Section 2. Protocol

The table below documents the history of the MTN 005 protocol along with Clarification Memos, Letter of Amendments, and Full Amendments. These documents are considered Essential Documents. A copy of each document should be available to staff and a copy should be maintained in your central files.

Document	Date
MTN 005 Protocol, Version 1.0	03 April 2008
MTN 005 Protocol, Version 2.0	19 October 2010

Note: Clarification Memos and Letters of Amendment are incorporated into subsequent full versions of the protocol.

To ensure that this manual continues to reflect current protocol specifications in the future:

- Upon receipt of any protocol clarification memos, add a copy of the memo to this section.
- Upon receipt of any additional letters of amendment, add a copy of the letter of amendment to this section.
- Upon receipt of any full protocol amendments, replace the contents of this section with the amended protocol.

Further information on the content and required handling of protocol clarification memos, letters of amendment, and full amendments is available in Section 9.2 of the MTN Manual of Operations.

MTN-005

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

A Study of the Microbicide Trials Network

Sponsored by:

Population Council

Grant #:
5-U01-AI068633-05

DAIDS Protocol #:
10635

Co-Sponsored by:

Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Mental Health
US National Institutes of Health

Population Council IND #: 109,767

Protocol Chair:
Craig Hoesley, MD

Final Version
Version 2.0

October 19, 2010

MTN-005

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

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

LIST OF ABBREVIATIONS AND ACRONYMS

ACASI	audio computer-assisted self interviewing
AE	adverse event
AIIMS	All India Institute of Medical Sciences
ASCCP	American Society for Colposcopy and Cervical Pathology
BV	bacterial vaginosis
CAB	community advisory board
CDC	(US) Centers for Disease Control
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendment
CRPMC	Clinical Research Products Management Center
CRF	case report form
CT	*Chlamydia trachomatis,* chlamydia
CTA	Clinical Trial Agreement
DAIDS	Division of AIDS
DAIDS PRO	Division of AIDS Protocol Registration Office
EAE	expedited adverse event
EC	Ethics Committee
EE	ethinyl estradiol
EIA	enzyme immunoassay
FHCRC	Fred Hutchinson Cancer Research Center
GC	*Neisseria gonorrhoeae,* gonorrhea
GCP	Good Clinical Practices
H_2O_2	hydrogen peroxide
hCG	human chorionic gonadotropin
HHS	Health and Human Services
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus-Type 1
HPTN	HIV Prevention Trials Network
HSV	herpes simplex virus
HSV-2	herpes simplex virus-type 2
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
IFA	immunofluorescence assay
IoR	Investigator of Record
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IVR	intravaginal ring
ISO	International Organization for Standardization

LDMS	Laboratory Data Management System
mg	milligram
mL	milliliter
mm	millimeter
MO	Medical Officer
MTN	Microbicide Trials Network
NAAT	nucleic acid amplification test
NES	Nestorone
NET-Ac	norethindrone acetate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NPOS	normal propylorthosilicate
OHRP	Office for Human Research Protections
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development Inc.
PSRT	Protocol Safety Review Team
PTID	Participant Identification
PVR	progesterone-releasing vaginal ring
RE	regulatory entity
RH	relative humidity
RPR	rapid plasma reagin
RSC	Regulatory Support Center
RTI	reproductive tract infection
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDA	strand displacement amplification
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SOP	standard operating procedure(s)
SSP	study specific procedure(s)
STI	sexually transmitted infection
T-Cu	Copper T 380 A
UA	urinalysis
UADE	unanticipated adverse device effect
UNAIDS	Joint United Nations Programme on HIV/AIDS
US FDA	United States Food and Drug Administration
UTI	urinary tract infection
WB	Western Blot
WHO	World Health Organization

MTN-005

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

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MTN-005
Expanded Safety and Adherence Study of a Non-medicated Intravaginal Ring

INVESTIGATOR SIGNATURE FORM

Version 2.0
October 19, 2010

A Study of the Microbicide Trials Network (MTN)

Sponsored by:
Population Council

Co-sponsored by:
US National Institute of Allergy and Infectious Diseases
US National Institute of Mental Health
US National Institutes of Health

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 at least two years 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 the Population Council for review prior to submission.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Site Investigator

_____ _____
Signature of Site Investigator Date

MTN-005

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

PROTOCOL SUMMARY

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

Protocol Chair: Craig Hoesley, MD

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: 102 (68 and 34 in the IVR and No IVR arms, respectively)

Study Population: Sexually active, HIV-uninfected women between the ages of 18 and 45 years

Sites: Bronx-Lebanon Hospital Center, Bronx, NY, USA
National AIDS Research Institute, Pune, India
University of Alabama at Birmingham, Birmingham, AL, USA

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

Study Duration: 16 weeks for each participant; 14 months approximate total study duration

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/Study Termination Visit

Table 1: Study Regimen

	Screening	Enrollment	4-Week	8-Week	12-Week	16-Week
	↓	↓	↓	↓	↓	↓
GROUP						
A		**[**	**STUDY IVR USE PERIOD**		**]**	**TERMINATION**
B		**[NO IVR (SAME STUDY VISITS AS GROUP A)]**				

Study Objectives

Primary Objectives

- Evaluate the safety of the study IVR in HIV-uninfected women over 12 weeks of use

- Evaluate the 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 of frequency of study IVR removal (voluntary and involuntary) and duration without IVR inserted in vagina over 12 weeks of use

Secondary Objectives

- 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 acceptability of the study IVR in HIV-uninfected women over 12 weeks of use

- Measure vaginal flora characteristics, and 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 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 as measured by Gram stain Nugent score and quantitative culture (note that these quantitative vaginal cultures will only be available from the US sites, therefore reducing the available sample size for this objective)

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)

Exploratory Endpoint

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

KEY ROLES

1.1 Protocol Identification

Protocol Title:	Expanded Safety and Adherence Study of a Non-medicated Intravaginal Ring
MTN Protocol Number:	MTN-005
Date:	October 19, 2010

1.2 Sponsor and Monitor Identification

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2 INTRODUCTION

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] Some studies have provided strong evidence that male circumcision can reduce female to male transmission of HIV[2] 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 safety of this delivery method as well as adherence, are necessary first steps prior to evaluating the efficacy of vaginal rings for the prevention of HIV.

2.2 Intravaginal Rings

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 was approved for use in India in November 2009.[6] Estring® (Pfizer) is a hormone replacement 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)

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 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 the Population Council's 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 (H_2O_2) producing *Lactobacillus* colonies as measured by quantitative culture. Presence of H_2O_2-producing lactobacilli is beneficial to vaginal health and it has been suggested that further studies be conducted to confirm these findings.

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 1/2 safety studies have been conducted by the International Partnership for Microbicides (IPM) for an IVR containing dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI).[22-25] The IVRs used in these studies (both active and placebo) have been well tolerated by most study participants.

2.3 Silicone Elastomer

Silicone has long been one of the materials of choice for medical applications. Common silicone medical components include catheters, feeding and drainage tubes, infusion sleeves, shunts and electrosurgical hand pieces. Silicones do not stain or corrode other materials, and can be formulated to comply with US FDA, International

Organization for Standardization (ISO), and Tripartite biocompatibility guidelines for medical products.[26]

2.4 Preclinical Studies

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

When a single dose of the NuSil silicone material extracted in 0.9% sodium chloride solution was injected intravenously in mice, there was no evidence of significant systemic toxicity for up to 72 hours after dosing.[27] Intracutaneous injection of the NuSil silicone material extracted in 0.9% sodium chloride solution and cottonseed oil (0.2 mL dose) in rabbits did not result in significant irritation or toxicity at up to 72 hours after dosing. Following intramuscular implantation of the NuSil silicone material in rabbits and examination of the implantation sites 90 days later, the material was classified as slightly irritant.[27]

In an *in vitro* biocompatibility study in which an extract of the NuSil silicone material in Minimal Essential Medium was incubated with L-929 mouse fibroblast cells for up to 72 hours, there was no evidence of cell lysis or cytotoxicity.[27] In an *in vitro* hemolysis test, in which whole rabbit blood was added to the NuSil silicone material in 0.9% sodium chloride solution and incubated for 1 hour to determine the effect due to direct contact with the material or the presence of leachables, the material was considered not to be hemolytic. In an Ames test, a saline extract of the NuSil silicone material was considered to be non-mutagenic.[27]

2.5 Clinical Studies

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 colleagues[28] 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.

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.[29] 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.

Data from these studies were compared with a historical control group (non ring users, N=107).[30] Although study results showed some differences in findings among the different clinics, there were no marked differences in vaginal lesions by ring type.[29] 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

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 another reservoir-type silicone elastomer non-medicated IVR was also evaluated in IPM 008.[22-25, 32] 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 (25 mg) IVR group and 3 women to the placebo IVR group. The women in both the treatment and placebo groups 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 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.[33, 34] 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 Silicone Elastomer 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[30]	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[30]	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[30]	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[35]	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 studies 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 a non-medicated tin-catalyzed, silicone elastomer vaginal ring.[30] This study is a recently completed, randomized, open-label crossover study among 170 healthy, sexually active women at four sites in Kenya, South Africa and Tanzania.[36] 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 was completed, participants then crossed over to the opposite group for an additional twelve weeks. In addition to the enrollment visit, the participants 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 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 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 participants. The most frequently reported AE was vaginal discharge (1.4%) and no other AEs were reported with a frequency of >1%.

2.6 Marketing Experience

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 a progesterone-only vaginal ring manufactured and supplied by Laboratorios Andromaco S.A. in Chile.

2.7 Study Hypothesis and Rationale

2.7.1 Study Hypothesis

MTN-005 hypothesizes that the study IVR will be safe and will be used as directed by US and non-US women over 12 weeks of use.

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 on the safety of and adherence to 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.

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 Kenya[37, 38], Malawi[39]; Zimbabwe[40], Thailand[41, 42], India[43], Vietnam[44] and Mexico[45] 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.[46] 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 colleagues[14] 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.

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. Currently there are very limited published acceptability data specifically reporting findings among Indian women for any IVR. The All India Institute of Medical Sciences (AIIMS) served as a study site for two WHO multi-center studies to assess the acceptability, side-effects, and contraceptive efficacy of a contraceptive vaginal ring releasing 20 micrograms of levonorgestrel per day.[47] Women who regularly attended the outpatient gynecology clinic at AIIMS were recruited for this study. Fifty women participated in the 12-month study and 46 women participated in the 24-month study. Among participants, 38% in the 12-month study and 35% in the 24-month study discontinued ring use as a result of menstrual irregularities and vaginal irritation. A total of 16% of the participants in the 12-month study and 17% of the participants in the 24-month study reported menstrual irregularities, whereas 12% of the participants in the 12-month study and 11% of the participants in the 24-month study reported vaginal irritation. A follow-up study at AIIMS showed that women preferred the vaginal contraceptive ring to any other available contraceptive method.[48] 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 IVR as a possible platform for microbicide delivery.

While data exist on tolerability for NuvaRing® among perimenopausal US and European women[5, 8, 49-52] and for Progering® among nursing women in Latin America[12, 30], acceptability data in perimenopausal Indian and US the non-medicated version of Progering® is lacking. As the thickness of the proposed study IVR is 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 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.

The availability of acceptability data in areas where there is a high risk of HIV acquisition is crucial. Smith and colleagues recently assessed the potential acceptability of an IVR among female sex workers and male clients in Kenya.[54] Findings from focus group discussions underscored the myriad attitudes and concerns that could impact the uptake of an IVR in a high-risk population.

Vaginal Flora

MTN-005 will also examine the impact of study IVR use on vaginal flora. Studies have shown that the presence of H_2O_2 producing lactobacilli in the vagina offer a protective effect against sexually transmitted infections.[55-60] For example, a study conducted in female sexual contacts of infected men, demonstrated correlation between reduced prevalence of *Chlamydia trachomatis*, *Trichomonas vaginalis*, and symptomatic *Candida* and presence of H_2O_2 producing lactobacilli.[61] Another study highlighted a lower prevalence of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis* in women with lactobacilli compared to women with little to no lactobacilli present in the vagina.[62] Furthermore, longitudinal studies conducted in Kenya[60] and Malawi[56], have clearly demonstrated a link between HIV acquisition and changes in vaginal flora. A third study conducted in South Africa showed a correlation between elevated vaginal pH levels and an increased risk of HIV acquisition.[57] These studies demonstrate a link between vaginal flora and susceptibility to sexually transmitted infections. There are currently no published data on the impact of three-month use of this type of IVR on quantitative measures of vaginal flora. MTN-005 also seeks to assess whether or not the study IVR can harbor organisms that are associated with biofilm formation. Studies have shown that the presence of biofilms can result in the expression of drug resistant genes as well as acute disseminated infection.[63, 64] Study site staff will perform a biofilm assessment via culture and/or other techniques, depending on site capacity, of the study IVRs when they are collected at the 12-Week Visit or when the IVRs are returned to the study site. The specimens will then be shipped to the Network Laboratory as appropriate. Given the time sensitive nature of specimen handling, the biofilm assessments will only be done at the US sites.

Currently, there are limited published data on the impact of contraceptive or hormonal vaginal rings on vaginal flora or the potential for biofilm formation.[19-21] Furthermore, the degree of microbiologic testing generally accepted for safety assessment of a hormone replacement or contraceptive vaginal ring may not be as extensive as what may be expected for safety assessment of a potential platform for HIV prevention. A drug delivery vehicle expressly designed to prevent male-to-female transmission of HIV must not enhance the risk of HIV acquisition. As such, documentation of flora changes noted

with use of this IVR is an important part of confirming the study IVR's overall safety. Due to site laboratory capacity and the rapid shipping required for quantitative vaginal culture, only sites with capacity will contribute specimens for this study objective.

Study Design

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 and vaginal hygiene practices during the study period.

3 OBJECTIVES

3.1 Primary Objectives

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

3.2 Secondary Objectives

- 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 acceptability of the study IVR in HIV-uninfected women over 12 weeks of use
- Measure vaginal flora characteristics, and descriptively examine changes in these characteristics over the course of study IVR use

3.3 Exploratory Objectives

- 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)

4 STUDY DESIGN

4.1 Identification of Study Design

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

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 of frequency of study IVR removal (voluntary and involuntary) and duration without IVR inserted in vagina over 12 weeks of use

4.3 Description of Study Population

The study population will include 252 generally healthy 18-45 year-old women who are HIV-uninfected, non-pregnant, sexually active and using adequate contraception, as described in Sections 5.3 and 5.4.

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 14 months, including the study follow-up period.

4.5 Study Groups

Two study groups are planned (IVR and no IVR). Both study groups will be assigned to complete four follow-up visits (4-Week, 8-Week, 12-Week, and 16-Week/Study Termination).

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 will ideally be completed within a specified ± 7 day window around target dates. Detailed information regarding visit windows will be thoroughly described in the MTN-005 Study-Specific Procedures (SSP) Manual.

4.7 Expected Duration of Participation

The expected duration of participation for an individual participant is 16 weeks.

4.8 Sites

Three study sites are planned:

- Bronx-Lebanon Hospital Center, Bronx, NY, USA
- National AIDS Research Institute, Pune, India
- University of Alabama at Birmingham, Birmingham, AL, USA

5 STUDY POPULATION

5.1 Selection of the Study Population

The inclusion and exclusion criteria outlined below will be utilized to ensure the appropriate selection of study participants for MTN-005.

5.2 Recruitment

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.

5.3 Inclusion Criteria

Women must meet all of the following criteria to be eligible for inclusion in the study:

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

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

3. Willing and able to provide adequate locator information, as defined in site SOPs

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

5. In general good health at Screening and Enrollment, as determined by the site Investigator of Record (IoR) or designee

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

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

8. Per participant report, using an effective method of contraception at Enrollment, and intending to use an effective method for the duration of study participation. Effective methods include hormonal methods (except contraceptive vaginal rings), IUD inserted at least 7 days prior to enrollment, study provided male condoms, and/or sterilization (of participant or her sexual partner(s) as specified in site SOPs)

9. 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

10. At Screening and Enrollment, agrees not to participate in other drug or device research study for the duration of study participation

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

5.4 Exclusion Criteria

Women who meet any of the following criteria will be excluded from the study:

1. Participant reported history of:
    a. Adverse reaction to silicone (ever)
    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, silicone, titanium dioxide or any components of the study product (as defined per SSP)
    e. Last pregnancy outcome within 30 days or less prior to enrollment
    f. Hysterectomy

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.

3. Pregnant at Screening or Enrollment, or per participant report intending to become pregnant during the period of study participation

4. At Screening or Enrollment:
   a. Unwilling to comply with study participation requirements
   b. Has a clinically apparent deep disruption of vulvar, vaginal, or cervical epithelium (colposcopic findings not visible by naked eye are not exclusionary)
   c. Is diagnosed with a symptomatic urinary tract infection (see additional information below)
   d. Is diagnosed with a reproductive tract infection (RTI) or syndrome requiring treatment per current US Centers for Disease Control (CDC) guidelines (see additional information below)
   e. Has any other abnormal physical or pelvic exam finding that, in the opinion of the investigator or designee, would contraindicate study participation

   Note: RTIs requiring treatment, per site specific treatment guidelines, include BV, 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.

5. At Screening or Enrollment, has 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

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

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

6 STUDY PRODUCT

6.1 Regimen

Study participants will be randomized to either Group A to receive the study IVR or Group B to receive no study IVR (see Table 3). Participants in Group A will receive instructions on study IVR insertion and use and will then self insert (or by clinician if necessary), the study IVR at the Enrollment Visit. The study IVR should remain in place for 12 consecutive weeks. The study IVR will be removed by the study clinician/designee at the 12-Week Visit. Follow-up will continue for an additional 4 weeks after the final removal of the study IVR.

Table 3: Study Regimen

Group	N	Group Description
A	168	IVR for 12 consecutive weeks
B	84	No IVR for 12 consecutive weeks

6.2 Administration

The study IVR will be inserted into the vagina, by the participant (or clinician if necessary), at the Enrollment visit.

Study participants will be given detailed instructions, in the clinic, on proper study IVR insertion and removal. Hands should be thoroughly washed before and after study IVR insertion and/or removal. Additional detail on administration (IVR insertion, removal, procedures in the event of expulsion or loss) will be provided in the SSP Manual.

6.3 Study Product Formulation

6.3.1 Study IVR

The study IVR is made of cured silicone elastomer composed of an elastomer base, normal propylorthosilicate (NPOS), and titanium dioxide but will contain no active pharmaceutical ingredient. The ring dimensions are as follows: outer diameter 58 mm, cross-sectional diameter 8.4 mm, core diameter 2 mm.

6.4 Study Product Supply and Accountability

6.4.1 Study Product Supply

The study IVRs will be manufactured by Laboratorios Andromaco S.A. (Santiago, Chile) and supplied by the Population Council (New York, NY).

The Pharmacist of Record (PoR) can obtain the study IVR for this protocol by following the instructions provided by the MTN CORE.

6.4.2 Storage and Dispensing

Based on stability studies of Progering®, the study IVRs have a shelf life of 24 months and should be stored at a controlled room temperature. Study IVRs (including replacement IVRs) are dispensed only to enrolled study participants or clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber.

6.4.3 Accountability

Each site PoR is required to maintain complete records of all study IVRs. The procedures to be followed will be provided by the MTN CORE.

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 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, joint pain, or difficulty breathing as these may be signs of an allergic reaction.

6.6 Assessment of Participant Adherence

Participant behaviors regarding 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.

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, nutritional supplements, and herbal preparations will be recorded on forms for concomitant medications.

6.7.1 Prohibited Products and Devices

Concomitant use of non-study vaginal products or other devices including but not limited to diaphragms, sex toys, douching, intravaginal cleansing practices, female condoms, 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. Participants who report such use will be counseled regarding the use of alternative methods and provided or referred to family planning services for provision of alternative methods as applicable.

6.7.2 Recommended Practices

Study sites will distribute an 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 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.

7 STUDY PROCEDURES

The following visits should take place for study participants:

7.1 Screening Visit

Table 4: Screening Visit

Screening Visit (up to and including 45 days prior to Enrollment Visit)	
Component	**Procedures**
Administrative and Regulatory	• Assign participant ID (PTID) • Obtain written informed consent for screening • Collect demographic information • Collect locator information • Assess eligibility • Provide available test results • Provide reimbursement for study visit • Schedule next study visit, if applicable

Behavioral		• Provide counseling
		  o Contraceptive
		  o HIV testing process and results
		  o HIV/STI (Sexually Transmitted Infection) risk reduction/male condom

Clinical		• Collect obstetric history • Collect medical/menstrual history • Collect concomitant medications • Perform complete physical exam (see Appendix III) • Collect urine sample • Collect blood sample • Perform pelvic exam (see Appendix III) • Perform naked eye examination • Collect pelvic samples • Treat or prescribe treatment for symptomatic Urinary Tract Infection (UTI)/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Qualitative human chorionic gonadotropin (hCG) • Dipstick urinalysis (UA) • Urine culture*
	Blood	• Syphilis serology • HIV-1 test
	Pelvic Samples	• Vaginal fluid tested for *Trichomonas vaginalis* by rapid test (Clinical Laboratory Improvement Amendment (CLIA) waived test) • Gram stained smear of vaginal fluid, obtained from lateral vaginal wall • Cervical swab for Nucleic Acid Amplification Test (NAAT) for *Neisseria gonorrhoeae*/*Chlamydia trachomatis* (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 (KOH for vulvovaginal candidiasis)*† • Vaginal fluid for wet mount microscopy (saline for BV)*† • Herpes culture†*
Study Product Supply		• Provide study specified male condoms

*If clinically indicated
†Per local standards/guidelines

7.2 Enrollment Visit

Table 5: Enrollment Visit

Enrollment Visit	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Obtain written informed consent for enrollment and storage and future testing of specimens • Confirm eligibility • Provide available test results • Follow procedures for randomization assignment • Schedule next study visit, if applicable • Provide reimbursement for visit

Behavioral		• Administer baseline behavioral assessment
		• Administer baseline acceptability assessment
		• Provide counseling
		  o Contraceptive
		  o HIV/STI risk reduction/male condom
		  o Protocol adherence
		  o For Group A, product use/adherence
		  o HIV testing process*

Clinical		• Update obstetric history • Update medical/menstrual history • Update concomitant medications • Document pre-existing conditions • 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*
Laboratory	**Urine**	• Qualitative hCG • Dipstick UA* • Urine culture*
	Blood	• Plasma archive • Syphilis serology* • HIV-1 test*
	Pelvic Samples	• Gram stained smear of vaginal fluid, obtained from lateral vaginal wall • Vaginal swabs for vaginal flora assessment • Cervical swab 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 (KOH for vulvovaginal candidiasis)*† • Vaginal fluid for wet mount microscopy (saline for BV)*† • Herpes culture†* • Cervical swab for NAAT for GC/CT*
Study Product Supply		• Provide study specified male condoms • For Group A, provide participants with instructions on study IVR insertion, self-insert one study IVR followed by digital exam by clinician to check placement. Instruct 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.

*If clinically indicated
†Per local standards/guidelines

7.3 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. If a study visit does occur during the participant's menses, all visit procedures (except pelvic exam/colposcopy and associated pelvic lab specimens) should be performed at that time. 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.

Table 6: Follow-up Visits

Follow-up Visits: 4-Week, 8-Week, and 12-Week Visits		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide available test results • Schedule next study visit • Provide reimbursement for visit
Behavioral		• Administer follow-up behavioral assessment • Administer follow-up adherence assessment (Group A only) • Administer final acceptability assessment (for Group A participants at 12-Week Visit) • Provide counseling o Contraceptive o HIV/STI risk reduction/male condom o Protocol adherence o For Group A, product use/adherence (4-and 8-Week Visit Only) o HIV testing process*
Clinical		• Update medical/menstrual history • Review/update concomitant medications • Perform targeted physical exam (see Appendix III) • 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*
Laboratory	**Urine**	• Qualitative hCG* • Dipstick UA* • Urine culture*
	Blood	• Syphilis serology* • HIV-1 test*

	Pelvic Samples	• Gram stained smear of vaginal fluid, obtained from lateral vaginal wall • Vaginal 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 (KOH for vulvovaginal candidiasis)*† • Vaginal fluid for wet mount microscopy (saline for BV)*† • Herpes culture†* • Cervical swab for NAAT for GC/CT* • 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. o 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		• Provide study specified male condoms • Study clinician/designee to remove used study IVR 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* o 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)

*If clinically indicated
†Per local standards/guidelines

7.4 16-Week/Study Termination Visit

Table 7: 16-Week/Study Termination Visit

16-Week/Study Termination Visit	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Provide available test results • Provide reimbursement for visit • Schedule next study visit, if applicable
Behavioral	• Administer final behavioral assessment (in the event that a participant drops out of the study prior to the 16-Week Visit, the final behavioral assessment will not be administered) • Provide counseling o Contraceptive o HIV testing process o HIV/STI risk reduction/male condom • Administer final acceptability assessment (for Group A in the event that use of the study IVR is permanently discontinued at an earlier visit)*

Clinical		• Update medical/menstrual history • Review/update concomitant medications • Perform complete 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 (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*
Laboratory	**Urine**	• Qualitative hCG • Dipstick UA* • Urine culture*
	Blood	• HIV-1 test • Syphilis serology*
	Pelvic Samples	• Gram stained smear of vaginal fluid, obtained from lateral vaginal wall • Vaginal swabs for vaginal flora assessments • Cervical swab 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 (KOH for vulvovaginal candidiasis)*† • Vaginal fluid for wet mount microscopy (saline for BV)*† • Herpes culture†* • Cervical NAAT for GC/CT*
Study Product Supply		• Provide study specified male condoms • Collection of used IVR (for Group A)*

*If clinically indicated
†Per local standards/guidelines

7.5 Follow up Procedures for Participants who Discontinue Study Product

Participants who discontinue study product will be encouraged to remain in the study if they are willing, for safety evaluations according to the study follow up schedule with the exceptions described below.

7.5.1 Participants Who Seroconvert to HIV

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

- HIV-1 test
- Further provision of study IVR (for Group A)

7.5.2 Participants Who Become Pregnant

Participants in Group A who become pregnant during study participation will discontinue study IVR use. All protocol-specified procedures will continue except:

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

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

All protocol-specified study procedures will continue except counseling related to study IVR use and adherence.

7.6 Interim Contacts and Visits

Interim contacts and visits (those between regularly scheduled follow-up visits) may be performed at participant request or as deemed necessary by the investigator or designee at any time during the study. 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. Participants will be encouraged to seek care for any vulvovaginal or other related complaints with the study staff. Laboratory analyses may be conducted according to the clinical judgment of the site investigator or designee. All interim contacts and visits will be documented in participants' study records and on applicable case report forms.

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff or require additional study supplies. Other interim contacts and visits may occur in response to AEs or social harms experienced by study participants. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide, or refer the participant to, appropriate medical care.

7.7 Clinical Evaluations and Procedures

See Appendix III for an outline of physical exam and pelvic exam components.

7.8 Adherence, Acceptability and Behavioral Change

7.8.1 Adherence

For participants in Group A, adherence will be measured at the 4-, 8- and 12-Week Visits. Adherence will be measured via several participant self-report strategies. 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.

7.8.2 Acceptability and Behavioral Change

Acceptability will be measured via questions about ease of insertion and removal, feeling the study IVR during daily activities and sex, partner awareness of the study IVR 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 study 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 study IVR arm and no ring arm.

7.9 Laboratory Evaluations

7.9.1 Local Laboratory Testing

Blood

- HIV-1 test (see Appendix II)
- Syphilis serology

Urine

- Qualitative hCG
- UA
- Urine culture

Pelvic Specimens

- Pap smear
- Vaginal pH
- Vaginal fluid for wet mount microscopy (saline for BV; KOH for vulvovaginal candidiasis)
- *Trichomonas vaginalis* test
- Herpes culture (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

7.9.2 Network Laboratory Testing

Blood

- HIV-1 confirmatory testing as needed (see Appendix II)
- Plasma archive

Pelvic Specimens

- Vaginal flora assessment (quantitative vaginal fluid cultures-US sites only)
- 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)

7.10 Specimen Collection and Processing

Each study site will adhere to the standards of Good Clinical Laboratory Practice, the MTN Network Laboratory Manual (www.mtnstopshiv.org), DAIDS Laboratory Requirements(http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/laboratorypolicy1.pdf), MTN-005 SSP manual (www.mtnstopshiv.org), and site SOPs for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-collect specimens.

7.11 Specimen Handling

Specimens will be handled in accordance with Requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/laboratorypolicy1.pdf).

7.12 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC and NIH. All biological specimens will be transported using packaging mandated by CFR 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. This applies to both US and international sites. Biohazardous waste (including used IVRs returned to the study site) will be contained according to institutional, transportation/carrier, and all other applicable regulations.

7.13 Final Contact

The 16-Week/Study Termination Visit ± 7 days for all participants will include laboratory testing. If results are not available, a final contact may be required to provide the final study test results, post-test counseling, and treatment or prescription for treatment. For

participants who become pregnant prior to the study end date, an additional contact may be required to ascertain the participant's pregnancy outcome. The sites may also use a final contact visit to follow-up on unresolved AEs at the 16-Week/Study Termination Visit. Study sites may complete the final contact visit(s) at the study site or at community based locations, depending on site capacities and site and participant preferences. All final contacts must be documented in participant study records.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

The 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 MO, MTN CORE Protocol Safety Physician, SDMC Clinical Affairs Safety Associate, Population Council Safety Physicians, and Protocol Statistician, will serve as the PSRT. The SDMC will prepare routine 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. The content, format and frequency of safety data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation.

8.2 Clinical Data Safety Review

A multi-tiered safety review process will be followed throughout the duration of this study. The site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the PSRT if unexpected concerns arise. Participant safety is also monitored at the Network level through a series of routine reviews conducted by the SDMC Clinical Affairs staff, the PSRT and study sponsors. Additional reviews may be conducted at each of these levels as dictated by the occurrence of certain events.

The MTN SDMC Clinical Affairs staff will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. 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.

In addition to the routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary, experts external to the MTN representing expertise in the fields of microbicides, biostatistics, HIV transmission and medical ethics may be invited to join the PSRT safety review. A recommendation to stop the trial may be made by the PSRT

at this time or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

Decisions regarding permanent discontinuation of study product in individual participants will be made by the PSRT based on careful review of all relevant data. In the unlikely event that the protocol team has serious safety concerns that lead to a decision to permanently discontinue study product for all participants and stop accrual into the study, the protocol team will request a review of the data by the Study Monitoring Committee (SMC) before recommending that the study be stopped. Members of the SMC will be independent investigators with no financial interest in the outcomes of this study. If at any time, a decision is made to discontinue study product in all participants, the Population Council will notify the FDA and the site IoR will notify the responsible Institutional Review Boards/Ethics Committees (IRB/EC) expeditiously.

8.3 Adverse Events Definitions and Reporting Requirements

8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant enrolled in a clinical trial and which does not necessarily have a causal relationship with an investigational product or study participation. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product or study participation, whether or not considered related to the product or study participation. This definition will be applied beginning at the time of random assignment. The term "investigational product" for this study refers to the study IVR.

Study participants will be instructed to contact the study site staff to report any AEs they may experience. In the case of a life-threatening event, participants will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek medical care where the study clinician is based, and to request that the clinician be contacted upon their arrival. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to AEs will be obtained and required data elements will be recorded on study case report forms. All participants reporting an AE (including pelvic exam abnormalities, excluding colposcopic findings) will be followed clinically until the AE resolves (returns to baseline) or stabilizes.

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, except that asymptomatic BV will not be a reportable AE. AEs not included in 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/.

Participants also will be encouraged to report to the study clinician any problems experienced by their male sex partners that might be potentially related to study product. AEs of male partners will be documented in the participant chart, but will not be reported on study case report forms. If any such problems are reported, study staff should evaluate and document the occurrence and the IoR (or designee) should inform the PSRT, so that this information can be considered during routine PSRT safety data reviews. Should any concerns arise with regard to partner safety, the PSRT will advise all study sites on appropriate action.

8.3.2 Serious Adverse Events

SAEs will be defined by the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010), as AEs occurring at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be immediately life-threatening, or require hospitalization but may jeopardize the participant or require intervention to prevent one of the outcomes listed in the definition above.

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 (Version 2.0, dated January 2010) and clinical judgment. The relationship categories that will be used for this study are:

- *Related*: There is a reasonable possibility that the AE may be related to the study agent(s)

- *Not related*: There is not a reasonable possibility that the AE is related to the study agent(s)

8.4 Expedited Adverse Event Reporting

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).

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

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/.

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)

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 the Manual for Expedited Reporting of EAEs to DAIDS (Version 2.0, January 2010) guidelines for expedited reporting.

8.6 Local Regulatory Requirements

Site investigators will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. This reporting will include site IRB/EC-mandated reporting of AEs, SAEs, and other relevant safety information.

8.7 Social Harms Reporting

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities. 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 PSRT on CRFs. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. While maintaining participant confidentiality, study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm.

9 CLINICAL MANAGEMENT

9.1 Toxicity Management

Toxicity is not expected in this study of a non-medicated IVR. Silicone allergy, while reported in the literature, has been described as extremely rare.[65] Participants exhibiting signs or symptoms of product toxicity, as determined by the clinical opinion of the site investigator or designee, may have the study IVR discontinued according to guidelines in Section 9.4.

9.2 Other Clinical Events

Management of sexually transmitted infections commonly referred to as STIs and other forms of vaginitis and cervicitis will be in accordance with current CDC guidelines (http://www.cdc.gov/std/treatment/) and in accordance with other country-specific guidelines. When clinically appropriate, investigators should use oral or parenteral (in the case of syphilis, for example) medications when at all possible to avoid intravaginal medication use.

In the absence of clinical evidence of cervicitis (as described below) and/or pelvic inflammatory disease, participants with gonorrhea and/or chlamydia detected during follow-up may be treated with the study IVR in place.

If suspected finding is reported by participant between scheduled visits, an interim visit may be scheduled at the discretion of the site investigator. Management of genital events observed at scheduled or interim visits will be in accordance with the following:

Superficial epithelial disruption (abrasion/peeling) excluding findings observed by colposcopy only

- Continue study IVR use
- Perform naked eye evaluation with or without colposcopy
- Re-evaluate by speculum examination in 48-72 hours
- 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

- Remove study IVR for deep epithelial disruption confirmed by site investigator
- Swab for herpes simplex culture (per clinical judgment of site investigator)
- Suspected syphilis chancre should be managed in accordance with current CDC guidelines
- Re-evaluate in 48-72 hours and reinstate study IVR use if resolved

- 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, continue temporary product hold, consult with PSRT regarding permanent discontinuation, and provide care per local standard
- If there is reoccurrence with no identified etiology, 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

- Continue study IVR use
- Perform naked eye evaluation with or without colposcopy
- If asymptomatic, re-evaluate at next regularly scheduled visit
- If symptomatic, re-evaluate by speculum examination in 48-72 hours
- If worsened significantly, temporarily hold study IVR use 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

- Remove study IVR
- Perform naked eye evaluation with or without colposcopy
- Re-evaluate in 48-72 hours and reinstate study IVR use if resolved
- 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, 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

- 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
- Perform vaginitis evaluation, including assessment of signs, symptoms, vaginal pH and wet mount microscopy for Candida vaginitis, Trichomoniasis, and BV
- 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

- Continue study IVR use (at study clinician's discretion)
- Perform naked eye evaluation with or without colposcopy

- If determined to be due to deep epithelial disruption, refer to guidelines above, otherwise continue study IVR use

Cervicitis (including findings on exam such as inflammation and/or friability) excluding findings observed by colposcopy only

- Remove study IVR
- Evaluate for GC/CT
- If 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

Genital petechia(e) excluding findings observed by colposcopy only

- Continue study IVR use
- Perform naked eye evaluation with or without colposcopy
- No further evaluation or treatment is required

Genital ecchymosis excluding findings observed by colposcopy only

- Continue study IVR use
- Perform naked eye evaluation with or without colposcopy
- No further evaluation or treatment is required

9.3 Pregnancy

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. Study staff will provide contraceptive counseling to enrolled participants as needed throughout the duration of study participation and will facilitate access to contraceptive services through direct service delivery and/or active referrals to local service providers. Study staff also will provide participants with male condoms and will counsel participants to ideally use these condoms during every sex act throughout study participation.

Pregnancy testing will be performed at the Screening, Enrollment, and 16-Week/Study Termination study visits, and when clinically indicated during study follow-up. Participants will be encouraged to report all signs or symptoms of pregnancy to study staff during the course of the study. The site IoR or designee will counsel any participants who become pregnant regarding possible risks of study IVR use according to site-specific SOPs. The IoR or designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care. Participants who are pregnant at the 16-Week/Study Termination visit will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Study staff will be

responsible for follow-up with the participant until the pregnancy outcome is determined. Pregnancy outcomes will be reported on relevant case report forms.

Participants who become pregnant during the course of the study will permanently discontinue study product use but will not routinely be withdrawn from the study. Rather, if the participant does not withdraw her consent, every effort will be made to complete all study visits. All protocol-specified procedures will continue except:

- Provision of study IVR (for participants randomized to the IVR arm)
- Pelvic exam including colposcopy (unless clinically indicated)

9.4 Criteria for Temporary or Permanent Discontinuation of Study Product

Participants may voluntarily discontinue product use for any reason at any time. Site IoRs will temporarily or permanently discontinue participants from product use per the specifications below, which may be further clarified in the SSP. Site IoRs also may, with the approval of the PSRT, temporarily or permanently discontinue participants from study IVR use for reasons not shown here or in the SSP, e.g., to protect their safety.

The criteria for temporary discontinuation of study IVR use for an individual participant are outlined in Section 9.2.

The criteria for permanent discontinuation of further study IVR use for an individual participant are outlined in Section 9.2, but also include:

- Pregnancy
- HIV-1 seroconversion
- Completion of regimen as defined in the protocol
- Request by participant to terminate treatment
- Clinical reasons as determined by the study clinician

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 the participant will not be using the study IVR).

9.5 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. Site IoRs may, with the approval of the PSRT, withdraw participants before their scheduled termination visit to protect their safety. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the Office for Human Research Protections (OHRP)), or site IRBs/ECs terminate the study prior to its planned end date. Site investigators are required to consult the Protocol Chair and Protocol Biostatistician prior to the site-initiated withdrawal of any study participant. Study staff will record the reason(s) for all withdrawals in participants' study records. In the event

that participants who voluntarily withdraw from the study wish to re-join the study, they may resume study procedures and follow-up, provided the participant is still within her original 16-week follow-up period.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and General Design

This is a multi-site, open-label, two-arm, 2:1 randomized, controlled trial comparing 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. A total of 252 women (168 and 84 in the IVR and no IVR arms, respectively) will be randomized, 150 in Pune, India (100 and 50 in the IVR and no IVR arms, respectively) and 102 (68 and 34 in the IVR and no IVR arms, respectively) for the two combined US sites (with competitive enrollment for the two US sites).

10.2 Study Primary and Secondary Endpoints

10.2.1 Study Primary Endpoints

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

Safety

- 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)

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

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 to measure vaginal flora characteristics, and changes of these over the course of study IVR use, the following endpoints will be assessed:

- Per participant report, changes in sexual behavior and vaginal hygiene practices

- For women randomized to the study IVR arm, participant report of 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 and quantitative culture (Note that these quantitative vaginal cultures will only be available from the US sites, therefore reducing the available sample size for this objective)

10.2.3 Exploratory Endpoint

- Changes in vaginal biomarkers (US sites only)

- Presence of biofilms on study IVR surface (US sites only)

10.3 Study Hypotheses

MTN-005 hypothesizes that the study IVR will be safe and will be used as directed by US and non-US women over 12 weeks of use.

10.4 Sample Size

10.4.1 Safety Endpoints

The proposed total sample size is N=252 randomized into 2 arms: 168 and 84 women in the study IVR and no IVR arms, respectively. Given that assessing adherence to the study IVR is a primary objective, and that this can only be assessed in the study IVR arm, a 2:1 randomization was selected to increase the precision on estimates of adherence and acceptability. A 2:1 randomization will slightly decrease the power for the comparison of safety profiles between the study IVR and no IVR arms, but the decrease in power is not substantial. Participants who are non-adherent to the study product and/or the study visit schedule will not be replaced.

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).

For the no IVR arm, if the true rate of a given safety and toxicity endpoint is 5%, 84 women provide 80% power to exclude safety and toxicity endpoint rates greater than 13.3%.

The safety and toxicity rates of women using the study IVR and the rates for those not using the study IVR will be formally compared. A sample size of 252 women with a 2:1 randomization (i.e. 2 IVR : 1 no IVR) will assure with 80% power that a 95% confidence interval for the difference between the study IVR and no IVR safety and toxicity rates has an upper limit no more than 6.9% when the true toxicity rates for study IVR and no IVR are both 5%. The above calculations have been performed assuming true rates of toxicity of 5%. However, it is anticipated that the true rates are smaller than 5%. If this is the case, the above power computations are conservative and the actual power will be slightly higher. Table 8 displays 95% confidence interval upper bounds for different assumptions on the safety and toxicity rates in the IVR and no IVR arms. 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 the Primary Safety Analysis.

Table 8: Confidence Interval for Upper Bound for the Difference Between IVR and no IVR Safety and Toxicity Rates

		Assumed rate in IVR arm					
Assumed rate in no IVR arm		**1%**	**5%**	**7.5%**	**10.0%**	**12.5%**	**15.0%**
1%		3.6%	9.8%	13.0%	-	-	-
5%		-	6.9%	10.1%	13.1%	-	-
7.5%		-	-	8.1%	11.3%	14.2%	-
10.0%		-	-	-	9.4%	12.3%	15.2%
12.5%		-	-	-	-	10.4%	13.2%
15.0%		-	-	-	-	-	11.2%

10.4.2 Adherence Endpoints

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.

10.4.3 Acceptability Endpoints

Several components of acceptability (e.g., report of discomfort, removal and insertion difficulties, episode of expulsions, bowel, urinary and sexual difficulties (see Section

7.8)) will be used to assess overall acceptability. Each component will be assessed by a dichotomous measure where women will be categorized into (1) those reporting no acceptability issues during the 12 weeks of study IVR use (e.g., those reporting no discomfort) and (2) those reporting at least one issue during the 12 weeks of study IVR use (e.g., those reporting some discomfort). Acceptability can only be assessed among the 168 women randomized to the study IVR arm. An acceptability endpoint is defined as a negative report by a participant, on any of the above components of acceptability. 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 acceptability of 80%. Substantial heterogeneities in acceptability between the Indian and the US sites might be observed in which case acceptability 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 acceptability of 80% while this precision would be 10.2% with a sample size of 68 US women using the study IVR. Due to the smaller sample size within each site, no formal comparison will be performed for comparing adherence and acceptability between sites.

10.4.4 Changes in Vaginal Flora and Biomarkers

Changes in Nugent scores will be assessed by comparing the Nugent score at enrollment with the one observed at 12 weeks. An abnormal Nugent score is defined as a Nugent score higher than 3 while a normal Nugent score is defined as a score of 3 or less. The proportion of changes between enrollment and week 12 from normal to abnormal will be compared as well as the one from abnormal to normal.

Changes in Nugent score over time are naturally occurring. Based on a sample of 1016 women,[66] 28.4% of women with a normal Nugent score at enrollment had an abnormal Nugent score 4 months later while 32.8% of women with an abnormal Nugent score at enrollment had a normal Nugent score 4 months later. Therefore, for the purpose of power calculations, we are estimating the proportion of changes in Nugent scores from enrollment to week 12 at 30% in the no IVR arm and this for both from normal to abnormal and from abnormal to normal. Furthermore, we are estimating that 55% and 45% of women will be normal and abnormal, respectively, at enrollment.

The proportion of women with a change in Nugent score from normal to abnormal, at enrollment and 12 weeks, respectively, will be compared between the study IVR and no IVR arms. Assuming that the true proportion of changes in the no IVR arm is 30%, a sample size of 252 women (138 normal women at enrollment and available for the analysis) with a 2:1 randomization will allow detection of an absolute difference of 25% with 80% power (i.e. 30% of women in the no IVR arm and 55% of women in the study IVR arm).

Similarly, the proportion of women with a change in Nugent score from abnormal to normal, at enrollment and 12 weeks, respectively, will be compared between the study IVR and no IVR arms. Assuming that the true proportion of changes in the no IVR arm is 30%, a sample size of 252 women (114 abnormal women at enrollment and available

for the analysis) with a 2:1 randomization will allow detection of an absolute difference of 28% with 80% power (i.e. 30% of women in the no IVR arm and 58% of women in the study IVR arm).

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) 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.

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.

10.5 Randomization Procedures

Women will be randomized using a 2:1 ratio to one of the two arms, i.e. two women will be randomized to the study IVR arm for each woman randomized to the no IVR arm. Randomization will be stratified by site to ensure a 2:1 balance within each site. The randomization scheme will be generated and maintained by the SDMC. The SDMC will provide each study site with one set of randomization envelopes to be stored and used in the study clinic. Clinic staff will assign these envelopes in sequential order, by envelope number, to eligible participants. Additional envelopes will be provided to each site for the purpose of enrolling a greater number of participants per site if enrollment "slots" need to be shifted from one site to another during the course of the study.

Assignment of the randomization envelope is considered the effective act of participant enrollment/randomization. The randomization document contained within the envelope indicates the study arm (study IVR or no IVR) to which the participant is assigned. For participants assigned to the study IVR arm, this randomization document is the study prescription. Clinic staff will store assigned randomization envelopes and copies of the randomization document in the participants' study charts.

10.6 Justification for the No IVR arm

Inclusion of a no IVR arm in this safety 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.

10.7 Participant Accrual and Retention

Based on previous studies of vaginal products with similar eligibility requirements conducted at these 3 sites (i.e. HPTN 059), the accrual of 252 eligible participants with normal reproductive tracts is expected to require the screening of approximately 380 volunteers. The target for retention will be 95% of enrolled participants over the 16 weeks follow-up period. Therefore, it is anticipated that approximately 252 women will be enrolled in the study. Accrual is anticipated to take approximately 6 months and 10 months at the US and non-US sites, respectively.

10.8 Data Monitoring and Analysis

10.8.1 Study Monitoring Committee (SMC)

In addition to the safety monitoring done by the PSRT (described in Section 8.2), the MTN SDMC will prepare study progress reports and reports of AEs experienced by study participants (blinded to treatment assignment when feasible) for review by the MTN SMC. The SMC will conduct interim reviews of study progress (blinded to treatment assignment when feasible), including rates of participant accrual, retention, rates of adherence to study IVR use, and product safety. These reviews will take place approximately every 90 days, or as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

10.8.2 Primary Analysis

When the use of descriptive statistics to assess group characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). Within-arm assessment of the change from the baseline measurement to a follow-up measurement will be analyzed using McNemar's test (for categorical response variables) or the paired t-test or Wilcoxon signed-ranks test (for continuous variables). When use of formal testing to assess differences between the study IVR arm and the no IVR arm is required, the following methods will be used: for binomial response variables, chi-square tests and logistic regression; for continuous variables, t-tests and linear regression nonparametric methods if data are non-Normal. To assess the adequacy of the randomization, study IVR and no IVR participants will be compared for baseline characteristics including

demographics, pelvic examination, and laboratory measurements using descriptive statistics. Due to the small sample size, formal baseline comparisons will not be done.

Primary Safety Analysis

The primary aim of the study is to assess the safety and toxicity of the study IVR. First, an intent-to-treat (ITT) analysis will be performed where data from all visits are included. To assess safety, the number and the percentages of participants experiencing the safety or toxicity endpoint described in Section 10.2.1, will be presented by arm. For each arm, binomial rates will be presented along with their corresponding exact 95% confidence interval estimates. For assessing the difference between the arms, a non-inferiority bound will be computed using an exact one-sided 95% confidence interval for the difference in rates between the two arms (see Section II in Therapeutic Equivalence in Encyclopedia of Biopharmaceutical Statistics).[67] Second, a per-protocol analysis will also be performed since non-adherent women in the IVR arm that are included in the ITT analysis might potentially lower the rate of safety endpoints in the IVR arm. Therefore a per-protocol analysis, where visits of non-adherent women will be excluded from the analysis, will be used to explore the sensitivity of the conclusions obtained via the primary safety analyses based on the ITT dataset. For this analysis, all visits of adherent women (defined as using the product 50% of the time or more) will be included where comparison of safety rates between arms will be performed using generalized estimating equation methods to take into account that the 4-week visits are not independent within a participant.

The above primary safety analysis will be supplemented by the following additional analyses. Adverse events will be analyzed using MedDRA preferred terms. The number and percentage of participants experiencing each specific adverse event will be tabulated by severity and by relationship to study product (for the study IVR arm only). For the calculations in these tables, each participant's adverse experience will be counted once under the maximum severity or the strongest recorded causal relationship to study product. Finally, a listing of AEs reported to the DAIDS Medical Officer and the Population Council will provide details of the event including severity, relationship to study product, onset, duration and outcome.

Boxplots of local laboratory values will be generated for baseline values and for values measured during the course of the study. Each boxplot will show the 1st quartile, the median, and the 3rd quartile. Outliers, or values outside the boxplot, will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

Primary Adherence Analysis

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.

10.8.3 Secondary and Exploratory Analyses

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.

Vaginal Flora

In order to assess the effect of the study IVR on the vaginal flora of sexually active, HIV-uninfected women, clinically significant changes in vaginal flora will be evaluated by the Nugent score with shift tables from baseline (Enrollment) to follow-up visits at week 4, 8, 12, and 16 to assess the effect on vaginal flora.

The Nugent score is graded 1 to 10 as follows:

1. Normal, 0 to 3
2. Intermediate, 4 to 6
3. BV, 7 to 10

Any shift from normal at baseline to intermediate or BV at a follow-up visit, or intermediate or BV at baseline to normal at a follow-up visit, will be considered a clinically meaningful change in vaginal flora. The proportion of changes within each arm will be reported and will be formally compared using the Fisher exact test (from the

derivation of the two-sample case of the McNemar's test of change). Please refer to Levin and Serlin[68] for more details. In addition, this analysis will be supplemented by an analysis using the change from baseline in Nugent score for each woman. Comparison for differences in change from baseline between arms will be assessed by using an unpaired t-test or a Mann-Whitney test (if distribution of change scores does not allow the use of the unpaired t-test).

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) and to assess differences in the quantitative levels of these flora between arms during follow-up. Note that this analysis can only be performed using women from the US sites since quantitative cultures will not be conducted for women at the India site.

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.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

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

11.2 Source Documents and Access to Source Data/Documents

Source documents and access to source data/documents will be maintained in accordance with current DAIDS policies.(http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Default.aspx)

The investigator will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with US regulations, the investigator will retain all study records on site for at least two years after study closure. Study records will not be destroyed prior to receiving approval for record destruction from DAIDS. Applicable records include source documents, site registration documents and reports, correspondence, informed consent forms, and notations of all contacts with the participant.

11.3 Quality Control and Quality Assurance

Quality control and quality assurance procedures for MTN-005 will be performed in accordance with current DAIDS policies. (http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/qmppolicy.pdf)

11.4 Study Coordination

Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trial Agreement (CTA) executed by NIAID and 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.

12 CLINICAL SITE MONITORING

Study monitoring will be carried out by PPD (Wilmington, NC). On-site study monitoring will be performed in accordance with Requirements for On-Site Monitoring of DAIDS Funded and/or Sponsored Clinical Trials. Site monitoring visits will be conducted to assess compliance with Health and Human Services (HHS) Regulations 45 Code of Federal Regulations (CFR) Part 46 and 21 CFR Parts 50, 56, and 312. Study monitors will visit the site to:

- Verify compliance with human subjects and other research regulations and guidelines, including confidentiality procedures, informed consent process, and regulatory documentation
- Assess adherence to the study protocol, study-specific procedures manual, and local counseling practices
- Confirm the quality and accuracy of information collected at the study site and entered into the study database, including the validation of data reported on case report and DataFax forms
- Assess the resolution of any past or ongoing issues identified at previous monitoring visits

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, 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, 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.

13 HUMAN SUBJECTS PROTECTIONS

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, the Population Council, and/or the US FDA.

13.1 Institutional Review Boards

Each participating institution is responsible for assuring that this protocol and the associated informed consent documents and study-related documents are reviewed by an IRB/EC prior to implementation of the protocol. Any amendments to the protocol, informed consents, or other study- related documents must be approved by the IRB/EC and DAIDS prior to implementation.

13.2 Protocol Registration

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 Amendment Registration Notification 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.

13.3 Risk Benefit Statement

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).

13.3.2 Benefits

Participation in this study likely will have no direct benefit to volunteers other than access to screening for RTIs/STIs and appropriate referral if RTIs/STIs are diagnosed. Participants will also have access to screening for HIV and appropriate referral if HIV is diagnosed. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis of syphilis. Pregnancy testing may offer the opportunity for early detection of pregnancy with expedient referral for pregnancy management. Pap smear may offer the opportunity for early detection of a cervical and/or vaginal abnormality with expedient referral if an abnormality is detected. Lastly, the participant may appreciate the opportunity to contribute to the body of knowledge in the field of microbicide research.

13.4 Informed Consent Process

Written informed consent will be obtained from all potential study participants prior to the initiation of any study-related procedures. Study staff will administer a comprehension checklist to potential participants prior to obtaining written informed consent to ensure that participants fully comprehend the nature of the study. In obtaining and documenting informed consent, the investigators and their designees will comply with applicable country-specific regulatory requirements and will adhere to Good Clinical Practices (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Protocol Documents for DAIDS Funded and/or Sponsored Clinical Trials (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/pages/protocols.aspx). Participants are provided with

copies of the informed consent forms if they are willing to receive them. Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendices 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. 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.

Prior to the beginning of the trial, site investigators will have IRB/EC written approval of the protocol, informed consent forms, and any other study-related information to be provided to participants.

The informed consent process will give individuals all of the relevant information they need to decide whether to participate, or to continue participation, in this study. Potential research participants will be permitted to ask questions and to exchange information freely with the study investigators. Listed study investigators or their designees will obtain informed consent from potential study participants. The investigators will keep research participants fully informed of any new information that could affect their willingness to continue study participation.

Community input has been sought for the development of the sample informed consent forms. The informed consent process covers all elements of informed consent required by research regulations. In addition, the process specifically addresses the following topics of importance to this study:

- The importance of adherence to the study visit and procedures schedule
- The potential risks of study participation (and what do if such risks are experienced)
- The potential social harms associated with study participation (and what do if such harms are experienced)
- The real yet limited benefits of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time

13.5 Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Each study site will establish a standard operating procedure for confidentiality protection that reflects the local study implementation plan (e.g., whether community-based visits will be conducted) and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study

staff. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified by a coded number only to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link Participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Participants' study information will not be released without their written permission, except as necessary for monitoring (see Section 12).

The MTN has obtained a Certificate of Confidentiality from the US Department of Health and Human Services that will be applicable for this study. This Certificate protects study staff from being compelled to disclose study-related information by any US Federal, State or local civil, criminal, administrative, legislative or other proceedings. It thus serves to protect the identity and privacy of study participants. Since the Certificate cannot be enforced outside of the US, however, it will apply only to US site staff and participants.

13.6 Special Populations

This section outlines considerations made for the inclusion or exclusion of special populations in this study.

13.6.1 Pregnant Women

Participants who test positive for pregnancy at screening or enrollment visits will not be eligible to participate in this study. During the informed consent process, women will be informed that the silicone elastomer IVR is not a method of contraception.

All potential participants will be required by the Eligibility Criteria for Screening and Enrollment to be currently using a reliable method of contraception, such as hormonal contraception (except IVR), intrauterine device, male condoms, or sterilization. Women who become pregnant during the study period following randomization and exposure to study product will discontinue product use but not be excluded from analysis.

13.6.2 Children

The NIH has mandated that children be included in research trials when appropriate. This study meets "Justifications for Exclusion" criteria for younger children as set forth by the NIH. Specifically, "insufficient data are available in adults to judge potential risk in children" and "children should not be the initial group to be involved in research studies." This study does not plan to enroll children under 18 years old.

13.7 Compensation

Pending IRB/EC approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits, childcare, and time away from work. Participants are reimbursed at each visit.

13.8 Communicable Disease Reporting

Study staff will comply with all applicable local requirements to report communicable diseases, including HIV, identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

13.9 Access to HIV-related Care

13.9.1 HIV Counseling and Testing

HIV pre-test and post-test counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study. Participants must receive their HIV test results to take part in this study. Participants who have positive or indeterminate results will have standard post-test counseling as well as limited follow-up confirmatory testing provided by the study. Referral for additional counseling related to testing or diagnosis will occur if necessary.

13.9.2 Care for Participants Identified as HIV-Infected

Study staff will provide participants with their HIV test results in the context of post-test counseling. According to site SOPs, study staff will refer participants found to be HIV-infected to available sources of medical and psychological care, social support, and local research studies for HIV-infected women. Participants at sites which have completed protocol registration for the MTN-015 seroconverter protocol may be offered participation in that study.

13.10 Study Discontinuation

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

14 PUBLICATION POLICY

DAIDS and MTN policies and a CTA between 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 the Population Council for review prior to submission.

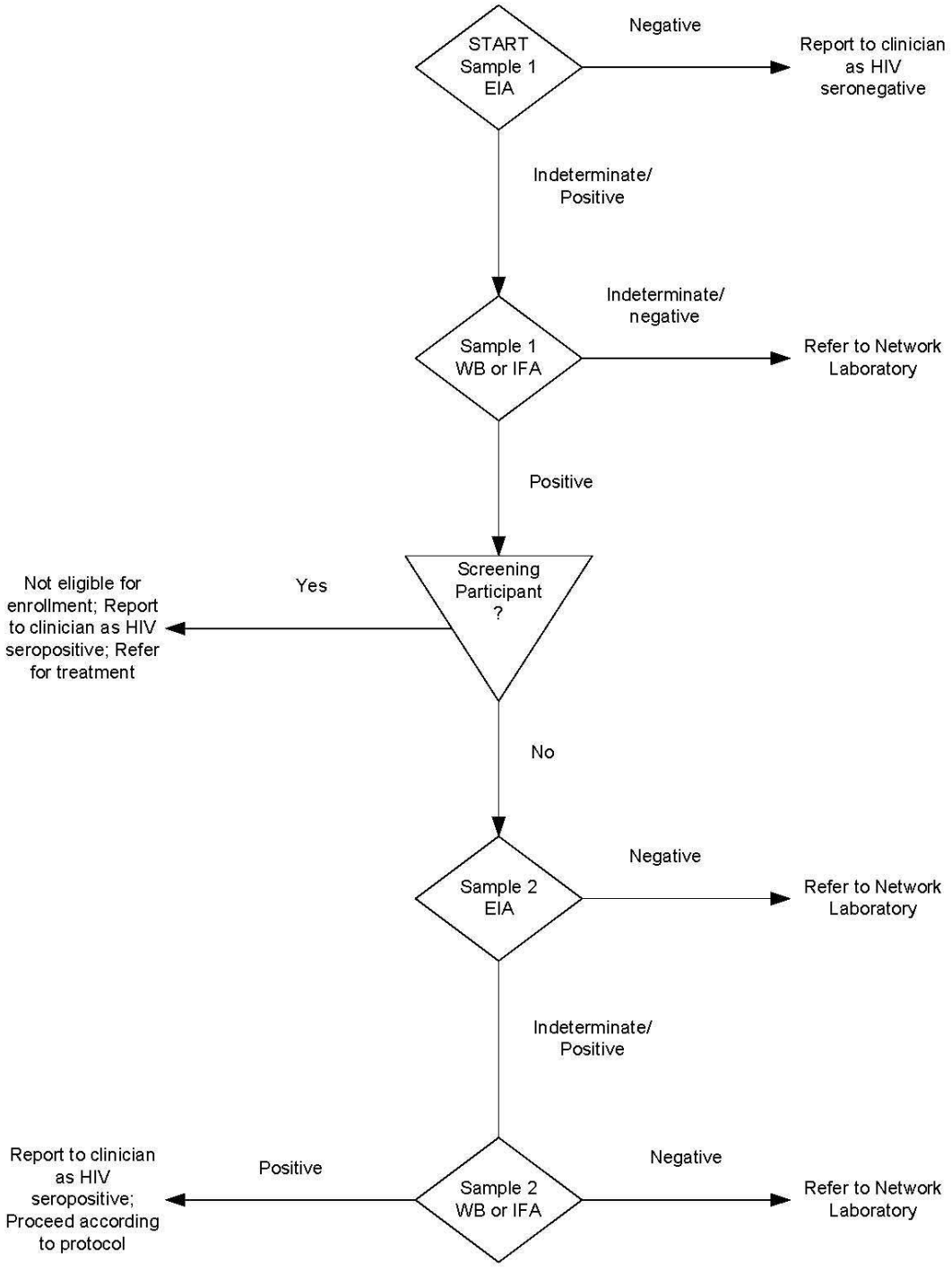
15 APPENDICES

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				
Informed Consent	x	x					
PTID	x						
Compr. Checklist		x					
Demographics	x						
Locator Information	x	x	x	x	x	x	x
Eligibility Assess/Confirm	x	x					
Reimbursement	x	x	x	x	x	x	
Provide Available Results	x	x	x	x	x	x	▲
Randomization		x					
Schedule Next Visit	+	+	x	x	x	+	+
Med./Mens. History	x	x	x	x	x	x	x
Obstetric History	x	x					
Pre-existing Cond.		x					
Behav. Assessment.		x	x	x	x	x	
Adher. Assessment			●	●	●		
Accept. Assessment		x			●	+	
Concomitant Meds	x	x	x	x	x	x	x
Compl. Phys. Exam	x					x	▲
Targ. Phys. Exam		x	x	x	x		▲
Contraceptive Coun.	x	x	x	x	x	x	▲
HIV Test Related	x	▲	▲	▲	▲	x	▲
HIV/STI/Male Condom Counseling	x	x	x	x	x	x	▲
Protocol Adher.Coun		x	x	x	x		▲
Product Use/Adher. Counseling		●	●	●			▲
Treat/Prescribe for UTI/RTI/STI	▲	▲	▲	▲	▲	▲	▲
Qualitative hCG	x	x	▲	▲	▲	x	▲
Dipstick UA	x	▲	▲	▲	▲	▲	▲
Urine Culture	▲	▲	▲	▲	▲	▲	▲
Plasma Archive		x					
Syphilis Serology	x	▲	▲	▲	▲	▲	▲
HIV-1 Test	x	▲	▲	▲	▲	x	▲
Pelvic Exam	x	x	x	x	x	x	▲
Vaginal pH	†▲	†▲	†▲	†▲	†▲	†▲	†▲
Cerv. NAAT for GC/CT	x	▲	▲	▲	▲	▲	▲
Test for Trichomonas	x	†▲	†▲	†▲	†▲	†▲	†▲
Wet Mount for Vulvovag. Candidiasis	†▲	†▲	†▲	†▲	†▲	†▲	†▲
Wet Mount for BV	†▲	†▲	†▲	†▲	†▲	†▲	†▲
Innate Factors (US sites only)		x				x	
Gram Stain	x	x	x	x	x	x	
Pap Smear	▲						▲
Colposcopy		x	▲	▲	x	x	▲
Naked Eye Exam	x	x	x	x	x	x	
Vaginal Flora Assessments		x	x	x	x	x	▲
Biofilm Assessment (at US sites only)			■	■	∞		■
Herpes Culture	†▲	†▲	†▲	†▲	†▲	†▲	†▲
Study IVR		●	+	+			+
Bottle of Water			+	+			
Male Condoms	x	x	x	x	x	x	▲
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

APPENDIX II: HIV ANTIBODY TESTING ALGORITHM



Note:

US Sites: 1 rapid EIA

India Site: 1 non-rapid EIA

APPENDIX III: COMPONENTS OF EXAMINATIONS

Complete Physical Exam

- Height (may be omitted after the Enrollment Visit)
- Weight (may be omitted after the Enrollment Visit)
- Vital signs
    - Temperature
    - Pulse
    - Blood pressure
- General appearance
- Abdomen
- Other components as indicated by participant symptoms

Targeted Physical Exam

- Components as indicated by participant symptoms

Pelvic Exam

- Vulva
- Perianal area
- Speculum exam
    - Vagina (including vaginal discharge)
    - Cervix (including cervical discharge)
- Bimanual exam, if clinically indicated
    - Cervix
    - Uterus
    - Adnexae

APPENDIX IV: SAMPLE INFORMED CONSENT FORM (SCREENING)

MTN-005

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

Version 2.0
October 19, 2010

PRINCIPAL INVESTIGATOR: **[insert]**
PHONE: **[insert]**
Short Title for the Study: **Safety and Adherence of a Non-medicated Intravaginal Ring (IVR)**

Introduction

You are being asked to take part in this screening process because you are a woman between the ages of 18 and 45 years and you may be able to join the research study named above. This Microbicide Trials Network (MTN) study is funded by the US National Institutes of Health (NIH). The Population Council is supplying the study product for MTN-005. The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. The screening process includes interview questions, urine and blood tests, a physical exam, including a pelvic (female genital) exam.

This is a screening consent form. It gives you information about the screening process. The study staff will explain this to you and what is expected of you. You are free to ask questions at any time. If you agree to take part in screening, you will be asked to sign this consent form or make your mark in front of a witness. You will be given a copy of this form to keep.

Why Are These Screening Exams and Tests Being Done?

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. 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, NuvaRing® is a vaginal ring that women use to avoid becoming pregnant. Women in the United States have been using NuvaRing® ever since it was approved by the United States Food and Drug Administration in 2002. NuvaRing® has also been approved for use in many other countries, including India. Progering® is another type of vaginal ring used 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.

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.

The United States National Institutes of Health is providing funds for this study to take place. A total of 252 women from India and 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 decide to join the study, you will have a study visit every 4 weeks.

Some women may not be able to join the study because of information found during the screening exams and tests.

What Do I Have To Do If I Take Part in Screening?

If you agree to have the screening exams and tests, you will have one or two screening visits here at the study site. Depending on what your screening exams and tests show more screening visits may be needed. Your first visit will continue today, after you read, discuss, and sign or make your mark on this form. No study exams or tests will be started before the screening exams and tests have been fully explained to you, you have let us know that you understand the screening process, and you have signed or made your mark on this form.

This visit will take about one to two hours. You will be asked to do these things if you decide you want to be in the study:

- Sign this form or make your mark after you have read it, understand it, and had the chance to ask questions about the study
- Answer some questions to see if you can join this study. 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 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 doctor or nurse thinks you have signs of herpes, like a blister or ulcer on the genitals)

- The vaginal ring used in this study will not 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, spermicidal male condoms, or silicone-based lubricants. If you are using male condoms, you must only use 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. The only known way to protect against HIV during sex is to use a condom every time you have 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
- 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 cervical fluid for these tests. 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.
- 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
- If you do not have results with you today of a Pap smear (a test to check for cervical cancer) that was done in the past 12 months the study doctor will also collect samples from your cervix to check for anything that is not normal. If the test is not normal, you may be asked to see your regular clinic for more tests. It takes about [SITES TO INSERT AMOUNT OF TIME] before Pap test results are ready.

We will give you the results as soon as they are ready. The results of your Pap test may affect whether you can use the vaginal ring being tested in this study
- Schedule your next visit, if you are found to be eligible for the study

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE]

[LOCAL/STATE/NATIONAL] regulations require study staff to report the names of people who test positive for HIV and other infections passed through sex to the [LOCAL HEALTH AUTHORITY]. Outreach workers from the [HEALTH AUTHORITY] may then contact you about informing your partners since they should also be tested. If you do not want to inform your partners yourself, the outreach workers will contact them according to the confidentiality guidelines of the [HEALTH AUTHORITY].

If your exams and tests show no problems, you will be able to enter the research study. You will receive a different informed consent form if you return for the Enrollment Visit.

Why Would the Doctor Stop the Screening Procedures Early?
The study doctor may need to stop the screening exams and tests early without your permission if:

- The study is cancelled by the US National Institutes of Health (NIH), the MTN, the Population Council, the US Office for Human Research Protections (OHRP), 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)
- Your exams, tests and answers to the questions show you cannot join the study
- The study staff feels that having the screening exams and tests would be harmful to you
- You do not want to find out your HIV test result
- You are not able to come to the visits or complete the screening exams and tests
- Other reasons that may prevent you from completing the study

What Are the Risks of the Screening Visit Tests?

Risk of Blood Draws:
You may have more than expected bleeding, feel discomfort or pain when your blood is drawn. You may feel dizzy, faint or lightheaded. You may have a bruise, swelling, or infection where the needle goes into your arm.

Risk of Genital Exams:
You may feel discomfort or pressure during the pelvic exam. You may have mild vaginal bleeding (spotting). The mild bleeding will stop shortly after the exam.

Other Possible Risks:
You may become embarrassed, worried, or nervous when discussing sex; ways to protect against HIV and other infections passed during sex and your test results. You

may become worried or nervous while waiting for your test results. If you have HIV or other infections, knowing this could make you worried, nervous, or sad. You may be referred to a trained counselor who can help you deal with any feelings or questions you have.

We will make every effort to protect your privacy while you are having the screening exams and tests. Your visits here will take place in private. However, it is possible that others may learn that you are taking part in the study here. Because of this, they may treat you unfairly.

Are There Benefits to Taking Part in This Study?

You may get no direct benefit from the screening exams and tests. However, you will have a physical exam and a pelvic exam, and counseling and testing for HIV and infections passed through sex. This study cannot provide you with medical care, but study staff will refer you to other available sources of care. If your Pap test result is not normal, you will be referred for treatment at the [INSERT NAME OF PROVIDER/CENTER].

You will get counseling and testing for HIV. You will get free male condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to get medical care for your HIV infection from your regular clinic or we will provide you with a referral to a center where you can receive appropriate care. You will get counseling and testing for infections passed through sex and other infections. If you are diagnosed with a sexually transmitted infection, you will get medicine or a prescription to treat it, if needed. You can bring your male partner(s) here so that we can also provide them with referral for diagnosis and treatment for potential infections passed through sex.

What Other Choices Do I Have Besides This Study?

You do not have to participate in this study, if you choose not to do so.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE: There may be other studies going on here or in the community for which you may be eligible. If you wish, we will inform you about other studies that are being conducted locally. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.] Please talk to your healthcare provider about these and other choices that may be available to you.

What About Confidentiality?

Efforts will be made to keep your personal information private. We cannot guarantee absolute confidentiality. If this study is published, your name will not be used and you will not be personally identified. To make sure that the study is being done the right way, we may ask you if you will allow a staff member working for the study sponsor to observe your study exams or questions. You can say no to this and still be in the study. You are encouraged but not required to tell sexual partners about your being in this study.

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US Food and Drug Administration (FDA), the US OHRP, NIH and/or contractors of the NIH
- [INSERT NAME OF SITE] IRB/EC
- Study staff
- Population Council, the organization supplying the ring for this study

[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. 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 screening exams and tests.

Will I Receive Any Payment?

You will be compensated for your time and effort for each screening visit. You will receive [INSERT SITE - SPECIFIC AMOUNT OF MONEY] for each visit. You will also be paid for other costs to you for coming to the screening visits [SUCH AS CHILD CARE, TRAVEL, AND LOSS OF WORK TIME – SITES TO COMPLETE]. There may be one or more screening visits.

What Happens If I Am Injured?

It is unlikely that you will be injured as a result of having the screening exams and tests. If you are injured as a result of having the screening exams and tests, you will be given immediate treatment for your injuries. However, you may have to pay for this care. The cost for this treatment will be charged to you or your insurance company if you have one. There is no program for compensation either through this institution or the US National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form. [SITES TO SPECIFY INSTITUTIONAL POLICY]

What Are My Rights As a Research Participant?

Taking part in the screening exams and tests is completely up to you. You may choose to not have the screening exams and tests any time. You will be treated the same no matter what you choose. If you choose to not have the screening exams and tests, you will not lose the benefit of services to which you would normally have at this clinic.

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know that you would like them.

What Do I Do If I Have Problems or Questions?

For questions about the screening exams and tests or if you have a research-related injury, you should contact:

- [SITE INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

For questions about your rights as a research participant, contact:

- [SITE INSERT NAME OR TITLE OF PERSON ON THE INSTITUTIONAL REVIEW BOARD (IRB) OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

SIGNATURE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

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 the screening procedures, please sign your name or make your mark below.

_____	_____
Participant's Name or Mark (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness's Signature and Date

APPENDIX V: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT)

MTN-005

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

Version 2.0
October 19, 2010

PRINCIPAL INVESTIGATOR: **[insert]**
PHONE: **[insert]**
Short Title for the Study: **Safety and Adherence of a Non-medicated Intravaginal Ring (IVR)**

Introduction

You are being asked to take part in this study because you are a woman between the ages of 18 and 45 years and you have passed the screening questions and tests for the research study named above. This Microbicide Trials Network (MTN) study is funded by the US National Institutes of Health (NIH). The Population Council is supplying the study product for MTN-005. The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. The enrollment process includes interview questions, urine and blood tests, a physical exam, including a pelvic (female genital) exam.

This is an enrollment consent form. It gives you information about the study product, study questions and exams, and what you have to do to be in the study. The study staff will explain the exams and tests to you and what is expected of you. You are free to ask questions about the study at any time. If you agree to take part in this study, you will be asked to sign this consent form or make your mark in front of a witness. You will be given a copy of this form to keep.

Why is This Study Being Done?

This study is being done to see if a kind of vaginal ring is safe. 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, NuvaRing® is a vaginal ring that women use to avoid becoming pregnant. Women in the United States have been using NuvaRing® ever since it was approved by the United States Food and Drug Administration in 2002. NuvaRing® has also been approved for use in many other countries, including India. Progering® is a vaginal ring that is used 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. 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.

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.

The United States National Institutes of Health is providing funds for this study to take place. A total of 252 women from India and 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 are in the study, you will have a study visit every 4 weeks.

What Do I Have To Do If I Take Part in the Study?

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: 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.

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

- Enrollment Visit
- 4-Week Visit
- 8-Week Visit
- 12-Week Visit
- 16-Week/Study Termination Visit

Enrollment Visit

Your Enrollment Visit will continue today, after you read, discuss, and sign or make your mark on this form. No study activities will be started before they have been fully explained to you, you have let us know that you understand the enrollment process and you have signed or made your mark on this form.

The Enrollment visit will take about one to two hours. You will be asked to do these things for the Enrollment Visit if you decide you want to be in the study:

- Sign this form or make your mark on it after you have read it, understand it, and had the chance to ask questions about the study

- 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
- Tell the study staff how they can stay in contact with you
- 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, 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 have had in the past as well as changes in your health or menstrual periods
- Tell the study staff about any medicines you are taking now
- Have a physical exam based on any signs or symptoms you report
- Hear about
    - how to avoid infections passed during sex while you are in the study
    - how to use the study provided male condoms
    - how to follow the rules of the study
- Provide a urine sample for a pregnancy test
- Provide a blood sample 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 if changes in the vagina or cervix are important for the research study results
- Provide samples of vaginal discharge that will be collected with a swab to check for vaginal infections
- 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)
- Receive male condoms. The only known way to protect against HIV during sex is to use a condom every time you have sex
- 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 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
    - If you need to remove your ring before your next scheduled visit, please go to the clinic as soon as you are able to so that a study clinician can

remove the ring. If you are not able to wait until you go to the clinic to have your ring removed, please save this ring in a special bag that we will give you and bring it back to your next visit
    - 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)

These procedures will take about an hour. You will have the following routine procedures at your 4 scheduled visits:

- Tell the study staff how they can stay in contact with you (let us know about any changes to your address, phone number or other ways to contact you)
- Tell the study staff about any medical problems, changes in your health or menstrual periods
- Tell the study staff about any medicines you are taking now
- Answer questions about your sexual behavior
- Have a physical exam based on any signs or symptoms you report
- Hear about
    - how to avoid pregnancy and infections passed during sex while you are in the study
    - how to use the study provided male condoms
    - how to follow the rules of the study
- Have a pelvic exam
- Provide samples of vaginal discharge that will be collected with a swab to check for types and amounts of bacteria in the vagina
- Receive male condoms
- 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:

- Learn how to use the vaginal ring, if you are in the group that uses the vaginal ring (4-Week and 8-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 a colposcopy (12-Week and 16-Week/Study Termination Visits)
- Have the study ring removed by the 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)
- Answer questions about what you thought about the ring (if you are in the group that uses the ring) (12-Week Visit)
- Provide a urine sample for a pregnancy test (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 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 provided or prescribed 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.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE]

[LOCAL/STATE/NATIONAL] regulations require study staff to report the names of people who test positive for HIV and other infections passed through sex to the [LOCAL HEALTH AUTHORITY]. Outreach workers from the [HEALTH AUTHORITY] may then contact you about informing your partners since they should also be tested. If you do not want to inform your partners yourself, the outreach workers will contact them according to the confidentiality guidelines of the [HEALTH AUTHORITY].

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?

The study doctor may need to take you off the study early without your permission if:

- The study is cancelled by the US National Institutes of Health (NIH), the Population Council, 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)
- The Study Monitoring Committee (SMC) recommends that the study be stopped early (A SMC reviews the progress of the study and the kinds of effects that people report while they are participating in the study)
- You are not able to keep appointments
- Other reasons that may prevent you from completing the study successfully

The study doctor 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:

- You are pregnant
- You become infected with HIV
- The study doctor decides that using the ring would be harmful to you or your partner
- You require a treatment that you may not take while using the ring
- You have a bad reaction to the ring

If the study doctor asks you to stop using the ring, you will still be advised to come in for all of the scheduled follow-up visits that are described above, including things like the physical exam, vital signs, pelvic exam (except if you are pregnant), blood tests, and questionnaires. You will stop using the ring until the study doctor decides it is safe for you to start using the ring again, if possible.

What Are the Risks of Being in the Study?

Risk of Pregnancy

The rings that will be used in this **study contain no medicine at all and will not protect you from pregnancy**; therefore you should not use this as a birth control method. 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. 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 think you may be pregnant at any time during the study, tell the study staff right away. The study staff will talk to you about your choices. If you have a positive pregnancy test and if you are in the group that is using the study ring, we will ask you to stop using the ring right away and return it to the clinic, but will ask you to continue to be in the study and to come in for your follow-up visits. You will continue to have all of the scheduled procedures except for the pelvic exam.

If you are pregnant at the 16-Week/Study Termination visit, you will continue to be followed by the study clinician until you are no longer pregnant. The study staff will

contact you to ask you a few questions about the outcome of your pregnancy. You must arrange for your care and your baby's care outside of this study. This study cannot provide care related to termination of pregnancy, though study staff can provide you with information about where you can access a termination of pregnancy as part of your pregnancy counseling.

Risks of Vaginal Ring

If you are in the group that uses the vaginal ring, you might have the following side effects that have been seen in women who have used a vaginal ring: more discharge from the vagina, irritation in the vagina, discomfort with sex, or pressure in the vagina. These effects, if you have them, would not be expected to be serious or permanent. There is also a chance that your partner may feel the vaginal ring.

Risk of Blood Draws

You may feel more than expected bleeding, discomfort or pain when your blood is drawn. You may feel dizzy, faint or lightheaded. You may have a bruise, swelling, or infection where the needle goes into your arm.

Risk of Genital Exams and Colposcopy

You may feel discomfort or pressure during the pelvic exam. You may have mild vaginal bleeding (spotting). The mild bleeding will stop shortly after the exam.

Other Possible Risks

You may become embarrassed, worried, or nervous when discussing how you have sex; ways to protect against HIV and other infections passed during sex, and your test results. You may become worried or nervous while waiting for your test results. If you have HIV or other infections, knowing this could make you worried or nervous. You may be referred to a trained counselor who can help you deal with any feelings or questions you have.

We will make every effort to protect your privacy while you are in the study. Your visits here will take place in private. However, it is possible that others may learn that you are taking part in the study here. Because of this, they may treat you unfairly.

Are There Benefits To Taking Part in This Study?

You may get no direct benefit from being in this study. However, you will have physical exams and pelvic exams, and counseling and testing for HIV and infections passed through sex. This study cannot provide you with medical care, but study staff will refer you to other available sources of care. If your Pap test result is not normal, you will be referred for treatment at the [INSERT NAME OF PROVIDER/CENTER].

You will get counseling and testing for HIV. You will get free male condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to get medical care for your HIV infection from your regular clinic or we will provide you with a referral to a center where you can receive appropriate care. You will get counseling and testing for infections passed through sex and other infections. If you are

diagnosed with a sexually transmitted infection, you will get medicine or a prescription to treat it, if needed. You can bring your male partner(s) here so that we can also provide them with referral for diagnosis and treatment for potential infections passed through sex.

What Other Choices Do I Have Besides This Study?
You do not have to be in this study, if you choose not to do so.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE: There may be other studies going on here or in the community for which you may be eligible. If you wish, we will inform you about other studies that are being conducted locally. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.] Please talk to your regular doctor about these and other choices that may be available to you.

What about Confidentiality?
Efforts will be made to keep your personal information private. We cannot guarantee absolute confidentiality. If this study is published, your name will not be used and you will not be personally identified.

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US Food and Drug Administration (FDA), the US OHRP, NIH, NIMH and/or contractors of the NIH
- [INSERT NAME OF SITE] IRB/EC
- Study staff
- Population Council, the organization supplying the ring for this study

[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. 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. You are encouraged but not required to tell sexual partners about your being in this study.

What Are The Costs To Me?
There is no cost to you for the study visits or study provided male condoms.

Will I Receive Any Payment?
You will be compensated for your time and effort for each study visit. You will receive [INSERT SITE - SPECIFIC AMOUNT OF MONEY] for each visit. You will also be paid for other costs to you for coming to the study visits [SUCH AS CHILD CARE, TRAVEL, AND LOSS OF WORK TIME – SITES TO COMPLETE].

What Happens If I Am Injured?

It is unlikely that you will be injured as a result of being in this study. If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. However, you may have to pay for this care. The cost for this treatment will be charged to you or your insurance company if you have one. There is no program for compensation either through this institution or the US NIH. You will not be giving up any of your legal rights by signing this consent form. [SITES TO SPECIFY INSTITUTIONAL POLICY]

What Are My Rights As A Research Participant?

Taking part in the study is completely up to you. You will be treated the same no matter what you decide. If you choose to not to be in the study, you will not lose the benefit of services to which you would normally have at this clinic.

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know that you would like them.

What Do I Do If I Have Problems or Questions?

For questions about this study or if you have a research-related injury, you should contact:

- [SITE INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

For questions about your rights as a research participant, contact:

- [SITE INSERT NAME OR TITLE OF PERSON ON THE INSTITUTIONAL REVIEW BOARD (IRB) OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

SIGNATURE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

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, please sign your name or make your mark below.

_____	_____
Participant's Name or Mark (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness's Signature and Date

APPENDIX VI: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS)

MTN-005

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

Version 2.0
October 19, 2010

PRINCIPAL INVESTIGATOR: **[insert]**
PHONE: **[insert]**
Short Title for the Study: **Safety and Adherence of a Non-medicated Intravaginal Ring (IVR)**

INTRODUCTION

You have decided to take part in a US National Institutes of Health (NIH) research study. While you are in this research study there may be some samples of blood and/or fluid from your vagina taken from you that might be useful for future research. You are being asked to agree to the storage of these samples. This consent form gives you information about the collection, storage and use of your samples. The study staff will talk with you about this information. If you have any questions, please ask them. If you agree to the storage of your samples, you will be asked to sign this consent form. You will be given a copy of this form to keep.

HOW WILL YOU GET THE SAMPLES FROM ME?

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?

Your samples will be used to look for evidence of your body's response to infection (such as examining cells, proteins, and other chemicals in your body) while you were in the study. Tests may also include examining your genes (DNA), since they might affect your response to disease in important ways. Your genes might make you more or less likely to become infected, affect your responses to infection, or make your responses to treatment stronger or weaker. No other kinds of genetic test will be done by anyone on your stored specimens without first explaining the test to you and getting your permission. The researchers do not plan to contact you or your regular clinic with any results from tests done on your stored samples. This is because research tests are often done with experimental procedures, so the results from one research study are generally not useful for making decisions on managing your health. 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. Your samples will not be sold or used directly to produce products that can be sold for profit.

Research studies using your samples will be reviewed by the US NIH, 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.

HOW LONG WILL YOU KEEP MY SAMPLES?
There is no time limit on how long your samples will be stored.

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 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.

DOES STORAGE OF MY SAMPLES BENEFIT ME?
There are no direct benefits to you.

WHAT ARE THE RISKS?
There are few risks related to storing your samples. When tests are done on the stored samples there is a small but possible risk to your privacy. It is possible that if others found out information about you that is learned from tests (such as information about your genes) it could cause you problems with your family (having a family member learn about a disease that may be passed on in families or learning who is the biological parent of a child) or problems getting a job or insurance.

WHAT ABOUT CONFIDENTIALITY?
To keep your information private, your samples will be labeled with a code that can only be traced back to your research clinic. Your personal information (name, address, phone number) will be protected by the research clinic. When researchers are given your stored samples to study they will not be given your personal information. The results of future tests will not be included in your health records.

[For US sites only:] We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with the research, such as the court system, about your participation. Also, any publication of the research will not use your name or identify you personally.

People who may review your records include: [INSERT NAME OF SITE] IRB, US 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. Having a Certificate of Confidentiality does not prevent you from giving information about yourself and your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

WHAT ARE MY RIGHTS?

Allowing your samples to be stored is completely voluntary. You may decide not to have any samples stored other than what is needed to complete this study and still be in this research study or any future study. If you decide now that your samples can be stored for future research, you may change your mind at any time. You must contact your study doctor or nurse and let them know that you do not want your samples used for future research. Your samples will then not be used and will be destroyed.

WHAT DO I DO IF I HAVE QUESTIONS?

For questions about the storage of your samples, contact (*insert the name of the investigator*) at *(insert telephone number)*.

For questions about your rights related to the storage of your samples for research, contact (*insert the name or title of person on the Institutional Review Board) at (insert telephone number)*.

SIGNATURE PAGE
[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

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.

_____	_____
Participant's Name or Mark (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness's Signature and Date

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