clinical Evaluations and Procedures*

Section(s) not modified.

52. Section 7.8, *Adherence, Acceptability, and Behavioral Change*, has been divided into two subsections: 7.8.1, *Adherence* and 7.8.2, *Acceptability and Behavioral Change*:

ACASI will be used to assess adherence and acceptability given the sensitive nature of the questions.

Section 7.8.1, *Adherence*:

~~All participants will be asked questions about sexual behavior and hypothetical study IVR use. For participants in Group A, acceptability of the study ring will be measured by 1) study continuation rates over the 12-week period, 2) participants' answers to questions regarding adherence to the prescribed ring schedule, ease of insertion, ease of removal, comfort with touching oneself, tolerance of foreign body, physical discomfort, partner perceptions especially awareness during and interference with sex, changes in sexual activity, and expulsion during urination and bowel movements, and 3) participants' perceptions of changes in the quantity, color and/or odor of vaginal discharge associated with use of the study ring as well as any resulting changes in vaginal hygiene practices. Background factors that will be considered in addition to demographic characteristics are type of toilet (applicable to India site only), marital status/partner change, experience with tampons and other vaginal products, current vaginal hygiene practices, prior clinical trial experience and usage of and knowledge about the contraceptive vaginal ring (NuvaRing[®]) as well as other contraceptive methods. For participants in Group A, adherence will be measured at the 4-, 8- and 12-Week Visits. Adherence will be measured via several strategies for participant self-report. The questions will assess the frequency of study IVR use for established periods prior to the scheduled follow-up visits. A series of questions will ask whether the study IVR was out, whether it was removed or expelled, under what conditions it was removed or expelled, and whether it was re-inserted. Additional~~

questions will assess sexual activity, as well as condom and study IVR use during sex. A combination of interviewer-administered questionnaires and ACASI will be employed to capture the above information. Study staff will provide participants with guidance on strategies to optimize recall of relevant behavioral and adherence data.

Section 7.8.2, *Acceptability and Behavioral Change*:

Acceptability will be measured via questions about ease of insertion and removal, feeling the ring during daily activities and sex, partner awareness of the ring during sex, partner attitude towards the ring, and willingness to use an HIV protective ring in the future, if one were available. Behavioral change potentially related to IVR use will be assessed via comparisons between sexual activity and vaginal hygiene at enrollment and at follow-up visits, and via comparisons of sexual activity and vaginal hygiene between the IVR arm and no ring arm.

53. Section 7.9.1, *Local Laboratory Testing*:

Blood:

- HIV-1 test (~~enzyme immunoassay (EIA), western blot (WB) if indicated; (see Appendix II). US FDA approved HIV test~~)
- Syphilis serology (~~with confirmatory tests as needed~~)

Urine:

- ~~Urinalysis-**UA**~~
- ~~NAAT for chlamydia and gonorrhea (US FDA approved for female urine)~~
- Urine culture (if clinically indicated)

Pelvic Specimens, third, fourth, sixth, and seventh bullets:

- Vaginal fluid for wet mount microscopy (saline for BV, ~~Trichomoniasis~~; KOH for vulvovaginal candidiasis)
- **Trichomonas vaginalis test**
- Herpes culture (if clinically indicated and if local standard of care)
- **Gram stained smear of vaginal fluid, obtained from lateral vaginal wall (India site only)**
- **Cervical swab for NAAT for GC/CT**

54. Section 7.9.2, *Network Laboratory Testing*:

Blood, second bullet:

- **Plasma archive**

Urine:

- ~~NAAT for chlamydia and gonorrhea (for US sites not currently able to perform this test on site (US FDA approved for female urine))~~

Genital/Pelvic Specimens:

- ~~Quantitative v~~Vaginal cultures (at sites with capacity) **flora assessments (quantitative vaginal fluid cultures-US sites only)**
These organisms will include ~~Lactobacillus species, Gardnerella vaginalis, Escherichia coli, Staphylococcus aureus, anaerobic gram negative rods~~

~~(Bacteroides, Prevotella, Porphyromonas), Enterococcus species, Group B Streptococcus, and Candida species.~~

- ~~o Gram stained vaginal smear with leukocyte quantification~~
- Biofilm **assessment** of used study IVRs (US sites only) ~~May include culture and/or other techniques)~~
- **Gram stained smear of vaginal fluid, obtained from lateral vaginal wall (US sites only)**
- **Cervical swab for innate factors (US sites only)**

55. Section 7.10, *Specimen Collection and Processing*; Section 7.11, *Specimen Handling*; Section 7.12, *Biohazard Containment*:

Section(s) not modified.

56. Section 7.13, *Final Contact*, first paragraph, second sentence:

~~As results are not expected to be available on the same day for participants,~~ a final contact may be required to provide the final study test results, post-test counseling, and treatment **or prescription for treatment** ~~from these visits.~~

57. Section 8.1, *Safety Monitoring*, first paragraph, second and third sentences:

The ~~study~~ site investigators are responsible for continuous close safety monitoring of all study participants, and for alerting the Protocol Team if unexpected concerns arise. A sub-group of the Protocol Team, including the Protocol Chair, DAIDS Medical Officer **MO**, MTN CORE Protocol Safety Physicians, ~~Statistical Data Management Center (SDMC) Clinical Affairs Nurse~~ **Safety Associate, Population Council Safety Physician** and Protocol Statistician, will serve as the PSRT; ~~the PSRT will be chaired by the MTN CORE Protocol Safety Physician.~~ The MTN-SDMC will prepare routine ~~safety~~ **AE and clinical** data reports for review by the PSRT, which will meet via conference call approximately once per month or as needed throughout the period of study implementation to review safety data, discuss product use management and address any potential safety concerns.

58. Section 8.2, *Clinical Data Safety Review*:

First paragraph, first sentences:

A multi-tiered safety review process will be followed ~~for~~ **throughout** the duration of this study.

Second paragraph, third sentence:

Adverse event reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded to the DAIDS MO and SDMC Clinical Affairs staff for review.

Fourth paragraph, last sentence:

If at any time, a decision is made to discontinue study product in all participants, the ~~site investigators of record~~ **Population Council will notify the FDA and the site IoR** will notify the responsible Institutional Review Boards/Ethics Committees (IRB/EC) expeditiously.

59. Section 8.3.1, *Adverse Events*:

First paragraph, third sentence:

This definition will be applied beginning ~~from~~ at the time of random assignment.

Third paragraph, second sentence:

Study site staff will report on study case report forms all AEs, excluding findings observed by colposcopy only, reported by or observed in enrolled study participants from the time of enrollment (random assignment) until study termination, regardless of severity and presumed relationship to study product. The DAIDS AE Grading Table Version 1.0, Dec 2004 (**clarification dated August 2009**), Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies), will be the primary tool for grading AEs for this protocol, ~~with the exception of~~ **except that** asymptomatic BV ~~which~~ will not be a reportable AE. AEs not included in ~~that addendum~~ **the Female Genital Table for Use in Microbicide Studies** will be graded by the DAIDS AE Grading Table Version 1.0, December 2004 (**clarification dated August 2009**). In cases where an AE is covered in both tables, the DAIDS AE Grading Table **1.0, Dec 2004 (clarification dated August 2009)**, Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies) will be the grading scale utilized. These tables are available at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

60. Section 8.3.2, *Serious Adverse Events*, first sentence:

SAEs will be defined ~~per US Code of Federal Regulations (CFR) 312.32 by the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010)~~, as AEs occurring at any dose that:

- ~~r~~**Results** in death
- ~~Are~~**Is** life-threatening AEs
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, ~~or~~
- ~~Are~~**Is** a congenital anomalies/birth defects
- **Is an** important medical events that may not result in death, be **immediately** life-threatening, or require hospitalization ~~may be considered serious when, based upon appropriate medical judgment, they~~ **but** may jeopardize the participant or require medical ~~or surgical~~ intervention to prevent one of the outcomes listed **in the definition** above.

61. Section 8.3.3, *Adverse Event Relationship to Study Product*:

The relationship of all AEs to study product will be assessed per the Manual for Expedited Reporting of Adverse Events to DAIDS ~~(dated 6 May 2004)~~ (**Version 2.0, dated January 2010**) and clinical judgment. The relationship categories that will be used for this study are:

- ~~*Definitely Related:*~~ AE and administration of study agent are related in time, and a direct association can be demonstrated with the study agent. **There is a reasonable possibility that the AE may be related to the study agent(s)**
- ~~*Probably related:*~~ AE and administration of study agent are reasonably related in time, and the AE is more likely explained by the study agent than by other causes.

- ~~*Possibly related:* AE and administration of study agent are reasonably related in time, and the AE can be explained equally well by causes other than the study agent.~~
- ~~*Probably Not related:* a potential relationship between administration of study agent and AE could exist, but is unlikely, and the AE is most likely explained by causes other than the study agent.~~
- ~~*Not related:* the AE is clearly explained by another cause unrelated to administration of the study agent. Reportable events must have documentation to support the determination of “not related”. There is not a reasonable possibility that the AE is related to the study agent(s)~~

62. Section 8.4, *Unanticipated Adverse Device Effect Reporting Requirements:*

~~Unanticipated Adverse Device Effects (UADE)~~

~~An unanticipated adverse device effect is any serious adverse effect on health or safety or any life threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.~~

~~UADEs must be documented on the DAIDS EAE Reporting Form available on the RSC website (<http://rsc.tech-res.com>) and submitted by study sites to the DAIDS Medical Officer and IPM.~~

63. Section 8.4.1 *Expedited Adverse Event Reporting to DAIDS:*

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the Regulatory Support Center (RSC) website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about EAE reporting, please contact the RSC (RSCSafetyOffice@tech-res.com).

64. Sections 8.4.2, *Reporting Requirements for this Study*

- **The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study**
- **The study agent for which expedited reporting is required is the study IVR**
- **In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are outlined in Section 8.3.2**
- **Study staff will also report on CRFs the following subset of AEs reported by or observed in enrolled participants:**
 - **All genital, genitourinary, and reproductive system AEs**
 - **All AEs of severity Grade 3 or higher**

65. Section 8.4.3, *Grading Severity of Events*

The most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, Dec 2004 (clarification dated August 2009), Addendum 1 (Female Genital Table for Use in Microbicide Studies) will be used and is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

66. Section 8.4.4, *Expedited AE Reporting Period*

- **The expedited AE reporting period for this study is as per the EAE manual**
- **After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information)**

67. Section 8.5, *Pregnancy and Pregnancy Outcomes*

Pregnant women are excluded from this study. If participants become pregnant at any time during the course of the study, participants will remain in the study per Section 7.5.2.

Pregnancy-related data will be collected using pregnancy CRFs for all pregnancies detected during the study. Pregnancy outcomes will not be expeditiously reported to the Population Council and the DAIDS MO unless there is an associated AE in the pregnant participant that meets expedited reporting criteria or the pregnancy results in a congenital anomaly meeting International Conference on Harmonisation (ICH) guidelines for expedited reporting.

68. Section 8.6, *Local Regulatory Requirements*, second and third paragraphs:

~~IRB/EC Notification by Investigator~~

~~Reports of all UADE (including follow-up information) must be submitted to the IRB/EC as soon as possible and in no event later than 10 working days after the investigator first learns of the event. Copies of each report and documentation of IRB/EC notification and receipt will be kept in the Clinical Investigator's binder.~~

FDA Notification by Sponsor

~~The study sponsor shall evaluate any UADE and submit a report of the evaluation to FDA as soon as possible but no later than 10 working days after the sponsor is notified. If a previous AE that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the AE in a written report to the FDA as soon as possible, but no later than 10 working days from the time the determination is made.~~

69. Section 8.7, *Social Harms*, third sentence:

Social harms that are judged by the IoR to be serious or unexpected will be reported to responsible site IRB/ECs at least annually, or according to their individual requirements and should also be reported to the ~~DAIDS Medical Officer and IPM~~ **the Population Council** on DAIDS EAE Reporting Forms.

70. Section 9.1, Toxicity Management:

Section(s) not modified.

71. Section 9.2, *Other Clinical Events*:

Superficial epithelial disruption (abrasion/peeling) excluding findings observed by colposcopy only subsection, fourth bullet:

- If condition worsens, **temporarily** hold study IVR use. Otherwise continue study IVR use
- If condition worsens, temporarily hold study IVR use **and consult the PSRT**. Otherwise continue study IVR use

Deep epithelial disruption (ulceration) excluding findings observed by colposcopy only subsection, first, second, fifth, and sixth bullets:

- ~~Hold~~ **Remove** study IVR for deep epithelial disruption confirmed by site investigator
- Swab for herpes simplex culture (per clinical judgment of site investigator) (~~herpes serology optional~~)
- If unresolved at 48-72 hours, re-evaluate in another 48-72 hours. If resolved at that time may reinstate study IVR use. If unresolved at this second reevaluation, ~~need to discontinue~~ **continue temporary** product ~~permanently hold~~, **consult with PSRT regarding permanent discontinuation**, and provide care per local standard
- If there is reoccurrence with no identified etiology, ~~then consider~~ **continue temporary product hold and consult the PSRT regarding** permanent discontinuation

Localized erythema or edema: area of less than 50% of vulvar surface or combined vaginal and cervical surface excluding findings observed by colposcopy only subsection, fifth bullet:

- If worsened significantly, **temporarily** hold study IVR use, ~~until further evaluation is scheduled~~ **and consult the PSRT**. Otherwise, continue study IVR use

Generalized erythema or severe edema: area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema excluding findings observed by colposcopy only subsection, first and fourth bullets:

- ~~Hold-Remove~~ study IVR
- If unresolved at 48-72 hours, re-evaluate in another 48-72 hours. If resolved at that time may reinstate use. If unresolved at this second reevaluation, ~~need to discontinue product permanently~~ **continue temporary product hold, consult with PSRT regarding permanent discontinuation**, and provide care per local standard.

Abnormal vaginal discharge excluding findings observed by colposcopy only Section, first and third bullets:

- Study IVR use may be continued without treatment in the presence of asymptomatic Candida vaginitis and/or asymptomatic BV **or treatment may be provided per local guidelines**
- Provide **or prescribe** treatment and continue study IVR use for all cases of Trichomoniasis, symptomatic Candida vaginitis, and symptomatic BV

Unexpected genital bleeding excluding findings observed by colposcopy only Section, first bullet:

- Continue study IVR use (at **study** clinician's discretion)

Cervicitis (including findings on exam such as inflammation and/or friability) excluding findings observed by colposcopy only, second and third bullet:

- Evaluate for ~~N. gonorrhoeae and C. trachomatis~~ **GC/CT**
- If ~~N. gonorrhoeae and C. trachomatis~~ **GC/CT** detected, provide **or prescribe** treatment and reevaluate in 72 hours. If all symptoms and signs are resolved at that time, may reinstate use with replacement study IVR

72. Section 9.2, *UADE that is judged by the site investigator or designee to be definitely, probably, possibly, or probably not related to the study IVR subsection*:

~~**UADE that is judged by the site investigator or designee to be definitely, probably, possibly, or probably not related to the study IVR**~~

- ~~For Grades <4, hold study IVR~~
- ~~Evaluate according to current clinical practice at the site~~
- ~~Provide treatment as clinically indicated, when resolved reinstate study IVR use at clinician's discretion~~
- ~~For Grade 4, permanently discontinue study IVR~~

73. Section 9.3, *Pregnancy*:

First paragraph, first sentence:

All study participants are required to be using an effective method of contraception at enrollment, and intending to use **the** same method for the duration of study participation.

First paragraph, fifth sentence:

Study staff also will provide participants with male condoms and **will counsel participants to ideally** ~~counseling on use of these condoms ideally~~ during every sex act ~~during~~ **throughout** study participation.

Second paragraph, first sentence:

Pregnancy testing will be performed at the Screening, Enrollment, and 16-Week/~~Early~~**Study** Termination study visits, and when clinically indicated during study follow-up.

Second paragraph, second sentence:

The site IoR or designee will counsel any participants who become pregnant regarding possible risks ~~if the pregnancy is continued~~ **of study IVR use** according to site-specific SOPs.

Fourth paragraph, second bullet:

- Pelvic exam **including colposcopy** (unless clinically indicated)

74. Section 9.4, *Criteria for Temporary or Permanent Discontinuation of Study Product*:

Second and fifth bullets:

- HIV-1 seroconversion
- **Clinical reasons as** determined by the ~~study physician~~ **clinician**

Last paragraph:

Participants who **temporarily or permanently** discontinue product use will continue to complete study visits and procedures as originally scheduled (except that study IVRs will no longer be provided **during the time** ~~for the participants randomized to~~ **will not be using** the study IVR ~~arm~~).

75. Section 9.5, *Criteria for Early Termination of Study Participation*

Section(s) not modified.

76. Section 10.1, *Overview and General Design*, first sentence:

This is a ~~three~~ **multi-site**, open-label, two-arm, 2:1 randomized, controlled trial comparing ~~acceptability and the~~ expanded safety of, **and adherence to**, a study IVR for 12 weeks of use to no IVR use among sexually active, HIV-uninfected women.

77. Section 10.2.1, *Study Primary Endpoints*:

Consistent with the primary study objectives to assess the **acceptability and safety and adherence** of the study IVR when used for 12 consecutive weeks, the following primary endpoints will be assessed:

10.2.1.1 Acceptability

- ~~For women randomized to the study IVR arm, participant report on acceptability including genitourinary discomfort, ring insertion/removal issues, expulsions (including context of expulsion), and changes in sexual function~~

10.2.1.2 Safety

- Evidence of Grade 2 or higher genitourinary events as defined by the DAIDS ~~AE Grading Table~~ **Table for Grading the Severity of Adult and Pediatric Adverse Events**, Version 1.0, Dec 2004 (**clarification dated August 2009**), Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies)

Adherence

- **For women randomized to the study IVR arm, participant report of frequency of study IVR removal (voluntary and involuntary) and duration without IVR inserted in vagina over 12 weeks of use**

78. Section 10.2.2, *Study Secondary Endpoints*:

Consistent with the secondary study objectives to **describe the changes in sexual behavior and changes in vaginal hygiene practices, to evaluate the acceptability of the study IVR, and** measure vaginal flora characteristics and changes of these over the course of study IVR use, the following endpoints will be assessed:

- ~~For women randomized to the study IVR arm, participant report of frequency of study IVR removal and duration of time without IVR inserted in vagina over 12 weeks of use~~
- ~~Changes from enrollment to week 12 in vaginal flora as measured by Nugent score~~
- **Per participant report, changes in sexual behavior and vaginal hygiene practices**
- **For women randomized to the study IVR arm, participant report on acceptability including genitourinary discomfort, ring insertion/removal issues, expulsions (including context of expulsion), and changes in participant and partner sexual feeling**
- **Changes in vaginal flora** from enrollment to week 12 as measured by **Gram stain** Nugent score **in and** quantitative vaginal culture [1] ~~as measured by count of *Lactobacillus* (H₂O₂ positive and negative strains), anaerobic gram negative rods, *Gardnerella vaginalis*, *Escherichia coli*, *Staphylococcus aureus*, *Candida* species, Group B *Streptococcus*, and *Enterococcus* species.~~ (Note that these quantitative vaginal

cultures will only be available from the two US sites, therefore reducing the available sample size for this objective).

- ~~Assessment of vaginal symptoms and signs suggestive of BV or vulvovaginal candidiasis~~
- ~~Changes in vaginal pH and vaginal wet mount microscopy~~

79. Section 10.2.3, Exploratory Endpoint

- **Changes in vaginal biomarkers (US sites only)**
- **Presence of biofilms on study IVR surface (US sites only)**

80. Section 10.3, *Study Hypotheses*:

MTN-005 hypothesizes that ~~12 weeks of the study IVR use will be safe and well tolerated. In addition, we anticipate that the study IVR will be acceptable to~~ **will be used as directed by US and non-US women over 12 weeks of use.**

81. Section 10.4.1, *Safety Endpoints*:

First paragraph, second sentence:

Given that assessing ~~acceptability of and adherence to the study IVR~~ **are-is a primary objectives**, and that ~~acceptability and adherence this~~ can only be assessed in the study IVR arm, a 2:1 randomization was selected to increase the precision on estimates of ~~acceptability and adherence~~ **and acceptability.**

Second paragraph, first sentence:

For the study IVR arm, if the true rate of a given toxicity endpoint is 5%, 168 women provide 80% power to exclude safety and toxicity endpoint rates greater than 10.0%, where the safety and toxicity endpoints for a woman are defined as the occurrence of the safety endpoint during follow-up, that is the occurrence during follow-up of evidence of Grade 2 or higher genitourinary events as defined by the DAIDS AE Grading Table, Version 1.0, Dec 2004 (**clarification dated August 2009**), Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies).

Fifth paragraph, last sentence:

These bounds correspond to non-inferiority bounds computed using an exact one-sided 95% confidence interval for the difference in rates between the two arms as described in ~~Section 10.8.2.1~~ **the Primary Safety Analysis.**

82. Section 10.4.2, *Adherence Endpoints*:

First paragraph:

Adherence will be measured by the percentage of women who keep the IVR inserted in the vagina over the course of 12 weeks. Adherence can only be assessed among the 168 women randomized to the study IVR arm. A sample size of 168 women will provide a precision of 6.4% (i.e. half-width of the 95% exact confidence interval) assuming an observed adherence of 80%. Substantial heterogeneities in adherence between the Indian and the US sites might be observed in which case adherence will be estimated separately for Indian and US women. For the Indian site, a sample size of 100 women using the study IVR will provide a precision of 8.3% assuming an observed adherence of 80% while this precision would be 10.2% with a sample size of 68 US women using the study IVR.

83. Section 10.4.3, *Acceptability Endpoints*:

First paragraph, final sentence:

Due to the smaller sample size within each site, no formal comparison will be performed for comparing **adherence and** acceptability between sites.

84. Section 10.4.4, *Changes in Vaginal Flora and Biomarkers*, fifth paragraph:

In addition to looking at shifts in the Nugent score, within arm descriptions, and between arm comparisons, will be done to assess clinically meaningful changes in quantitative measures of vaginal flora (defined by more than ≥ 1 log change in dominant members of the microflora, including ~~*Lactobacillus* (H₂O₂ positive and negative strains), anaerobic gram negative rods, *Gardnerella vaginalis*, *Escherichia coli*, *Staphylococcus aureus*, *Candida* species, Group B *Streptococcus*, and *Enterococcus* species)~~ and to assess differences in the quantitative levels of these **microflora** between arms during follow-up. Quantitative vaginal cultures **and vaginal biomarkers** will be assessed only at the US sites and therefore the available sample size for these analyses will be 102 women (68 in the study IVR arm and 34 in the no IVR arm). A sample size of 102 women with a 2:1 randomization will **allow** detection of a medium effect size of 0.59 with 80% power in comparing quantitative levels between arms.

85. Section 10.4.5, *Sexual Behavior and Vaginal Hygiene Practice*:

The behavior measures will be collected via ACASI at the Enrollment Visit, follow-up visits, and at the 16-Week/Study Termination Visit. The sexual behaviors and vaginal hygiene practices include the number of sexual partners in the past 3 months, the number of new partners (not asked at enrollment), frequency of sex in the past 7 days, condom use in the past 7 days, condom use during the last sex act, anal sex in the past month, condom use during anal sex in the past month, and vaginal hygiene practices (list of various items/products inserted) in the past 7 days.

86. Section 10.5, *Randomization Procedures*, first paragraph, last sentence:

~~If for some reason a site experiences difficulty reaching its accrual target, consideration will be given to shifting enrollment "slots" to the other site, with prior approval of the Protocol Chair.~~

87. Section 10.6, *Justification for the No IVR Arm*:

Inclusion of a no IVR arm in this safety, ~~acceptability~~, and adherence study will enable investigators to compare the incidence of AEs as well as changes in vaginal flora, **sexual behavior and vaginal hygiene practices** among women using the study IVR to that of women using no IVR.

88. Section 10.7, *Participant Accrual and Retention*, last sentence:

~~Monthly accrual targets by site are given in the table below. Note: The accrual targets for the US sites are projections as there will be competitive enrollment at these sites.~~

Table 1: Monthly Accrual Target for MTN-005

Study Month	Monthly Accrual Target	Monthly Accrual Target	Monthly Cumulative Accrual Target
	US Sites	Non-US Site	
1	12 (6 per site)	6	18
2	18 (9 per site)	16	34
3	18 (9 per site)	16	34
4	18 (9 per site)	16	34
5	18 (9 per site)	16	34
6	18 (9 per site)	16	34
7	0	16	16
8	0	16	16
9	0	16	16
10	0	16	16
Total	102 (51 per site)	150	252

89. Section 10.8.1, Study Monitoring Committee (SMC)

Section(s) not modified.

90. Section 10.8.2, *Primary Analysis*:

Third paragraph, second and third sentences:

Adverse ~~experiences~~ **events** will be analyzed using MedDRA preferred terms. The number and percentage of participants experiencing each specific adverse ~~experience~~ **event** will be tabulated by severity and by relationship to study product (for the study IVR arm only).

Third paragraph, fourth sentence:

Finally, a listing of ~~UADE~~ **AEs** reported to the DAIDS Medical Officer and ~~IPM~~ **the Population Council** will provide details of the event including severity, relationship to study product, onset, duration and outcome.

Fifth paragraph:

Primary ~~Acceptability~~ **Adherence** Analysis

~~To assess acceptability of women randomized to the study IVR arm, the number and the percentage of participants experiencing during follow-up at least one negative report on acceptability including genitourinary discomfort, ring insertion/removal issues, expulsions,~~

~~and/or changes in sexual function will be presented. This binomial proportion will be used to assess the acceptability of the study IVR along with its corresponding 95% confidence interval.~~

~~The above primary acceptability analysis will be supplemented by presenting the above proportion by site along with its corresponding 95% confidence interval.~~

To assess adherence of women randomized to the study IVR arm, the proportion of participants who kept the study IVR inserted at all times during the first 12 weeks of follow-up will be calculated along with its 95% confidence interval. For women who are not completely adherent, the average period of time during follow-up when the study IVR was outside the vagina as well as the average number of removals of the study IVR from the vagina will be computed. All enrolled women in the study IVR arm will be included in this analysis.

91. Section 10.8.3, *Secondary and Exploratory Analyses*:

First five paragraphs:

Adherence

~~To assess adherence of women randomized to the study IVR arm, the proportion of participants who kept the study IVR inserted at all times during the first 12 weeks of follow-up will be calculated along with its 95% confidence interval. For the not completely adherent women, the average period of time during follow-up when the study IVR was outside the vagina as well as the average number of removals of the study IVR from the vagina will be computed. All enrolled women in the study IVR arm will be included in this analysis.~~

Sexual behavior and vaginal hygiene practice

The behavior measures will be collected via ACASI at the Enrollment Visit, follow-up visits, and at the 16-Week/Study Termination Visit. The sexual behaviors and vaginal hygiene practices include the number of sexual partners in the past 3 months, the number of new partners (not asked at enrollment), frequency of sex in the past 7 days, condom use in the past 7 days, condom use during the last sex act, anal sex in the past month, condom use during anal sex in the past month, and vaginal hygiene practices (list of various items/products inserted) in the past 7 days

For each of the longitudinal behavioral measures, the mean (or the percentage if binary) in each visit in each arm will be computed and tabulated. The generalized estimation equation (GEE) method will be used to assess the difference of each measure between the two arms, accounting for within-subject correlation.

Acceptability

To assess acceptability of the study IVR, the number and percentage of participants in the study IVR arm experiencing at least one negative report of acceptability, including genitourinary discomfort, ring insertion/removal issues, expulsions, and/or changes in participant and/or partner sexual feeling during follow-up will be presented. This binomial proportion will be used to assess the acceptability of the study IVR along with its corresponding 95% confidence interval.

The above acceptability analysis will be supplemented by presenting the above proportion by site along with its corresponding 95% confidence interval.

Seventh paragraph, first sentence:

In addition to looking at shifts in the Nugent score **and changes in biomarkers**, within arm descriptions, and between arm comparisons will be done to assess clinically meaningful changes in quantitative measures of vaginal flora (defined by more than ≥ 1 log change in dominant members of the microflora, including ~~*Lactobacillus* (H₂O₂ positive and negative strains)), anaerobic gram negative rods, *Gardnerella vaginalis*, *Escherichia coli*, *Staphylococcus aureus*, *Candida* species, Group B *Streptococcus*, and *Enterococcus* species)~~ and to assess differences in the quantitative levels of these **microflora** between arms during follow-up.

Eighth paragraph:

Biofilms

In the US sites, the percentage of women with biofilms on study IVR surface after 12 weeks of use will be computed for the IVR arm.

92. Section 11.1, Data Management Responsibilities

Study case report forms will be developed by the SDMC. Quality control reports and queries **will be** routinely ~~will be~~ generated and distributed by the SDMC to the study sites for verification and resolution.

93. Section 11.2, *Source Documents and Access to Source Data/Documents*, first paragraph:

Source documents and access to source data/documents will be maintained in accordance with ~~the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials~~ **current DAIDS policies.** (<http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Default.aspx>)

94. Section 11.3 *Quality Control and Quality Assurance*, first paragraph:

Quality control and quality assurance procedures for MTN-005 will be performed in accordance with ~~Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites~~ **current DAIDS policies.** (<http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/qmppolicy.pdf>)

95. Section 11.4, *Study Coordination*, first sentence:

Assignment of all sponsor responsibilities for this study will be specified in a Clinical **Trial Agreement (CTA)** executed by NIAID and ~~IPM~~ **the Population Council**. Study site staff will be provided with the DAIDS SOPs for Source Documentation and Essential Documents, the DAIDS AE Grading Table, **Version 1.0, Dec 2004 (clarification dated August 2009)** and the DAIDS AE Grading Table, Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies). Training and written instructions outlining management and reporting, study IVR dispensing to participants, product accountability, and other study operations will be provided by FHI, SCHARP, and the MTN Network Laboratory.

96. Section 12.0, *Clinical Monitoring*, second paragraph, second sentence:

Site investigators will allow study monitors and MTN CORE staff to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, ~~case report forms and/or CRFs~~), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the MTN CORE, MTN Network Laboratory, FHI, SCHARP, ~~NIAID~~, **NIH or appointed agents, FDA, OHRP**, local regulatory authorities, and US regulatory authorities. A site visit log will be maintained at the study site to document all visits.

97. Section 13, *Human Subjects Protection*:

The investigators will make efforts to minimize risks to human participants. Volunteers will take part in a thorough informed consent process. Before beginning the study, the investigators will have obtained IRB/EC approval. The investigators will permit audits by the **NIH or any of their appointed agents, IPM, the Population Council, and/or the US FDA, or any of their appointed agents.**

98. Section 13.1, *Institutional Review Boards*

Section(s) not modified.

99. Section 13.2, *Protocol Registration*:

~~Each study site will complete protocol registration with the DAIDS Regulatory Compliance Center (RCC) Protocol Registration Office. For additional information, refer to the protocol registration documents located at <http://rcc.tech-res.com/forms.htm>. Protocol registration must occur as a condition for site-specific study activation; no participants may be screened or enrolled in this study prior to obtaining protocol registration approval and completing all other study activation requirements. Protocol registration material can be sent electronically to epr@tech-res.com. For questions regarding protocol registration, please call 1-301-897-1707. MTN CORE (FHI) staff will notify each study site when all activation requirements have been met by issuing a site-specific study activation notice. Study implementation may not be initiated until the activation notice is issued.~~

~~The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and NIAID Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB/EC(s) and the RCC prior to implementing the amendment.~~

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local IRB/EC and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) *WILL NOT* be reviewed or approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the

DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for this amendment (Version 2.0), sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the final amendment Registration Notification issued by the DAIDS PRO should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

100. Section 13.3.1, *Risks*:

Phlebotomy may lead to **excessive bleeding**, discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Pelvic examination, including colposcopy, may cause mild discomfort and/or vaginal bleeding or spotting. Disclosure of STI status may cause sadness or depression in volunteers. Participation in clinical research includes the risks of loss of confidentiality and discomfort with **the** personal nature of questions. Use of the study IVR may lead to vaginal symptoms, including irritation, increased discharge, and discomfort (including with vaginal intercourse).

101. Section 13.3.2, *Benefits*:

Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis ~~and treatment~~ of syphilis.

102. Section 13.4, *Informed Consent Process*:

First paragraph, Fourth sentence:

Study staff must document the informed consent process in accordance with the Requirements for ~~Source Documentation in~~ **Protocol Documents** for DAIDS Funded and/or Sponsored Clinical Trials (<http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/pages/protocols.aspx>).

First paragraph, sixth and seventh sentence:

Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendices ~~VI, VII, VIII~~ **IV, V, and VI** that describe the purpose of screening and of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. ~~The If applicable, the study site~~

also is responsible for translating the template forms into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

Fourth paragraph, first sentence:

Community input ~~will have~~ **has** been sought for the development of the sample informed consent forms.

103. Section 13.5, *Participant Confidentiality*; Section 13.6, *Special Populations*; Section 13.7, *Compensation*; 13.8, *Communicable Disease Reporting*; Section 13.9 *Access to HIV-related Care*:

Section(s) not modified.

104. Section 13.10, *Study Discontinuation*:

This study may be discontinued at any time by ~~NIAID~~**NIH**, the MTN, **US FDA**, the ~~IPM~~**Population Council**, the OHRP, site IRBs/ECs, or other country-specific government or regulatory authorities.

105. Section 14, *Publication Policy*:

DAIDS and MTN policies and a Clinical Trial Agreement (CTA) between ~~IPM~~**the Population Council** 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, and ~~IPM~~**the Population Council** for review prior to submission.

106. Appendix I: Schedule of Study Visits and Evaluations:

	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				
Behavioral Eligibility Assess/Confirm	x	x					
Provide Available Results	x ▲	x ▲	x ▲	x ▲	x ▲	x ▲	▲
Schedule Next Visit	x +	x +	x	x	x	x ▲+	x ▲+
Obstetric History	x	x					
Adher. Assessment			●	●	●	▲ ●	
Accept. Assessment		x	▲ ●	▲ ●	●	▲ ●+	
Compl. Phys. Exam	x	x				x	▲

	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				
Targ. Phys. Exam		x	x	x	x		▲
Protocol Adher. Coun		x	x	x	x	*	▲
Treat/Prescribe for UTI/RTI/STI	▲	▲	▲	▲	▲	▲	▲
Plasma Archive		x					
Vaginal pH	†▲*	†▲*	†▲*	†▲*	†▲*	†▲*	†▲
Cerv. NAAT for GC/CT	x	▲	▲	▲	▲	▲	▲
Test for Trichomonas	x	†▲	†▲	†▲	†▲	†▲	†▲
Vaginal-Wet Mount for Vulvovag. Candidiasis	†▲*	†▲*	†▲*	†▲*	†▲*	†▲*	†▲
Wet Mount for BV	†▲	†▲	†▲	†▲	†▲	†▲	†▲
Innate Factors (US sites only)		x				x	
Colposcopy		x	▲	▲	x	x	▲
Naked Eye Exam	x	x	x	x	x	x	
Vaginal Cultures/Flora Assessments		x	x	x	x	x	▲
Biofilm Assessment (at US sites only)			●▲■	●▲■	▲∞	●▲	●▲■
Herpes Culture	†▲	†▲	†▲	†▲	†▲	†▲	†▲
Study IVR		●	●▲+	●▲+			●▲+
Bottle of Water			+	+			
Collect Used IVR			●▲+	●▲+	●	●▲+	●▲+

▲ if clinically indicated; ● For group A (randomized to Study IVR); ■ For group A (if permanently discontinued and removed by study clinician); ∞ For group A (randomized to Study IVR and removed by study clinician); † Per local standards; + For Group A if indicated, + if applicable

107. Appendix II: *HIV Antibody Testing Algorithm* has been revised to combine the HIV Antibody Testing Algorithms for both Screening and Follow-up Visits.

108. Appendices IV-VI: Sample Informed Consent Documents (*Screening, Enrollment, and Storage and Future Testing of Specimens*):

Short Title for the Study: Safety and Acceptability **Adherence** of a Non-medicated Intravaginal Ring (IVR)

109. Appendix IV: *Sample Informed Consent Documents (Screening)*:

Introduction, first paragraph, third sentence:

The ~~International Partnership for Microbicides (IPM)~~ **Population Council** is supplying the study product for MTN-005.

Why are these Screening Exams and Tests Being Done?, first paragraph:

These exams and tests are being done to see if you can be in this study. The research study will try to find out more about whether using vaginal rings for twelve weeks is safe ~~and acceptable for women~~. **Another purpose of this study will be to see how closely participants follow instructions on how to use the ring.** A vaginal ring is a ring that is placed in the vagina and can release certain medicines to prevent pregnancy or can release hormones to lessen the symptoms of menopause. A member of the study staff will show you a vaginal ring. For example, ~~Femring~~ **NuvaRing[®]** is a vaginal ring that ~~postmenopausal women use to lessen the symptoms of menopause such as hot flashes and night sweats~~. **avoid becoming pregnant.** Women in the United States have been using ~~Femring~~ **NuvaRing[®]** ever since it was approved by the United States Food and Drug Administration in ~~2003~~. ~~The type of~~ **2002. NuvaRing[®] has also been approved for use in many other countries, including India. Progering[®] is another type of vaginal ring that will be used in this study is made from the same materials as Femring[®], except that the to prevent pregnancy in women who are breastfeeding. Progering[®] is currently available to women in Bolivia, Chile, Ecuador, and Peru. The rings that will be used in this study are made from the same materials as Progering[®] but do not contain any medicine at all. The rings used in this study will not protect you from pregnancy, HIV or any infection passed through sex.** About two-thirds of the women in this study will be asked to use the ring for twelve weeks and some women will not use anything at all. The other purpose of this study is to find out what women think about using a vaginal ring.

Why are these Screening Exams and Tests Being Done?, second paragraph:

Although vaginal rings have been approved by the United States Food and Drug Administration ~~and the Progering[®] has been approved by regulatory authorities in Chile~~, this particular research study would like to find out more information about how the rings affect the vagina. For example, if you ~~can~~ **decide to** join the study, some of the tests that will be done will look for changes in the bacteria that are normally found in the vagina.

Why are these Screening Exams and Tests Being Done?, third paragraph:

A total of 252 women from ~~Pune, India, Alabama, USA, and New York, USA,~~ **the US** will join this study (150 in India and 102 in the US). Each woman will be in the study for a total of 16 weeks. If you ~~can~~ **decide to** join the study, you will have a study visit every 4 weeks.

What Do I Have To Do If I Take Part in Screening? First paragraph, first sentence:

If you agree to have the screening exams and tests, you will have one ~~to~~ **two** screening visits here at the study site. Depending on what your screening exams and tests show more screening visits ~~will~~ **may** be needed.

What Do I Have To Do If I Take Part in Screening? All modified bullets:

- ~~To find out if you can join the study you will be asked some questions.~~ **Answer some questions to see if you can join this study.** Some of the ~~q~~**Questions will be about you, how we can contact you and where you live. You will be asked questions about your health, the medicine you take, and your periods**
- **Tell the study staff about previous pregnancies, how many children you have, and hear about ways to avoid becoming pregnant**
- If your answers to those questions show that you may join the study, you will have to give urine for a pregnancy test **and to check for urine infection.** You will receive the result of your pregnancy test today. If you are pregnant, you will not be able to join the study. However, site staff will talk to you about options available to you. They will refer you to available sources of medical care and other services you may need **if you are found to be pregnant or have a urinary tract infection**
- If you are not pregnant, study staff will talk to you about HIV and other infections passed through sex. You will have tests for HIV, gonorrhea, chlamydia, **Trichomoniasis and syphilis. You will have tests for bacterial vaginosis, and/or yeast, trichomoniasis, and herpes if the study doctor or nurse thinks you have signs of these infections. These tests may require samples of blood and/or vaginal and cervical fluids to be taken. You will be tested for herpes simplex virus (you will be tested for herpes only if the study nurse or doctor or nurse thinks you have signs of herpes, like a blister or ulcer on the genitals).** ~~You will talk about HIV/AIDS and other infections passed through sex.~~
- You will also talk about ways that HIV and other infections passed through sex are passed from one person to another, and things you can do to protect yourself from them. You will talk about what it may mean to know the results of these tests. You can talk about whether or not you are prepared to know these test results. **You must hear your HIV test results to join the study. It will take about [INSERT LENGTH OF TIME] to get the results of your tests. We will give you your results as soon as they are ready. You will talk with the study staff about the meaning of your test results and how you feel about them**
- The vaginal ring used in this study will not ~~stop~~**prevent** you from becoming pregnant; therefore you should not use this as a birth control method. You must agree to use **an** effective method of birth control such as birth control pills or another hormonal based method (except **contraceptive** vaginal rings), an intrauterine device (IUD), study provided male condoms, be sterilized, or have sex with a partner who is sterilized. You may not use diaphragms, spermicides, ~~or~~ spermicidal male condoms, **or silicone-based lubricants.** If you are using male condoms, you must only use ~~the ones provided in this study~~ **approved condoms.** Study staff will talk to you about the different ways to avoid becoming pregnant. The study staff will provide male condoms to you free of charge
- If you are willing to have HIV testing and testing for infections passed through sex, you will be asked to give blood (about a tablespoon) [SITES TO INSERT LOCAL EQUIVALENT] and ~~urine~~**cervical fluid for these tests. You must hear your HIV test results.** ~~If you are having health problems that may be a result of infections passed through sex, the study staff will provide or prescribe you medicine to treat them or refer you for treatment . Your partner may also need to be referred for treatment. In some cases we may ask you to come back here after a few days for another exam to see if you are able to join the study.-~~
- **If your exams and tests show that you have HIV you will not be able to join the study. The study staff will refer you to available sources of medical care and other services you may need for HIV. They will tell you about other studies you may be able to join.**

- ~~If a sore (or other problem) is seen during the exam of your vagina, you may need medicine to treat it. You will be asked to see your regular clinic for medicine or be given medicine here. We will ask you to come back here after a few days for another exam. If the sore (or other problem) has cleared up when you come back, you may be able to join the research study.~~
- ~~Your urine will also be checked for gonorrhea and chlamydia, and to see if you are pregnant.~~
- You will have a physical exam and a pelvic exam. If you do not know what will be done during a pelvic exam, the study staff will show you pictures of what happens. The study doctor or nurse will check for discharge, or other signs of infection, and other possible problems. ~~They will also take some fluids to check for bacterial vaginosis, vaginal yeast infection, or trichomoniasis~~
- ~~If your exams and tests show that you have HIV you will not be able to join the study. The study staff will refer you to available sources of medical care and other services you may need for HIV. They will tell you about other studies you may be able to join.~~
- **Schedule your next visit, if you are found to be eligible for the study**

What Do I Have To Do If I Take Part in Screening?, third paragraph (old):

~~It takes about [SITES TO INSERT AMOUNT OF TIME] before results for HIV and infections passed through sex are ready. You will talk to with the study staff about the meaning of your test results and how you feel about them.~~

What Do I Have To Do If I Take Part in Screening?, third paragraph (new), last five sentences:

~~If your exams and tests show that you have an infection passed through sex, you may need medicine to treat it. The study staff will refer you to your regular clinic for medicine or give you medicine here to treat the infection. Your partner may also need to be treated. You will be asked to come back here after taking all the medicine. At that time, you may be able to enter the research study.~~

What Do I Have To Do If I Take Part in Screening?, last paragraph:

~~If at any time during the screening it is found that you cannot join the study, the screening process and your visit will end.~~

Why Would the Doctor Stop the Screening Procedures Early?, first bullet:

- The study is cancelled by the US National Institutes of Health (NIH), the MTN, the ~~International Partnership for Microbicides~~**Population Council**, ~~the Ethics Committees~~, the **US** Office for Human Research Protections (**OHRP**), the local government or regulatory agency, or the Institutional Review Board (IRB)/Ethics Committees (EC).

What Are the Risks of the Screening Visit Tests?, *Risk of Blood Draws*, first sentence:

You may have **more than expected bleeding**, feel discomfort or pain when your blood is drawn.

Are There Benefits to Taking Part in This Study?, second paragraph, seventh sentence:

If you have any of these infections **are diagnosed with a sexually transmitted infection**, you will be referred for treatment **get medicine or a prescription to treat it**, if needed.

What Other Choices Do I Have Besides This Study?, second paragraph:

~~The only known way to protect against HIV during sex is to use a condom every time you have sex.~~

What About Confidentiality?, bullet points:

- ~~The~~**Representatives of the US Federal Government, including the US Food and Drug Administration (US-FDA), the US National Institutes of Health (NIH) Office for Human Research Protections (OHRP), NIH and/or contractors of the NIH**
- [INSERT NAME OF SITE] IRB/EC
- Study staff
- Study monitors
- Ethics committees
- **Population Council, the Organization supporting-supplying the ring for this study**(International Partnership for Microbicides)

What About Confidentiality?, Second paragraph:

*[For US sites only:] In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the US Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. ~~Even with the Certificate of Confidentiality, however~~ **However**, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.*

Will I Receive Any Payment?, first sentence:

You will be ~~paid~~**compensated** for your time and effort for each screening visit

What Are My Rights As a Research Participant?, title modified for grammatical clarity.

SIGNATURE, first paragraph:

*If you have read the informed consent (or had it read and explained to you), and all your questions have been answered, you have let us know that you understand, and you agree to take part in ~~this study~~**the screening procedures**, please sign your name or make your mark below.*

SIGNATURE, Participant Signature Line:

*Participant's Name **or Mark** (print)*

Participant's Signature and Date

110. Appendix V: Sample Informed Consent Document (Enrollment):

Introduction:

The ~~International Partnership for Microbicides (IPM)~~ **Population Council** is supplying the study product for MTN-005.

Why is This Study Being Done?, first paragraph, first through sixth sentences:

This study is being done to see if a kind of vaginal ring is safe ~~and acceptable to women.~~ . **Another purpose of this study will be to see how closely participants follow instructions on how to use the ring.** A vaginal ring is a ring that is placed in the vagina and can release certain medicines to prevent pregnancy or hormones to lessen the symptoms of menopause. For example, ~~Femring~~ **NuvaRing[®]** is a vaginal ring that ~~postmenopausal women use to lessen the symptoms of menopause such as hot flashes and night sweats.~~ **avoid becoming pregnant.** Women in the United States have been using ~~Femring~~ **NuvaRing[®]** ever since it was approved by the United States Food and Drug Administration in 2003. ~~The type of~~ **2002. NuvaRing[®] has also been approved for use in many other countries, including India. Progering[®] is a vaginal ring that will be used in this study is made from the same materials as Femring[®], except that the to prevent pregnancy in women who are breastfeeding. Progering[®] is currently available to women in Bolivia, Chile, Ecuador, and Peru. The rings that will be used in this study are made from the same materials as Progering[®] but do not contain any medicine at all. The rings used in this study will not protect you from pregnancy, HIV or any infection passed through sex.** About two-thirds of the women in this study will be asked to use the ring for 12 weeks and about one third will not use the ring. ~~As this is a randomized trial, w~~ **Women who join this study will not be able to choose their group assignment since this is a randomized trial, which means that group assignment is selected randomly (e.g. flip of a coin).** The other purpose of this study is to find out what women think about using a vaginal ring.

Why is this Study Being Done?, second paragraph:

~~Vaginal rings have been developed to prevent pregnancy and to provide hormones to older women, and have been tested in many thousands of women since 1970. Although these vaginal rings have been approved by the United States Food and Drug Administration, this particular research study would like to find out more information about how rings without medication might affect the vagina. For example, if you can join the study, some of the tests that will be done will look for changes in the bacteria that are normally found in the vagina.~~

Although vaginal rings have been approved by the United States Food and Drug Administration and the Progering[®] has been approved by regulatory authorities in Chile, this particular research study would like to find out more information about how the rings affect the vagina. For example, if you decide to join the study, some of the tests that will be done will look for changes in the bacteria that are normally found in the vagina.

Why is this Study Being Done?, third paragraph, second sentence:

A total of 252 women from Pune, India, Alabama, USA, and New York, USA, ~~the US~~ will join this study (150 in India and 102 in the US).

What Do I Have To Do If I Take Part in the Study, first paragraph:

If you agree to be in the study, you must not use, or plan to use, the following at enrollment, during the period of study participation, ~~and for an extra month after the study ends:~~ non-study vaginal products or other devices including diaphragm, sex toys, douching and other intravaginal cleansing practices, female condom, intravaginal ring (except for the one provided in this study if you are in the group that will use the ring), spermicide, and/or menstrual cup. You will be allowed to use tampons.

What Do I Have To Do If I Take Part in the Study?, fifth bullet :

You will also have these study visits hereat the study site:

- 16-Week/**Study Termination** Visit

Enrollment Visit, all modified bullets:

- **Answer questions to confirm that you are able to participate in this study and that you understand what will be asked of you if you agree to participate**
- Answer questions about your sexual behavior and what vaginal products you have used before **or may like using**
- Tell the study staff about previous pregnancies, ~~and~~ how many children you have, **and hear about ways to avoid becoming pregnant**
- Tell the study staff about any medical problems **you are currently having or had in the past, as well as** changes in your health or menstrual periods
- Have a physical exam **based on any signs or symptoms you report**
- Hear about (first and fourth sub-bullet)
 - ~~how to avoid pregnancy and~~ infections passed during sex while you are in the study
 - ~~how to use the vaginal ring, if you are in the group that uses the vaginal ring~~
- Provide a urine sample for a pregnancy test, ~~and to test for urine infection~~
- Provide a blood sample for syphilis testing (if you have signs of syphilis) **in case there are questions about your test results**
- Have a pelvic exam and colposcopy. During the colposcopy, the study doctor or nurse will look at your genital area and into your vagina through a lens called a colposcope. The lens works like a magnifying glass to help the nurse or doctor see anything that may not be normal. The lens will not be inside your body. They may take digital video pictures of the colposcopy with a camera. You may tell the study staff not to record these images. These images will be kept strictly confidential and used only by study physicians to decide upon the significance of possible ~~if~~ changes in the vagina or cervix **are important for the research study results**
- ~~Provide a urine sample to test for gonorrhea and chlamydia~~
- ~~Provide a blood sample for HIV testing (if the study doctor thinks you need an HIV test)~~
- Provide samples of vaginal discharge that will be collected with a swab to check for vaginal infections ~~and vaginal cultures (types and amounts of bacteria in the vagina)~~

- **Provide samples of vaginal discharge that will be collected with a swab to check for vaginal cultures (types and amounts of bacteria in the vagina)**
- ~~Have a test for herpes infection if you have signs of herpes infection (like a sore or blister on the genitals)~~
- If you are in the group that uses the vaginal ring, the study staff will **give you a study ring and will also discuss the following** with you:
 - The study staff will tell you how to insert the ring, and then give you privacy so that you can put the ring in yourself. A study doctor or nurse will then check to see that you have put the ring in the right way. If you ~~are having~~**have** difficulty putting in the ring, you can ask questions and receive more advice. Please let the **study** doctor or nurse know if you do not think that you will be able to put the ring in by yourself
 - If your ring falls out before your next visit and you do not feel comfortable rinsing the ring in clean, warm water and putting it back in your vagina, you will need to save this ring in a special bag that we will give you and bring it back to your next visit, **some participants may also receive a bottle of water**
 - **Receive test results if available**
 - **Schedule your next visit, if you are found to be eligible for the study**

Scheduled Monthly Visits (4-Week, 8-Week, 12-Week and 16-Week/Study Termination Visits), all modified bullets:

- ~~Provide a urine sample to test for urine infection (if you have signs of urine infection)~~
- ~~Provide a blood sample for syphilis testing (if you have signs of syphilis)~~
- Have a physical exam **based on any signs or symptoms you report**
- Provide samples of vaginal discharge that will be collected with a swab to check for vaginal infections and vaginal cultures (types and amounts of bacteria in the vagina)
- ~~Have a test for herpes infection if you have signs of herpes infection (like a sore or blister on the genitals)~~
- Receive test results **if available** ~~If your test results are not available at your 16-Week/Study Termination Visit, study staff may contact you at a later time to provide you with this information.~~
- **Schedule your next visit (except at the 16-Week/Study Termination Visit)**

Additional Procedures:

You will complete all of the regular monthly procedures plus **the following at the visits indicated:**

- ~~Provide a urine sample for a pregnancy test (if the study doctor thinks you need a pregnancy test) (4-Week, 8-Week, and 12-Week Visits)~~
- ~~Provide a urine sample for gonorrhea and chlamydia (if you have signs of gonorrhea or chlamydia) (4-Week, 8-Week, and 12-Week Visits)~~
- Answer questions about **using** the vaginal ring (if you are in the group that uses the ring) (4-Week, 8-Week, and 12-Week Visits)
- **Have samples of cervical fluid taken to answer questions about how your body works to protect you from infections. This testing will only be done for US participants. Results will not be provided to participants since this is for research purposes only. (Enrollment and 16-Week Visits only)**
- Have the study ring removed by the ~~physician~~**study doctor**. The study staff will then take a sample of the fluid that is on the ring for testing. You will not get the results of this

test because the test is for research purposes only and will not result in information that could be used for your health. **This testing will only be done for US participants** (12-Week Visit)

- ~~Provide a urine sample for gonorrhea and chlamydia (16-Week/Study Termination Visit)~~
- ~~Provide a blood sample for an HIV test (16-Week/Study Termination Visit)~~

It takes about [SITES TO INSERT AMOUNT OF TIME] before results for colposcopy, HIV and infections passed through sex are ready. You will not receive the results of the ~~vaginal culture~~ **tests for the types and amounts of bacteria in the vagina**, because these types of tests do not give information that can be used for medical care. You will talk to the study staff about the meaning of your test results and how you feel about them.

If your exams and tests show that you have an infection passed through sex, you may need medicine to treat it. You will ~~be asked to see your regular clinic~~ **provided or prescribed medicine or be given medicine here or be referred to another clinic for treatment**. The study staff will ask you to stop using the vaginal ring, if you are in the group that uses the ring. You will be asked to come back here after taking all the medicine.

At Any Time in the Study:

At Any Time in The Study

If the study doctor thinks you have health problems that may be caused by infections, including those passed through sex, if you have signs of infections, or if local rules apply, you may:

- **Have an exam of your genital area and your vagina**
- **Give blood, cervical, and/or vaginal fluid to test for infections**
- **Provide a urine sample for a pregnancy test or to check for a urine infection**
- **Get treatment or a prescription or a referral for most types of infections if you need it**
- **Counseling about HIV testing if the study doctor thinks you need to be tested for HIV**

Why Would the Doctor Take Me Off This Study Early?

First bullet, first sentence:

- The study is cancelled by the US National Institutes of Health (NIH), the ~~International Partnership for Microbicides~~ **Population Council**, the ~~Ethics Committee~~, the **US** Office for Human Research Protections (OHRP), the MTN, the local government or regulatory agency, or the Institutional Review Board (IRB)/Ethics Committee (EC). (An IRB is a committee that watches over the safety and rights of research participants)

Second paragraph, first sentence:

The study doctor ~~will~~ **may** ask you to stop using the ring (if you are in the group that uses the ring) but continue to come in for your follow up visits and procedures if:

What Are the Risks of Being in the Study?, Risk of Pregnancy, first paragraph, second sentence:

You must agree to use effective method of birth control such as birth control pills or another hormonal based method (except **contraceptive** vaginal rings), an intrauterine device (IUD), study provided male condoms, be sterilized, or have sex with a partner who is sterilized while you are participating in the study ~~and for an extra month after the study has ended.~~

What Are the Risks of Being in the Study?, Risk of Pregnancy, third paragraph, final sentence:

This study cannot provide care related to termination of pregnancy, though study staff can provide you with information about ~~you~~**where you can** access ~~tea~~ termination of pregnancy as part of **your pregnancy** counseling ~~you about your pregnancy test results.~~

What Are the Risks of Being in the Study?, Risk of Blood Draws, first sentence:

You may feel **more than expected bleeding**, discomfort or pain when your blood is drawn.

Are There Benefits to Taking Part in This Study?, second paragraph, seventh sentence:

If you ~~have any of these infections~~ **are diagnosed with a sexually transmitted infection**, you will be referred for treatment ~~get medicine or a prescription to treat it, if needed.~~

What Other Choices Do I Have Besides This Study?, second paragraph:

~~The only known way to protect against HIV during sex is to use a condom every time you have sex.~~

What about Confidentiality?, bullet points:

- ~~The~~**Representatives of the US Federal Government, including the** US Food and Drug Administration (US-FDA), ~~the~~ US National Institutes of Health (NIH) Office for Human Research Protections (OHRP), **NIH and/or contractors of the NIH**
- [INSERT NAME OF SITE] IRB/EC
- Study monitors
- Ethics committees
- **Population Council, the** ~~Organization supporting~~ **supplying the ring for this** study (~~International Partnership for Microbicides~~)

What About Confidentiality?, Second paragraph:

*[For US sites only:] In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the US Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. ~~Even with the Certificate of Confidentiality, however~~ **However**, if the study staff learns of possible child abuse and/or*

neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

What Are The Costs To Me?

There is no cost to you for the study visits, **or** study provided male condoms ~~or treatment for treatable infections passed by sex.~~

Will I Receive Payment?

You will be ~~paid~~ **compensated** for your time and effort for each study visit.

What Happens If I Am Injured?

There is no program for compensation either through this institution or the US National Institutes of Health ~~(NIH).~~

Signature, participant signature line:

Participant's Name **or Mark** (print)

Participant's Signature and Date

111. Appendix VI: *Sample Informed Consent (Storage and Future Testing of Specimens), Introduction*, first paragraph, first sentence:

You have decided to take part in a US National Institutes of Health (**NIH**) research study.

Appendix VI: *Sample Informed Consent (Storage and Future Testing of Specimens), Introduction*, first paragraph, fifth sentence:

If you have any questions, ~~if you have some, please ask them.~~

How Will You Get the Samples From Me?, first and second sentences:

The research doctors want to save any extra blood and vaginal/**cervical** fluid leftover from your tests during the study. This leftover blood and vaginal/**cervical** fluid will be kept and used for future research.

How Will You Use My Samples?, seventh, eighth, and ninth sentences:

~~If a rare situation came up where the researchers decided that one of the test results would provide important information for your health, the researchers would notify your study doctor and your study doctor would try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your address and/or phone number. If you want your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name, address and phone number.~~

How Will You Use My Samples?, last paragraph:

Research studies using your samples will be reviewed by the US ~~National Institutes of Health (NIH), an Ethics Committee, and~~ an Institutional Review Board (IRB)/Ethics Committee (EC), a special committee at the researcher's institution whose purpose is to protect you as a research participant.

What About Confidentiality?, third paragraph, first sentence:

People who may review your records include: [INSERT NAME OF SITE] IRB, US ~~National Institutes of Health (NIH)~~ **and/or contractors of the NIH**, Office for Human Research Protections (**OHRP**), **US FDA, Population Council**, [INSERT NAME OF SITE] IRB/EC, **and** study staff.

How Will My Samples Be Stored?

Your samples may be **stored at your site or** sent to the United States for storage and testing. Your samples will be stored at ~~special~~ facilities that are designed to store samples safely and securely. The storage facilities are designed so that only approved researchers will have access to the samples. ~~Some employees of the storage facilities will need to have some access to your samples to store them and to keep track of where they are, but these people will not have information that directly identifies you (a code number will be on these samples, but not your name). An Institutional Review Board/Ethics Committee will oversee the storage facilities to protect you and other research volunteers from harm.~~

Signature Page:

Please carefully read the statements below and think about your choice. No matter what you decide, it will not affect your participation in this study or your medical care. If you have read the informed consent (or had it read and explained to you), understand it, and all your questions have been answered and you agree to take part in this study, please **initial or mark your choice and** sign your name or make your mark below.

[Insert signature blocks as required by the local IRB/EC]

I agree to allow my leftover samples to be stored for future testing.

OR

I do not agree to allow my leftover samples to be stored for future testing.

Signature Page, participant signature line:

Participant's Name **or Mark** (print) Participant's Signature and Date

- 112. The protocol title, version number and date are updated throughout the protocol document
- 113. Correction of minor editorial and typographical edits and updates are made throughout the protocol document