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MATRIX-003

Trial to Assess Acceptability and Safety of Two Placebo Intravaginal Ring (IVR) Designs

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A Non-IND Study

Pharmaceutical Collaborator:
Oak Crest Institute of Science (OCIS)

Protocol Co-Chair:
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Version 1.0

29 June 2023

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MATRIX
Advancing R&D of Innovative
HIV Prevention Products for Women

MATRIX-003

Trial to Assess Acceptability and Safety of Two Placebo Intravaginal Ring (IVR) Designs

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LIST OF ABBREVIATIONS AND ACRONYMS

ACRO	African Clinical Research Organisation
AGYW	Adolescent girls and young women
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
API	Active pharmaceutical ingredient
ARV	Antiretroviral
AST	Aspartate aminotransferase
BV	Bacterial vaginosis
CAB	Community advisory board
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention (US)
CDM	Clinical data manager
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Act
CRF	Case report form
CRM	Clinical research manager
CRS	Clinical research site
CT	Chlamydia trachomatis
CVF	Cervicovaginal fluid
DAIDS	Division of AIDS
DRA	Drug regulatory authority
DSMB	Data and Safety Monitoring Board
ECS-HSR	Education and Compliance Support for Human Subject Research
FDA	U.S. Food and Drug Administration
GC	Neisseria gonorrhea
GCP	Good Clinical Practice
GDP	Good Documentation Practices
GMP	Good Manufacturing Practice
HHRC	Harare Health and Research Consortium
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IATA	International Air Transport Association
ICH E6	International Conference for Harmonization Guideline for Good Clinical Practice
IDE	Investigational Device Exemption
IDI	In-depth interview
IEC	Independent Ethics Committee
IND	Investigational New Drug
IoR	Investigator of Record
IRB	Institutional Review Board

ISP	Independent Safety Physician
IUD	Intrauterine device
IVR	Intravaginal ring
KOH	Saline/potassium hydroxide
LDMS	Laboratory Data Management System
MPT	Multipurpose prevention technology
MWRIF	Magee-Womens Research Institute and Foundation
NAAT	Nucleic acid amplification test
NIH	National Institutes of Health
OCIS	Oak Crest Institute of Science
OHRP	Office for Human Research Protections
PEP	Post-exposure prophylaxis
PHI	Protected health information
PI	Principal Investigator
PID	Pelvic inflammatory disease
PrEP	Pre-exposure prophylaxis
PSRT	Protocol Safety Review Team
PTID	Participant identifier
QA	Quality assurance
QC	Quality control
RTI	Reproductive tract infection
SAE	Serious adverse event
SAHPRA	South African Health Products Regulatory Authority
SEV	Study Exit Visit
SMS	Short message service
SOP	Standard operating procedures
SSA	Sub-Saharan Africa
SSP	Study specific procedures
STI	Sexually transmitted infection
TFA	Theoretical Framework of Acceptability
UPT	Urine pregnancy test
USAID	US Agency for International Development
UTI	Urinary tract infection
UTMB	University of Texas Medical Branch
Wits RHI	Wits Reproductive Health and HIV Institute
WHO	World Health Organization

MATRIX-003

Trial to Assess Acceptability and Safety of Two Placebo Intravaginal Ring (IVR) Designs

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MATRIX-003

Trial to Assess Acceptability and Safety of Two Placebo Intravaginal Ring (IVR) Designs

INVESTIGATOR SIGNATURE FORM

Version 1.0; 29 June 2023

MATRIX: A USAID Project to Advance the Research and Development of Innovative HIV Prevention Products for Women

Funded by:
US Agency for International Development (USAID)

A Non-IND Study

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); USAID regulations (2 CFR 200 and 22 CFR 225); standards of the International Conference for Harmonization Guideline for Good Clinical Practice (ICH E6); Institutional Review Board/Independent Ethics Committee (IRB/IEC) determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., USAID) and institutional policies.

I agree to maintain all study records in accordance with protocol-specified protections of participants' confidentiality and with site IRB/IEC policies and procedures. Study records must be maintained on-site for the entire implementation period of the study and a minimum of at least three years after completion of research. OCIS will inform the investigator/institution as to when these documents no longer need to be retained.

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

_____
Name of Investigator of Record (print)

_____ _____
Signature of Investigator of Record Date

MATRIX-003

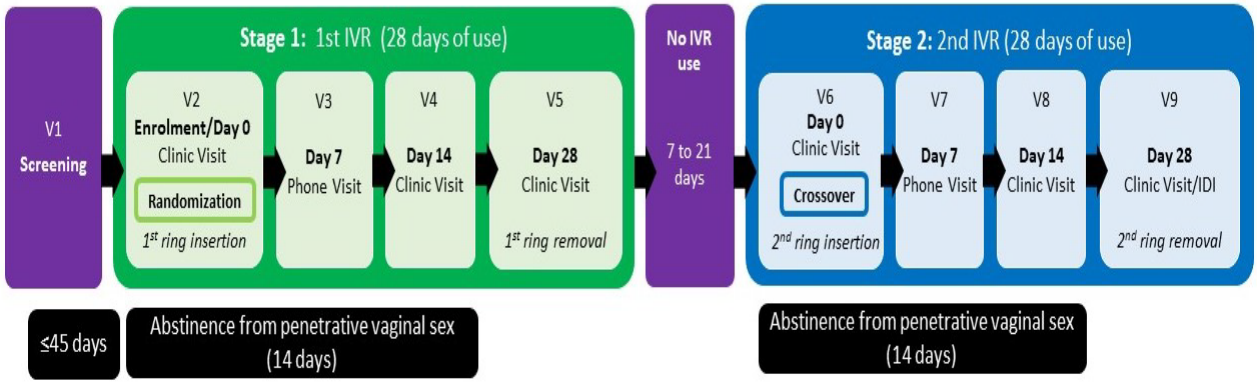
Trial to Assess Acceptability and Safety of Two Placebo Intravaginal Ring (IVR) Designs

PROTOCOL SUMMARY

Short Title:	OCIS Placebo Ring Study
Pharmaceutical Collaborator:	OCIS
Funders:	USAID
Protocol Co-Chair:	Kathryn T. Mngadi, MBChB, MSc Clin Trials, MPhil Pall Med, Dip HIV Man SA, Dip Epi
Protocol Co-Chair:	Krishnaveni Reddy, MMedSci
Sample Size:	MATRIX-003 will enroll approximately 100 evaluable participants. MATRIX-003 will also enroll a subset of up to 30 sexual partners of evaluable participants for in-depth interviews (IDI).
Study Population:	HIV seronegative adult (18-45 years old) persons assigned female sex at birth who are at low risk of acquiring HIV infection (henceforth referred to as "participants"), and sexual partners of evaluable participants (henceforth referred to as "sexual partners").
Study Sites:	Five sites in the US and sub-Saharan Africa (SSA): • Aurum Institute – Tembisa Clinic#4 clinical research site (CRS); • Centre for the AIDS Programme of Research in South Africa (CAPRISA) – Vulindlela CRS; • Harare Health and Research Consortium (HHRC) – Zengeza CRS; • University of Pittsburgh (Pitt)/Magee-Womens Research Institute and Foundation (MWRIF) CRS; and • Wits RHI CRS.
Study Design:	Randomized, partially blinded, crossover trial with 2 arms, each assigned a different sequence of placebo intravaginal ring (IVR) use (A then B or B then A).
Study Duration:	Approximately 9-11 weeks of follow-up per participant is planned with a projected accrual period of approximately 3-5 months. The total duration of the study will be approximately 5-8 months.
Study Products:	Placebo IVR (i.e., blank IVR that does not deliver any substances) A and B, which differ by material mechanical attributes and physical properties such as flexibility or hardness.

Study Regimen: Participants will use the assigned placebo IVR (A or B) for approximately 28 days, then crossover to the other IVR for approximately 28 days, with 7-21 days between the two product use periods.

Figure 1: Study Visit Schedule



Primary Objective:

Acceptability

- To compare the acceptability of two placebo IVR types (A and B).

Primary Endpoints:

Acceptability

- Proportion of participants preferring each placebo IVR (A or B).
- Mean rating of overall satisfaction with using each placebo IVR.

Secondary Objective:

Safety

- To compare the safety of two placebo IVR types (A and B).

Secondary Endpoint:

Safety

- Proportion of participants with urogenital Grade 2 or higher Adverse Events deemed related to each study product.

Exploratory Objectives:

Participant acceptability, attitudes and experiences

- To explore multiple dimensions of acceptability of two placebo IVRs (A and B) and participants' attitudes towards and experiences with each IVR.

Sexual partner attitudes and experiences

- To explore sexual partners' attitudes towards and experiences with participants' IVR use.

Vaginal microbiota

- To assess the impact of placebo IVR use on the vaginal microbiome.

Social harms and social benefits

- To describe the reported experiences of social harms and social benefits over the course of IVR use.

Exploratory Endpoints:

Participant acceptability, attitudes and experiences

- Participant responses to quantitative (i.e., questionnaires) and qualitative (i.e., IDI) assessments. Multiple dimensions will be explored, including:
    - Past experience with IVRs, if any (e.g., Nuvaring, dapivirine IVR)
    - Insertion/removal techniques
    - Ease of insertion/removal
    - Comfort during use
    - Experience with/awareness of inserted IVR
    - Spontaneous expulsions and voluntary removals
    - Experience with IVR use during vaginal sex or menses
    - Perceived benefits and concerns/challenges with the IVR as a future HIV and/or dual purpose (HIV and pregnancy) prevention option
    - Perceptions of sexual partner(s)

Sexual partner attitudes and experiences

- Sexual partner responses during IDI related to:
    - IVR attributes, including acceptability and preferences
    - Perception of participant's experience using the IVR during the study
    - Physical sensation of the participant's IVR use during sex (as relevant)
    - Perceived benefits and concerns/challenges with the IVR as a future HIV and/or dual purpose (HIV and pregnancy) prevention option

Vaginal microbiota

- Change from baseline in composition of vaginal microbiome following each placebo IVR use.
- Change from baseline in Nugent score following each placebo IVR use.

Social harms and social benefits

- Participant or sexual partner self-report of social harms (i.e., non-clinical adverse consequences of study participation or product use that may manifest in social, psychological, or physical ways).
- Participant or sexual partner self-report of social benefits (e.g., positive consequences of product use disclosure, self-confidence, improved communication with intimate partner) resulting from IVR use and/or study participation.

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	Trial to Assess Acceptability and Safety of Two Placebo Intravaginal Ring (IVR) Designs
Protocol Number:	MATRIX-003
Short Title:	OCIS Placebo Ring Study
Date:	29 June 2023

1.2 Funding Agency and Monitor Identification

Funding Agency:	USAID Bureau of Global Health, Office of HIV/AIDS, Research Division 500 D Street Southwest Washington, DC 20547 USA
Pharmaceutical Collaborator:	Oak Crest Institute of Science (OCIS) 132 W. Chestnut Avenue Monrovia, CA 91016 USA
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1.3 Study Product Supply

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2 INTRODUCTION

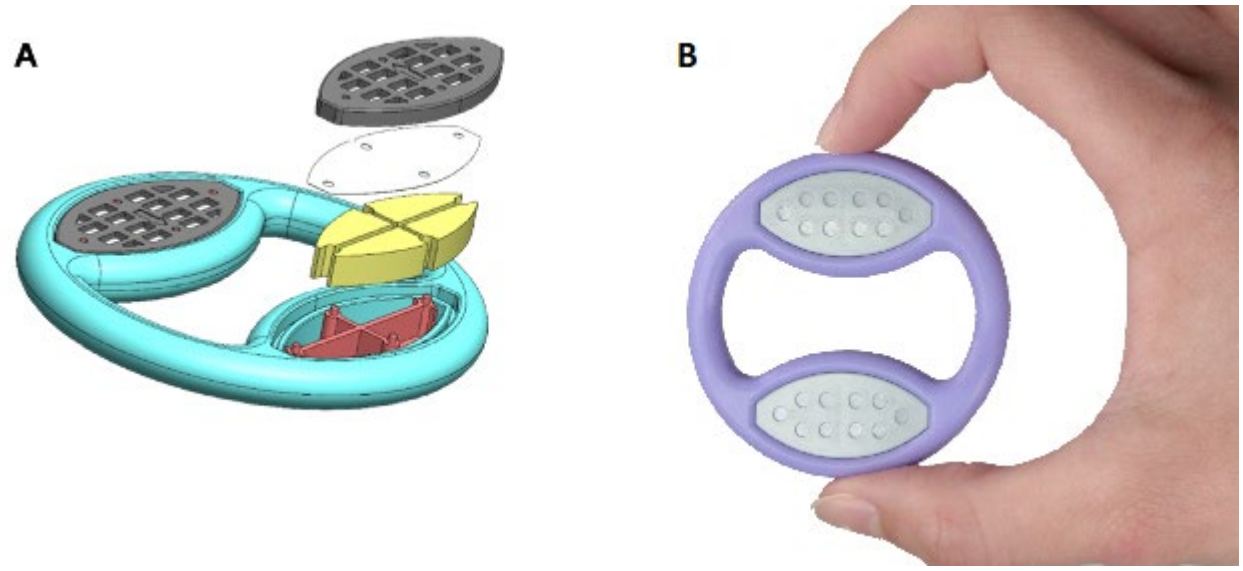
2.1 Background

The OCIS team's overarching goal is the accelerated development of a long-acting (up to 90 days) IVR delivering a broad-spectrum antiviral peptide and a small-molecule nonhormonal contraceptive (that blocks human sperm functions essential for fertilization) to protect women from HIV and to prevent unplanned pregnancy. Successful development of this innovative IVR will fill an unmet need in sexual reproductive health. The dual purpose prevention technology aspect of the OCIS IVR is expected to drive uptake and adherence, particularly among adolescent girls and young women (AGYW). Not having an antiretroviral (ARV) or hormonal agent could potentially differentiate it from other IVRs on the market.

IVRs have the advantage of being female-controlled, not coitally dependent, not dependent on daily use, completely reversible, and easily inserted/removed without assistance. As of January 2023 [1], there were 12 other multi-purpose technology (MPT) IVRs at various stages of development using one of the following three IVR designs: 1) silicone matrix ring, 2) segmented, dual reservoir polyurethane (PU) ring, 3) pod-IVR (also developed by OCIS) [2-4].

The IVR design to be tested in the proposed study is expected to have the capacity to deliver multiple drugs and novel active pharmaceutical ingredients (API) through a single device in future trials. The ring size is similar to that used in US Food and Drug Administration (FDA)-approved devices and to those used in multiple clinical trials, but the geometry and design are novel.

Figure 2. Next generation Cassette IVR.



(A) Solid model indicating one lobe fully assembled (top left) and a second lobe with the components stacked. Brick red = reservoir support structure; yellow = drug particle-paste kernel; white = rate-controlling membrane; grey = reservoir end-cap. (B) Photograph of prototype human-sized Cassette IVR. The lavender toroidal ring is made of silicone.

Device fitting studies in sheep did not reveal any safety concerns (unpublished work). A short-term use (1 hour) study in humans was conducted at the University of Texas Medical Branch (UTMB) – Galveston using a series of IVRs of differing designs, geometries, and hardness/stiffness. Women inserted the IVR and performed various physical activities (i.e., coughing, bearing down, performing deep knee bends, lifting a 10 lb. object from the ground, jumping up and down in place, walking up and down stairs), and then removed the IVR themselves. There were no safety or usability concerns (publication pending). The short-term use study at UTMB guided the design of the IVRs to be used in MATRIX-003.

The MATRIX-003 study will allow us to gather acceptability, usability, and safety data with longer-term use of the placebo IVR. These data will guide the final design of the OCIS IVR for delivery of APIs (*e.g.*, a broadly antiviral peptide and non-hormonal contraceptive) in a future Phase 1 clinical trial(s).

The MATRIX-003 study with placebo IVRs (i.e., blank IVRs that do not deliver any substances) does not present a potential for serious risk to the health, safety, or welfare of a subject and qualifies as a nonsignificant risk per US FDA guidelines below:

> "A nonsignificant risk device study requires only IRB approval prior to initiation of a clinical study. Sponsors of studies involving nonsignificant risk devices are not required to submit an IDE application to the FDA for approval. Submissions for nonsignificant device investigations are made directly to the IRB of each participating institution. Sponsors should present to the reviewing IRB an explanation why the device does not pose a significant risk. If the IRB disagrees and determines that the device poses a significant risk, the sponsor must report this finding to the FDA within five working days [§812.150(b)(9)]. The FDA considers an investigation of a nonsignificant risk device to have an approved IDE when the IRB concurs with the nonsignificant risk determination and approves the study."

Despite this being a nonsignificant risk device per the US FDA, other national drug regulatory authorities (e.g., South African Health Products Regulatory Authority [SAHPRA]) may have additional requirements. All local regulatory guidelines will be followed.

2.2 Description of Placebo IVRs

2.2.1 Placebo IVR A

The OCIS placebo IVR A consists of a flexible lavender silicone scaffold, with an outer diameter of 55 mm and a durometer value of 40A. The ring holds two grey cassettes.

2.2.2 Placebo IVR B

The OCIS placebo IVR B consists of a flexible lavender silicone scaffold, with an outer diameter of 55 mm and a durometer value of 50A. The ring holds two grey cassettes.

2.3 Acceptability of IVR Formulations

Ridgeway et al. found in a meta-analysis of IVR studies conducted worldwide that acceptability was much greater in actual users (85.6%) when compared to hypothetical users (27.6%) [5], which is why this real-world acceptability study is critical in early development. The meta-analysis included 50 studies and almost 20,000 actual users and concluded that most users found IVRs comfortable during sex (82.7%) and easy to use (90.9%) [5]. African participants reported respectable but lower acceptability rates than European or Asian studies (59% vs. 90.6% and 97.1% respectively).

There seems to be a strong preference for MPTs over solo HIV prevention. In the MTN-038 study of the tenofovir reservoir ring conducted at multiple sites in the U.S., a majority of the participants (77%) expressed a preference for an MPT over HIV prevention alone [6]. The CUPID study (MTN-045) conducted in heterosexual couples in Zimbabwe and Uganda found an even stronger preference; 91% of participants said they would prefer using an MPT over two separate products for HIV and pregnancy prevention [7]. Participants expressed that an MPT would allow them to achieve HIV protection while avoiding stigmatizing discussions about HIV by focusing partner discussions on more comfortable topics like family planning.

Currently the best predictor of acceptability and uptake of the IVR as a delivery method in the Sub-Saharan Africa (SSA) population targeted for this project is the Phase 3 ASPIRE trial of the dapivirine (DPV) IVR conducted at 15 sites in Africa (Malawi, South Africa, Uganda, Zimbabwe). They enrolled 2629 women aged 18–45 and looked at acceptability after 3 months of use and again at 24 months [8]. Acceptability varied significantly by country with approximately 50% of participants in Malawi and South Africa saying they were "very likely" to use a monthly vaginal ring compared to ~75% of participants in Uganda and Zimbabwe. Attitudes to IVR use during sex also varied greatly by country; participants in Malawi (35%) and Uganda (85%) did not like wearing the ring during sex compared to South Africans (10%) and Zimbabweans (< 1%). Despite this most participants (58%) reported that IVR use during sex did not impact their sexual pleasure. Interestingly, 39% of participants even reported that the IVR increased their sexual pleasure. Participants that were bothered by IVR use during sex were also more likely to be bothered by IVR use during menses. ASPIRE participants had differing perceptions and concerns about IVR use during sex, menses, and impact on/ preferences for natural vaginal lubrication, once again highlighting the fact that there is no one size fits all approach to prevention methods.

2.4 Rationale for Study Design

While the short-term use study at UTMB (described above) guided the design of the IVRs to be used in this study, MATRIX-003 will allow us to gather acceptability, usability, and safety data with longer-term use. Previous research has supported the safety and acceptability of similarly sized IVRs over 28 days or more of continuous use, but more research is needed to assess the acceptability of these novel OCIS IVR designs before beginning costly and time-consuming Phase 1 clinical trials of APIs delivered by these IVRs.

The primary objective of this study is to assess the acceptability of two placebo IVR designs (A and B) when used continuously for approximately 28 days without dispensing any substance (e.g., APIs or excipient). The crossover design allows each participant to act as their own control.

While the two placebo IVRs are similar in size and design, they have slight differences in characteristics such as flexibility and stiffness that may or may not impact user acceptability. By evaluating two placebo IVRs we hope to understand if there are differences in performance (e.g., acceptability, insertion success, expulsion frequency) and what attributes potentially contribute to these outcomes.

Acceptability will be assessed through quantitative questionnaires and qualitative in-depth interviews (IDI) with users and, among a subset, IDIs with their sexual partners. Instructional materials will be utilized to familiarize users with the insertion process. These materials will be designed based on participant feedback from previous trials. Importantly, experiences of the participants in the context of sex will also be explored after an initial 2-week period of abstinence with each IVR.

The safety of participants will be monitored during IVR use through a combination of clinical and phone visits. Only participants at low risk for acquiring HIV and other STIs as determined by the eligibility criteria outlined in Sections 5.2.1 and 5.3 will be enrolled in the study. The impact on vaginal microbiota will also be assessed and may provide valuable baseline data for future Phase 1 trials.

3 OBJECTIVES

3.1 Primary Objective

Acceptability

- To compare the acceptability of two placebo IVR types (A and B).

3.2 Secondary Objective

Safety

- To compare the safety of two placebo IVR types (A and B).

3.3 Exploratory Objectives

Participant acceptability, attitudes and experiences

- To explore multiple dimensions of acceptability of two placebo IVRs (A and B) and participants' attitudes towards and experiences with each IVR.

Sexual partner attitudes and experiences

- To explore sexual partners' attitudes towards and experiences with participants' IVR use.

Vaginal microbiota

- To assess the impact of placebo IVR use on the vaginal microbiome.

Social harms and social benefits

- To describe the reported experiences of social harms and benefits over the course of IVR use.

4 STUDY DESIGN

4.1 Identification of Study Design

MATRIX-003 is a randomized, partially blinded, crossover trial with 2 arms, each assigned a different sequence of placebo IVR (A then B or B then A) to use for approximately 28 days each, with 7-21 days between the two product use periods.

4.2 Summary of Major Endpoints

Primary Endpoints:

Acceptability

- Proportion of participants preferring each placebo IVR (A or B).
- Mean rating of overall satisfaction with using each placebo IVR.

Secondary Endpoint:

Safety

- Proportion of participants with genitourinary Grade 2 or higher Adverse Events deemed related to each study product.

Exploratory Endpoints:

Participant acceptability, attitudes and experiences

- Participant responses to quantitative (i.e., questionnaires) and qualitative (i.e., IDI) assessments. Multiple dimensions will be explored, including:
    - Past experience with IVRs, if any (e.g., Nuvaring, dapivirine IVR)
    - Insertion/removal techniques
    - Ease of insertion/removal
    - Comfort during use
    - Experience with/awareness of inserted IVR
    - Spontaneous expulsions and voluntary removals
    - Experience with IVR use during vaginal sex or menses
    - Perceived benefits and concerns/challenges with the IVR as a future HIV and/or dual purpose (HIV and pregnancy) prevention option
    - Perceptions of sexual partner(s)

Sexual partner attitudes and experiences

- Sexual partner responses during IDI related to:
    - IVR attributes, including acceptability and preferences
    - Perception of participant's experience using the IVR during the study

- Physical sensation of the participant's IVR use during sex (as relevant)
- Perceived benefits and concerns/challenges with the IVR as a future HIV and/or dual purpose (HIV and pregnancy) prevention option

Vaginal microbiota

- Change from baseline in composition of vaginal microbiome following each placebo IVR use.
- Change from baseline in Nugent score following each placebo IVR use.

Social harms and social benefits

- Participant or sexual partner self-report of social harms (i.e., non-clinical adverse consequences of study participation or product use that may manifest in social, psychological, or physical ways).
- Participant or sexual partner self-report of social benefits (e.g., positive consequences of product use disclosure, self-confidence, improved communication with intimate partner) resulting from IVR use and/or study participation.

4.3 Description of Study Population

The study population will consist of HIV seronegative adult (18-45 years old) persons assigned female sex at birth who meet the criteria outlined in Sections 5.2.1 and 5.3, and sexual partners who meet eligibility criteria as described in Section 5.2.2.

4.4 Time to Complete Accrual

The time to complete accrual at each site is anticipated to be approximately 3-5 months.

4.5 Study Groups

MATRIX-003 will enroll approximately 100 evaluable participants across the study sites, randomized (1:1) to sequence of placebo IVR use. MATRIX-003 will also enroll a subset of up to 30 sexual partners for an IDI. See Section 10.3 for more details.

4.6 Expected Duration of Participation

Once randomized to placebo IVR use sequence, participants will complete approximately 9-11 weeks of follow-up. The total duration of the study will be approximately 5-8 months at each site.

4.7 Sites

The following five sites in the United States and sub-Saharan Africa (SSA) will take part in MATRIX-003:

- Aurum Institute – Tembisa Clinic#4 clinical research site (CRS)
- Centre for the AIDS Programme of Research in South Africa (CAPRISA) – Vulindlela CRS
- Harare Health and Research Consortium (HHRC) – Zengeza CRS
- University of Pittsburgh (Pitt)/Magee-Womens Research Institute and Foundation (MWRIF) CRS
- Wits RHI Research Centre CRS

5 STUDY POPULATION

5.1 Selection of the Study Population

The inclusion and exclusion criteria in Sections 5.2 and 5.3 will be used to ensure the appropriate selection of study participants. In addition, a sample of up to 30 sexual partners (across the study sites) for whom participants have given permission to contact will be selected for participation in an IDI.

5.1.1 Recruitment

Participants will be recruited from a variety of sources across sites including, but not limited to, existing databases (as permitted by local guidelines on protected health information [PHI]), primary care health clinics, family planning clinics, HIV testing facilities, gynecology clinics, institutions of higher learning, other community-based organizations, and through community outreach activities. Recruitment materials will be approved by site Institutional Review Boards/Independent Ethics Committees (IRB/IEC) prior to use per local requirements. Community education strategies, including group sessions, may be employed as part of participant/partner outreach. Prior to study start and during the study, community stakeholders may be consulted for the purpose of facilitating recruitment, outreach and access to referrals for local health and/or social services. Sites will develop and implement local standard operating procedures (SOP) to engage with communities and target potential participants for recruitment.

5.1.2 Retention

Once a participant is enrolled in MATRIX-003, study sites will make every effort to retain the participant in follow-up to minimize possible bias associated with loss-to-follow-up (LTFU). An average retention rate of 90% will be targeted across sites. Sites will develop and implement local SOPs to target and ensure high rates of retention.

5.2 Inclusion Criteria

5.2.1 Participants

Potential participants must meet all the following criteria prior to Enrollment (unless otherwise specified):

1) Aged 18 to 45 years (inclusive) at Screening, verified per site SOP.

2) Assigned female sex at birth.

3) Able and willing to provide written informed consent to be screened for and enrolled in MATRIX-003 in one of the study languages (as specified in site SOP).

4) Able and willing to provide adequate contact/locator information, as defined in site SOP.

5) Able and willing to comply with all protocol requirements, including:
    - Abstaining from other intravaginal products or practices for the duration of the study (as specified in Section 6.7).

- Abstaining from penetrative vaginal intercourse (i.e., oral-, digital-, penile-penetration) for the first 14 days of each product use period.
- Refraining from participation in other research studies involving drugs, medical devices, vaginal products, or vaccines starting 2 weeks before the Screening Visit and for the duration of the study, or in observational or qualitative studies for the duration of the study, unless approved by the Protocol Safety Review Team (PSRT).
- Reliable access to a private phone for scheduled phone contacts.

6) HIV-uninfected based on testing performed at Screening and Enrollment (per protocol algorithm in Appendix II).

7) Per participant report, must be either not currently sexually active or in a mutually monogamous relationship with only one partner who is not known to be HIV positive or to currently have a sexually transmitted infection (STI).

8) Negative urine pregnancy test at Screening and Enrollment.

9) Participants over the age of 21 (inclusive) must have documentation of a Grade 0 Pap smear within the past 3 years prior to Enrollment, or a Grade 1 Pap smear at Screening with no treatment required, per the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 (Dated November 2007) to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017.

10) Protected from pregnancy starting at least 2 weeks before Screening and continuing for the duration of study participation by an effective contraceptive method as confirmed by site SOP; effective methods include:
    - Hormonal methods except vaginal rings
    - Copper intrauterine device (IUD)
    - Sterilization of participant or (if applicable) sterilization of monogamous partner
    - Correct and consistent condom use at study entry, and agrees to use site-provided condoms during study (for US site only)

5.2.2 Sexual Partners

Potential participants for the sexual partner IDI subset must meet all of the following criteria to be eligible for inclusion in the study:

1. Identifies as a sexual partner of a MATRIX-003 participant.
2. Identified by participant as a sexual partner during MATRIX-003 for whom the participant has given permission to contact (as specified in site SOP).
3. Able and willing to provide written informed consent in one of the study languages (as specified in site SOP).
4. Able and willing to complete the required study procedures.
5. Must be 18 years old or above at the time of their study participation, verified per site SOP.

5.3 Exclusion Criteria

Potential participants must not meet any of the following criteria prior to Enrollment (unless otherwise specified):

1) Per participant report at Screening and Enrollment, intends to do any of the following during the study participation period:

- Become pregnant.
- Breastfeed.
- Relocate away from the study site.
- Travel away from the study site for a time period that would interfere with product resupply and/or study participation.

2) Positive HIV test at Screening or Enrollment.

3) Positive test for *Trichomonas vaginalis* (TV), *Neisseria gonorrhea* (GC), *Chlamydia trachomatis* (CT), or *Treponema pallidum* (Syphilis) at Screening and (per participant report) treated for potential STI within past 12 months.

4) Diagnosed with urinary tract infection (UTI), pelvic inflammatory disease (PID), or reproductive tract infection (RTI) requiring treatment per WHO guidelines at Enrollment.

   Note: Otherwise eligible participants diagnosed during screening with a UTI, symptomatic yeast infection or symptomatic BV infection are offered treatment consistent with WHO recommendations. If treatment is completed and symptoms have resolved within 45 days of obtaining informed consent for screening, the participant may be enrolled.

5) Clinically apparent Grade 2 or higher pelvic exam finding per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addenda 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007]) at Enrollment.

   Note: Otherwise eligible participants with exclusionary pelvic exam findings at Screening may be enrolled/randomized if treatment is completed at least 7 days prior to enrollment and findings have improved to a non-exclusionary severity grading or resolved by the time of enrollment. Spotting/bleeding will be considered exclusionary only if greater than what would be expected from contraceptive use.

6) Participant report and/or clinical evidence of any of the following:
   - Known adverse reaction to silicone (ever).
   - Use of diaphragm, NuvaRing, or spermicide for contraception starting 2 weeks prior to Screening through Enrollment.
   - Use of any of the following in the past 12 months: stimulants (cocaine [including crack], methamphetamine, or non-physician prescribed pharmaceutical-grade stimulants), or inhaled nitrates, or illicit injection drug use of any kind.
   - Prior use of post-exposure prophylaxis (PEP) or oral pre-exposure prophylaxis (PrEP) (including FTC/TDF) in the past 4 weeks or any prior use of long-acting systemic PrEP (including cabotegravir or islatravir).
   - Antibiotic, steroid, or antifungal (oral or intravaginal) therapy within 14 days of Enrollment.
   - Hysterectomy.
   - Gynecologic or genital procedure (e.g., tubal ligation, dilation and curettage, piercing, IUD insertion or removal, colposcopy) within 21 days prior to Enrollment.
   - At Screening or Enrollment, as determined by the Investigator of Record (IoR)/designee, has any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease.

7) Has any of the following laboratory abnormalities at Screening:
    - Grade 2 or higher Aspartate aminotransferase (AST), alanine transaminase (ALT), creatinine, or Hemoglobin per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017.

8) Has any other condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

5.4 Co-enrollment Guidelines

Participants must not take part in other research studies involving drugs, medical devices, vaginal products, or vaccines starting 2 weeks before the Screening Visit and while taking part in MATRIX-003, unless approved by the PSRT. Participants must not take part in observational or qualitative studies while taking part in MATRIX-003, unless approved by the PSRT. Each site will be responsible for defining procedures for management and prevention of co-enrollment prior to initiation.

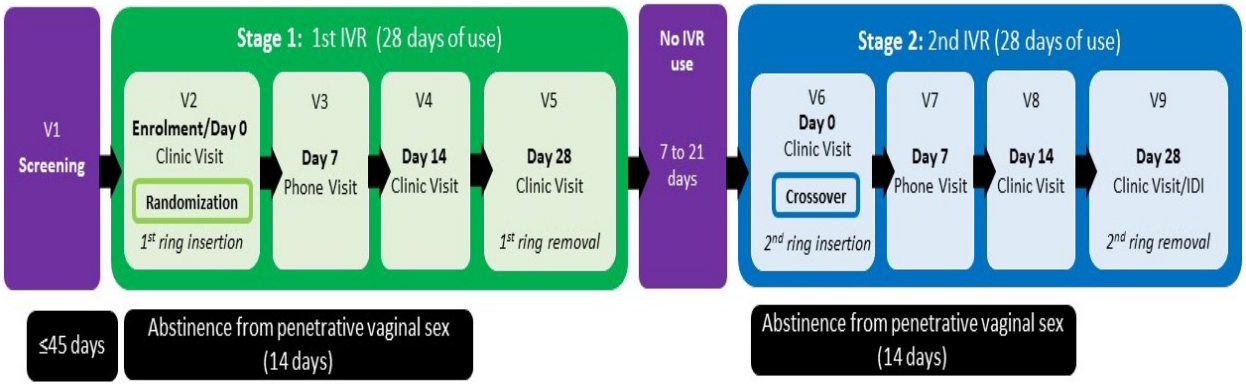
Should any participant report concurrent participation in contraindicated studies after enrolling in MATRIX-003, the IoR/designee will consult the PSRT regarding ongoing product use and other potential safety considerations associated with co-enrollment, or regarding potential product acceptability considerations associated with co-enrollment.

6 STUDY PRODUCT

6.1 Regimen

The products being used in this study are the placebo IVRs A and B. The two IVRs differ by material mechanical attributes and physical properties such as flexibility or hardness. At each of the study sites, participants will be randomized (1:1) to receive either placebo IVR A or B first. Each participant will use each IVR for approximately 28 days, for a total of approximately 56 days of placebo IVR use.

Figure 3: Study Product Regimen



6.2 Administration

Scheduled insertion and removal of the study products will occur in the clinic. Participants will be asked to self-insert and self-remove the ring at the clinic. Prior to insertion the participant will receive instructions for self-placement and on how to replace the IVR in case of expulsion. A clinical team member will confirm correct placement of the IVR in the vagina (i.e., firmly, but comfortably seated in the vagina without protruding or causing discomfort with ambulation). If the participant has difficulty with insertion or removal, after 2 attempts a clinical team member may assist with the procedure. Any difficulties will be captured per the exploratory acceptability objective. In case of expulsion, the participant will be instructed to clean the IVR by rinsing with drinking water before reinserting it. If the IVR that the participant is wearing is expelled and the participant is not able to clean and re-use it (e.g., it falls in the toilet), the participant will be instructed to return to clinic for a replacement IVR as soon as possible.

6.3 Study Product Formulation and Storage

Study products will be stored in the clinic at 15°C – 30°C (59°F – 86°F) prior to dispensing.

6.4 Supply and Accountability

6.4.1 Study Product Supply

The IVRs provided for this study will be manufactured by OCIS under non-GMP conditions according to OCIS SOPs that ensure no contamination of the study product. The study product will be made of medical-grade elastomers, will be fabricated using methods and machines commonly used in the biomedical engineering field, and will be sanitized prior to packaging.

All study products will be shipped from OCIS to the clinical sites. Each IVR will be packaged in an individual pouch and labeled with the following information as shown below in the sample label.

Serial #: xx
Placebo Ring for Intravaginal Use
Type of Intravaginal Ring: XX

Lot #: xx
Date of Manufacture (DOM): DDMONYYYY

Expiration/Re-test Date: 2 years after DOM

Store at 15°C – 30°C (59°F – 86°F)

Caution: New Product – limited by law to investigational use only

Sponsor/Manufacturer:
Oak Crest Institute of Science
132 W Chestnut Ave, Monrovia, CA 91016

6.4.2 Study Product Dispensing

Study product will be dispensed by the clinical study site pharmacist(s) to clinic staff only upon receipt of a written prescription signed by an authorized prescriber.

6.4.3 Study Product Accountability

The clinical study site pharmacist(s) will maintain complete accountability records of all study products received for this protocol and dispensed to participants. Unused product will be returned to OCIS or disposed of with the permission of OCIS. Additional documentation will be required for study product returns and destruction (if applicable).

6.5 Ancillary Study Supplies

Clinic staff will offer male condoms to all participants at Visits 4-5 and 8-9, approximately Days 14 and 28 of each product use period.

6.6 Concomitant Medications

All concomitant medications will be recorded on case report forms (CRF) for participants starting at Screening. Concomitant medications include any prescription, over the counter or herbal medication or preparation. Enrolled study participants may use concomitant medications during study participation except for medications and products noted as prohibited in Section 6.7.

6.7 Prohibited Medications, Products and Practices

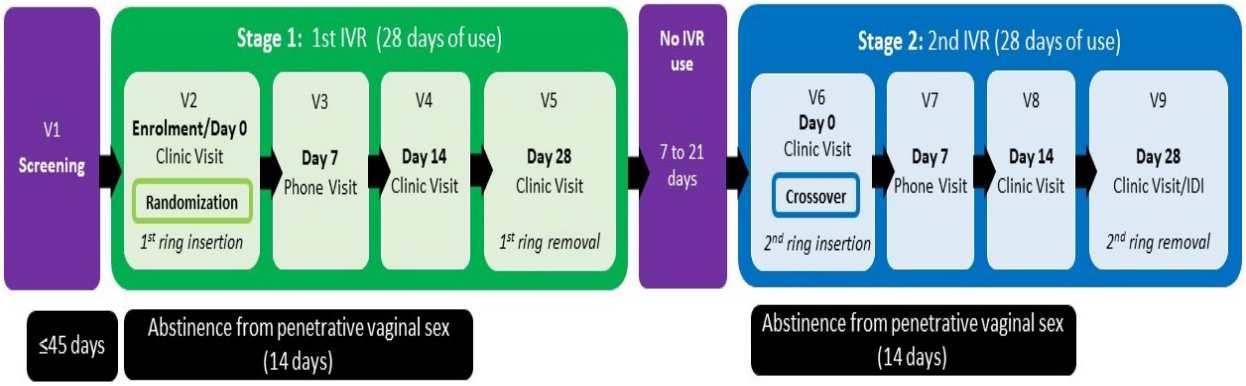
Participants will be instructed to abstain from penetrative vaginal sex (i.e., oral-, digital-, penile-penetration, or with the use of an instrument that penetrates past the labia majora) for the first half (i.e., first 14 days) of each product use period. This means nothing should enter the vagina: fingers, penis, toys, etc. If a participant reports an instance of penetrative vaginal sex during the scheduled periods of abstinence (i.e., Days 1-14 of each product use period) the site staff will counsel the participant about the importance of adhering to the protocol, document as a protocol deviation, and record on the appropriate CRF. There are no restrictions on penetrative vaginal sex during the second half of each product use period.

Participants will also be instructed to abstain from intravaginal product use and practices other than sex (e.g., vaginal steaming, insertion of herbal preparations) for the duration of the study, including medications, menstrual cups, tampons, and douches. If a participant reports the use of an intravaginal product or prohibited practice, the site staff will counsel the participant about the importance of adhering to the protocol and record the intravaginal product use or practice on the appropriate CRF. Please reference the MATRIX-003 Study Specific Procedures (SSP) Manual for additional details.

7 STUDY PROCEDURES

An overview of the study visits and evaluations schedule is provided in Appendix I. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across sites as well as to specify the visit windows are provided in the MATRIX-003 SSP Manual.

Figure 4: Study Visit Schedule



7.1 Pre-Screening

As part of participant outreach and recruitment strategies, study staff may pre-screen potential study participants in person or over the phone. During these interactions, study staff may explain the study to potential participants and ascertain elements of presumptive eligibility, to be confirmed at an on-site screening visit. Potential participants invited for screening visits may be advised to bring identity documentation and the required locator information. Additionally, they will be asked to bring documentation of a normal Pap test within 3 years prior to enrollment if available. Process information (e.g., number of potential participants contacted, number presumptively eligible) may be recorded and stored at the study site in the absence of written informed consent from potential participants (waivers of consent and HIPAA authorization are for pre-screening purposes only) provided the information is collected in such a manner that it cannot be linked to participant identifiers. Procedures and documentation will comply with local IRB/IEC requirements. Sites will be responsible for defining pre-screening procedures prior to initiation.

7.2 Screening Visit

Potential participants will provide written informed consent prior to any study procedures, including all screening assessments to determine their eligibility to take part in the study. Participants will be counselled to abstain from penetrative vaginal sex for the first 14 days after each insertion of study product, and from use of intravaginal products and practices (see Section 6.7) for the full duration of study participation. Eligibility determination will include baseline demographics and medical history, physical and pelvic examination, urine pregnancy test (UPT), and HIV and STI screening. If a potential participant is not eligible, screening will be discontinued once ineligibility is determined. If a potential participant has symptoms of an STI, RTI or UTI, they will be referred to local care and treatment services or (at sites with capacity and per site SOP) be given treatment according to the local standard of care.

If eligible, potential participants will return within 45 days for their Enrollment Visit. For women with a regular menstrual cycle, the Enrollment Visit (and Visit 6 if enrolled) will ideally be scheduled when the potential participant is not menstruating.

Note: Multiple visits may be conducted to complete all required screening procedures, including any procedures that need to be repeated (e.g., blood draw), if necessary.

Note: Potential participants who fail their first screening attempt may be re-screened once.

Table 1: Screening Visit

Screening Visit – Visit 1		
Component		**Procedures**
Administrative and Regulatory		• Obtain written informed consent for screening and enrollment (sites may split screening and enrollment consent if requested/required by IRB/IEC) • Assign a unique Participant Identification (PTID) number • Assess eligibility • Collect demographic information • Collect locator information • Provide reimbursement • Schedule next visit/contact*
Behavioral/Counseling		• HIV pre- and post-test counseling • HIV and STI risk reduction counseling • Protocol counseling (including contraception and restrictions around vaginal activity)
Clinical		• Collect medical and menstrual history • Collect concomitant medications • Perform full physical examination • Perform pelvic examination (including bimanual exam) • Provide available test results • Treat or prescribe treatment for RTI/UTI/STIs*
Laboratory	**Saliva**	• HIV test(s) (only at sites with CLIA certification)
	Urine	• Urine pregnancy test • Urine dipstick/culture*
	Blood	• HIV test(s) (not required for sites that conduct saliva testing) • Complete blood count (CBC) • Serum creatinine • AST/ALT • Syphilis serology
	Pelvic	• Nucleic acid amplification test (NAAT) for GC/CT/TV • Pap test^ • Saline/potassium hydroxide (KOH) wet mount for candidiasis and/or bacterial vaginosis (BV)*

*If indicated and/or per local standard of care; ^ if indicated (if participant is unable to provide documentation of a normal Pap test within 3 years prior to enrollment)

7.3 Follow-up Visits/Contacts – Stages 1 and 2

Within 45 days of the Screening Visit, willing and eligible participants will have their eligibility confirmed and be randomized (1:1) to IVR sequence at Enrollment (Visit 2). If not enrolled within 45 days, participants will need to be rescreened. Stage 1 (1st assigned IVR) and Stage 2 (2nd assigned IVR) are almost identical with a period of no fewer than 7 days and no more than 21 days of no product use between stages. Participants will be retested for pregnancy and HIV at the beginning of Stage 2 (Visit 6). Any participants testing positive for either will be withdrawn from the study.

7.3.1 Insertion Visits – Visit 2 (Enrollment/Stage 1 Day 0) and Visit 6 (Stage 2 Day 0)

Participants will be counselled to abstain from penetrative vaginal sex for the first 14 days of product use, and from use of intravaginal products and practices (see Section 6.7) for the full duration of study product use. Study staff will review instructional materials about the IVR with participants prior to insertion of the ring. Participants will be asked to provide a urine sample for a UPT, undergo HIV and STI screening and a pelvic examination, and at Visit 2 complete an interviewer-administered baseline acceptability questionnaire about the IVR. Participants will be given instructions regarding ring insertion and then asked to self-insert the ring at the study clinic. After insertion, ring placement will be checked by a clinical team member. If the participant is unable to self-insert the ring correctly after 2 attempts, a clinical team member will assist the participant. Participant attempts to insert the ring will be documented on the appropriate CRF.

Table 2: Insertion Visits – Visit 2 (Enrollment/Stage 1 Day 0) and Visit 6 (Stage 2 Day 0)

Insertion Visits – Visit 2 (Enrollment/Stage 1 Day 0) and Visit 6 (Stage 2 Day 0)	
Component	**Procedures**
Administrative and Regulatory	• Obtain written informed consent for enrollment (for sites that split screening and enrollment consent as requested/required by IRB/IEC) – at Visit 2 only • Assess and confirm eligibility – at Visit 2 only • Review/update locator information • Randomization – at Visit 2 only • Provide reimbursement • Schedule next visit/contact* (required at Visit 6)
Behavioral/Counseling	• HIV pre- and post-test counseling • HIV and STI risk reduction counseling • Protocol counseling (including restrictions regarding vaginal activity and product use) • Review instructional materials • Baseline behavioral questionnaire – at Visit 2 only • Post-insertion behavioral questionnaire • Social harms assessment

Insertion Visits – Visit 2 (Enrollment/Stage 1 Day 0) and Visit 6 (Stage 2 Day 0)		
Component		**Procedures**
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • AE assessment • Perform symptom-directed physical exam* • Perform pelvic examination with speculum before IVR insertion • Digital exam by clinical team member to confirm IVR placement • Clinician assessment of ring insertion experience (# insertion attempts, comfort) • Provide available test results • Treat or prescribe treatment for RTI/UTI/STIs*
Laboratory	**Saliva**	• HIV test(s) (only at sites with CLIA certification)
	Urine	• Urine pregnancy test • Urine dipstick/culture*
	Blood	• HIV test(s) (not required for sites that conduct saliva testing) • Plasma for archive – at Visit 2 only • CBC* • Serum creatinine* • AST/ALT*
	Pelvic	• Vaginal pH • Vaginal Gram stain • Vaginal swab(s) for microbiota • Vaginal swab(s) for archive – at Visit 2 only • NAAT for GC/CT/TV* • KOH wet mount for candidiasis and/or BV*
Study Product/Supplies		• Provide assigned IVR for self-insertion at clinic • Clinical team member insertion of IVR at clinic (only if participant fails 2 attempts)

*If indicated and/or per local standard of care

7.3.2 Telephone Contacts – Visits 3 and 7 (Day 7)

Approximately 7 days after the insertion of each IVR, a member of the study team will contact the study participant via telephone or short message service (SMS) to assess participant wellness, comfort with the ring, and any concerns. Participants who report AEs or express concerns may be asked to come in for an Interim Visit, if willing, to conduct additional counseling and/or testing as needed. Participants who prefer to complete these procedures in-person may elect to do so.

Table 3: Telephone Contacts – Visits 3 and 7 (Day 7)

Telephone Contacts – Visits 3 and 7 (Day 7)	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Provide reimbursement • Schedule next visit/contact
Behavioral/Counseling	• HIV and STI risk reduction counseling* • Protocol counseling* • Telephone-based brief questionnaire

Telephone Contacts – Visits 3 and 7 (Day 7)	
Component	**Procedures**
Clinical	• Review/update medical and menstrual history • Review/update concomitant medications • AE assessment • Provide available test results

*If indicated

7.3.3 Mid-point Clinic Visits – Visits 4 and 8 (Day 14)

Approximately 14 days after the insertion of each IVR, participants will come to the clinic for a safety evaluation for each ring to assess comfort with the ring and any concerns. Participants will be asked to undergo a pelvic examination and complete a brief questionnaire.

Table 4: Mid-point Clinic Visits – Visits 4 and 8 (Day 14)

Mid-point Clinic Visits – Visits 4 and 8 (Day 14)		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact
Behavioral/Counseling		• HIV pre- and post-test counseling* • HIV and STI risk reduction counseling* • Protocol counseling • Mid-point behavioral questionnaire • Social harms assessment
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • AE assessment • Perform symptom-directed physical exam* • Perform pelvic examination with speculum • Provide available test results • Treat or prescribe treatment for RTI/UTI/STIs*
Laboratory	**Saliva**	• HIV test(s) (only at sites with CLIA certification)*
	Urine	• Urine pregnancy test* • Urine dipstick/culture*
	Blood	• HIV test(s) (not required for sites that conduct saliva testing)* • CBC* • Serum creatinine* • AST/ALT*
	Pelvic	• Vaginal pH • Vaginal Gram stain • Vaginal swab(s) for microbiota • NAAT for GC/CT/TV* • KOH wet mount for candidiasis and/or BV*
Study Product/Supplies		• Offer male condoms

*If indicated and/or per local standard of care

7.3.4 Removal Visits – Visits 5 and 9 (Day 28)

Approximately 28 days after the insertion of each IVR, participants will come to the clinic for acceptability and safety evaluations for each ring. Participants will be given instructions regarding removal of the ring and then asked to remove the ring at the study clinic. If the participant is unable to remove the ring after 2 attempts, a clinical team member will assist the participant. Participants will be asked to provide a urine sample for a UPT and undergo HIV and STI screening (required at Visit 9), to undergo a pelvic examination, and complete an interviewer-administered follow-up acceptability questionnaire about the IVR and a social benefits assessment. Participant attempts to remove the ring will be documented on the appropriate CRF.

Visit 9 will constitute the Study Exit Visit (SEV). Visit 9 will also constitute the Early Termination Visit for participants who permanently discontinue study product use due to HIV acquisition, pregnancy, or other clinician-initiated reasons.

Table 5: Removal Visits – Visits 5 and 9 (Day 28)

Removal Visits – Visits 5 and 9 (Day 28)		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact – at Visit 5 only • Confirm permission to contact sexual partner for IDI (subset) and invite per site Sexual Partner Contact SOP – at Visit 9 only
Behavioral/Counseling		• HIV pre- and post-test counseling* (required at Visit 9) • HIV and STI risk reduction counseling* (required at Visit 9) • Protocol counseling (including regarding sexual partner IDI component and [at Visit 5] product use) • Follow-up behavioral questionnaire • Social harms assessment • Social benefits assessment • Conduct participant IDI (subset)** – ideally at or within 1 week of Visit 9/SEV but no later than 3 weeks after Visit 9/SEV
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • AE assessment • Perform symptom-directed physical exam* • Clinician assessment of ring removal experience (# removal attempts, comfort) • Perform pelvic examination with speculum after IVR removal • Provide available test results • Treat or prescribe treatment for RTI/UTI/STIs*
Laboratory	**Saliva**	• HIV test(s) (only at sites with CLIA certification)* (required at Visit 9)
	Urine	• Urine pregnancy test* (required at Visit 9) • Urine dipstick/culture*

Removal Visits – Visits 5 and 9 (Day 28)		
Component		**Procedures**
	Blood	• HIV test(s) (not required for sites that conduct saliva testing)* (required at Visit 9) • CBC* • Serum creatinine* • AST/ALT*
	Pelvic	• Vaginal pH • Vaginal Gram stain • Vaginal swab(s) for microbiota • NAAT for GC/CT/TV* • KOH wet mount for candidiasis and/or BV*
Study Product/Supplies		• Collect assigned IVR after removal at clinic • Clinical team member removal of IVR at clinic (only if participant fails 2 attempts) • Offer male condoms

*If indicated and/or per local standard of care
** See Section 7.6.2 for further details about the IDI subset

7.3.5 Sexual Partners – IDI Visit

Up to 30 sexual partners will be screened and enrolled to take part in a single IDI within 1 month of their participant partner's completion of product use (Visit 9 or SEV). Members of the protocol team and site teams will collaboratively determine which sexual partners to contact from among those that participants have given written permission during screening and enrollment for the study team to contact. Permission to contact sexual partners will be confirmed at Visit 9/SEV, and – if confirmed – sites will contact sexual partners according to site SOP and/or local IRB/IEC guidelines. Participants may change their decision about their sexual partners' involvement at any time during the study. Selection of sexual partners to invite for an IDI will be purposive so that characteristics/experiences of the enrolled study participant, order of IVR use, study site, and a breadth of perspectives and experiences are represented. Selection criteria and procedures are further described in the MATRIX-003 SSP Manual. See Section 7.6.2 for further details about the IDI subset.

Table 6: IDI Visit with Sexual Partner Subset

IDI Visit with Sexual Partner Subset – Screening and Enrollment Procedures	
Component	**Procedures**
Administrative and Regulatory	• Confirm eligibility • Obtain written informed consent • Assign a unique PTID Number • Collect demographic data • Collect locator information • Provide reimbursement for study visit
Behavioral	• Administer brief behavioral questionnaire (including social harms/benefits assessment) • Conduct sexual partner IDI – within 1 month of participant Visit 9

Multiple visits may be conducted to complete all required procedures, if necessary.

7.4 Follow-up Procedures for Participants Who Permanently Discontinue Study Product

7.4.1 Participants Who Become Infected with HIV

If a participant tests positive for HIV after the Enrollment Visit, the participant will be referred to local care and treatment services and (at sites with capacity to offer as standard of care and per site SOP) may return to the research clinic for additional testing, counseling, and other support services as needed. Continued study participation would be of no added benefit to the participant, thus follow-up visits and procedures will be discontinued, study product use will cease, and the participant will be considered terminated from the study. An Early Termination Visit will be conducted, if the participant is willing (see Section 7.3.4). Please reference the MATRIX-003 SSP Manual for additional details.

7.4.2 Participants Who Become Pregnant

If a participant becomes pregnant after the Enrollment Visit, the participant will be referred to local health care services and (at sites with capacity to offer as standard of care and per site SOP) may return to the research clinic for additional counseling services as needed. Continued study participation would be of no added benefit to the participant, thus study product use will cease, follow-up visits and procedures will be discontinued, and the participant will be considered terminated from the study. An Early Termination Visit will be conducted, if the participant is willing (see Section 7.3.4). Please reference the MATRIX-003 SSP Manual for additional details.

7.4.3 Participants Who Permanently Discontinue Study Product Use for Other Clinician-Initiated Reasons

Participants who permanently discontinue study product use for any clinician-initiated reason other than HIV infection or pregnancy may, after consultation with the PSRT and MATRIX-003 Management Team, have their remaining study follow-up visits and procedures discontinued. Participants will, however, be asked to complete an Early Termination Visit, if willing (see Section 7.3.4). In the event study follow-up is continued, participants will have the protocol-specified visits until completion of the current study stage. Sites should contact the PSRT and management team to determine whether the participant should be followed on study and what study procedures should be completed.

Participants who permanently discontinue study product use due to an adverse event (AE) must continue to be followed up in the study, if willing, until resolution (return to baseline) or stabilization of the AE is documented.

7.5 Interim Visits/Contacts

Interim visits/contacts (i.e., between regularly scheduled visits) may be performed as needed (e.g., participant reports an AE) at any time during the study, and any visit/contact procedures may be conducted as indicated. All interim contacts and visits will be documented in participants' study records. If a participant misses a visit, the participant can come to the clinic for an interim visit to make up certain missed visit procedures and specimen collections, and the instance(s) will

be documented as a protocol deviation. Refer to the MATRIX-003 SSP Manual for additional details.

7.6 Behavioral Evaluations

The study will address questions related to the primary and exploratory objectives of acceptability, exploratory objective of social harms and social benefits, and both participants' and sexual partners' attitudes towards and experiences with the IVR. The study will assess ring use facilitators and challenges experienced by participants, from the perspectives of both participants and a subset of sexual partners. The study will also explore participants' and sexual partners' views on acceptable approaches to support study product adherence. These questions will be assessed via behavioral questionnaires and IDIs conducted by trained interviewers/facilitators. In addition, the study aims to gain further insight on:

- Product insertion and removal
- Attitudes towards and experiences with using the IVR
- Previous IVR use experience
- Perspectives on any changes in vaginal environment
- Comparisons between the two IVRs and comparisons to existing HIV prevention options
- Factors related to future willingness to use/recommend the IVR
- Sexual partner attitudes towards and experiences with the IVR, and their perspective of participant's attitudes and experiences

Additional questions and probes will be designed to delve further into the social and cultural norms that may play a role more broadly in product use.

Table 7 outlines a summary of the assessment methods that will be used and the specific components of acceptability that will be assessed, informed by previous work and the Theoretical Framework of Acceptability (TFA) as presented in Ortblad et. al. [9]

Table 7: Summary of behavioral assessments and alignment with TFA

Assessments and Timepoints	Acceptability components measured
Baseline questionnaire (Visit 2)	Affective attitude, burden, opportunity costs, barriers/benefits
Telephone-based brief questionnaires (Visits 3 and 7)	N/A
Mid-point questionnaires (Visits 4 and 8)	N/A
Follow-up questionnaires (Visits 5 and 9)	Affective attitude, burden, opportunity costs, overall satisfaction, usability, appropriateness, preferences, perceived barriers/benefits
Social harms assessments (All clinic visits after Screening)	N/A
Social benefits assessments (Visits 5 and 9)	N/A

Assessments and Timepoints	Acceptability components measured
Participant IDI (Ideally at or within 1 week of Visit 9/SEV but no later than 3 weeks after SEV)	Affective attitude, burden, satisfaction, usability, appropriateness, perceived barriers/benefits
Sexual partner IDI (Within 1 month of Visit 9/SEV)	Affective attitude, burden, satisfaction, usability, appropriateness, perceived barriers/benefits

7.6.1 Quantitative Behavioral Assessments

Behavioral questionnaires at enrollment and during follow-up will measure key dimensions of acceptability pertinent to the IVR in its current phase of development alongside women's experiences in using the ring during the study. In addition, behavioral questionnaires will measure vaginal practices, contraceptive use, HIV prevention behaviors, sexual behavior and relationship factors, social harms, and social benefits. These questionnaires will be used to assess factors correlated with placebo IVR acceptability and use experiences. Additionally, quantitative questionnaire data will be complemented by data captured through structured SMS/phone visits, and through IDIs with subsets of participants and sexual partners.

7.6.2 Qualitative Behavioral Assessments

Two sets of IDIs will be completed. The first will be conducted with a subset (up to 30, approximately 6 per site) of participant ring users who will be purposively selected and invited to complete an IDI after their scheduled removal of the second ring. The IDI will ideally take place at or within 1 week of Visit 9/SEV but no later than 3 weeks after Visit 9/SEV. Selection of participant ring users to invite for an IDI will be purposive so that order of IVR use, study site, and a breadth of perspectives and experiences are represented. Selection criteria and procedures are further described in the MATRIX-003 SSP Manual. Additionally, a subset of sexual partners of participants (up to 30, approximately 6 per site) will be purposively selected to participate in an IDI, which will take place within approximately 1 month of receipt of confirmation of permission to contact the sexual partner at Visit 9/SEV. We will explore participant experiences using the IVR, acceptability of different attributes of the ring, and social factors influential to attitudes toward the IVR as a future HIV and/or dual purpose (HIV and pregnancy) prevention option. We will also explore sexual partner views on the IVR and their perceptions of and experience with the IVR during sexual activity. IDIs will be conducted separately with participants and sexual partners to assess these topics. IDIs will include, but not be limited to, the following topics:

- Descriptions of ring insertion practices
- Main challenge(s) encountered with ring use, especially during sex
- Potential changes to the ring
- Other factors (e.g., situational, relationship, trial-specific, social/cultural/economic, sex and menstruation related, vaginal practices, previous IVR use) influencing ring acceptability and use experience
- Sexual partner attitudes towards and experiences with the IVR, and their perspective of participant's attitudes and experiences
- Perspectives and attitudes regarding monthly IVR use for HIV prevention and/or as a dual purpose IVR for HIV and pregnancy prevention

The IDIs with sexual partners will also include the following discussion topics:

- Knowledge/understanding of MATRIX 003 and the study product
- Experiences of sex with clinical study participant during the time they were using study product

Semi-structured IDI guides will be developed by qualified social scientists and administered by trained interviewers. Guides will contain key research questions relating to the main topics of interest and suggested probes. Interviews and discussion sessions will be audio-recorded and transcribed.

7.7 Protocol and Product Adherence Counseling

Counseling will be provided by different site staff than those conducting the behavioral questionnaires when feasible, in accordance with standard study methods and as specified in site SOPs. Contraception counseling will be provided to participants of childbearing potential at Screening and, if indicated, at subsequent clinic visits. Protocol adherence counseling will be provided at all clinic visits beginning at the Screening Visit. Participants will receive study product counseling upon enrollment into the study and at subsequent follow-up visits as appropriate to the visit. Study staff will document administration of study product (at Visits 2 and 6) and that the counseling was provided. Counseling also will include reminders regarding concomitant medication, sexual activity, intravaginal product use and practices, and behavioral restrictions during study participation (as specified in Section 6.7).

7.8 Clinical Evaluations and Procedures

Physical Examination and Medical History

The full physical examination will include the following assessments:

- Vital signs
    - Blood pressure
- Measurements of weight and height
- General appearance
- Cardiac exam
- Respiratory exam
- Abdomen

Participants will be asked about medications/therapies at every visit, including Screening. Study staff will ask about adverse events at all visits beginning at Enrollment. A full physical examination will be completed by a clinician at Screening. Thereafter, a directed physical examination will be performed to assess any complaints or symptoms with which the participant presents at the follow-up visits as clinically indicated.

Pelvic Examination (at all regularly scheduled clinic visits and as needed for AE assessment)

- Pelvic exams will be performed using visual inspection of external genitalia.
- Speculum examination for visualization of the cervix and vagina.
- Bimanual exam may be performed as needed (required at Screening Visit).
- Digital exam to assess ring placement (required at Insertion Visits).
- Cervicovaginal fluid (CVF) will be collected using swabs to characterize the microbiome and assess for STI as indicated in Appendix I.

Additional clinical assessments/procedures may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam/procedure.

7.9 Laboratory Evaluations

Local Laboratory

- Saliva (only at sites with CLIA certification)
  - HIV test(s)
- Urine
  - Urine pregnancy test
  - Urine dipstick/culture (as indicated and/or per local standard of care)

- Blood
  - HIV test(s) (not required for sites that conduct saliva testing)
  - CBC
  - Serum creatinine
  - AST/ALT
  - Syphilis serology

- Pelvic
  - NAAT for GC/CT/TV (at sites with capacity)
  - Pap test (if indicated [if participant is unable to provide documentation of a normal Pap test within 3 years prior to enrollment])
  - Vaginal pH
  - KOH wet mount for candidiasis and/or BV (if indicated)

Designated Laboratory

- Blood
  - Plasma for archive

- CVF
  - NAAT for GC/CT/TV (at sites without capacity)
  - Gram stain for Nugent score
  - Microbiota (Quantitative PCR)
  - Vaginal swab(s) for archive

Only Local Laboratory test results will be provided to the participant. Once all required study analyses of collected specimens are complete, any remaining samples may be shipped to OCIS for use in study-related quality assurance and quality control testing. If study samples will be used for assay validation or proficiency testing that is not study related, all participant identifiers (PTID) will be removed from the samples prior to use. Specimens obtained from participants who do not consent to long term storage will not be used for assay validation or proficiency testing purposes.

7.10 Specimen Management

Study sites will adhere to the standards of good clinical laboratory practice, in accordance with the MATRIX-003 SSP Manual and site SOPs for proper collection, processing, labeling, transport, and storage of specimens. 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, or out of range and the site IoR/designee determines reasonable to repeat, the site is permitted to re-draw specimens. No genetic testing (limited or genome-wide) is planned on leftover samples that are stored for the purposes of future research.

7.11 Laboratory Oversight

All laboratories participating in this study will adhere to MATRIX's Laboratory Policy (www.matrix4prevention.org).

7.12 Biohazard Containment

As the acquisition 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 Centers for Disease Control (CDC), National Institutes of Health (NIH), and other applicable national regulatory authorities. All biological specimens will be transported using packaging mandated by Code of Federal Regulations (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. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

Site IoRs/designees 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 Co-Chairs, Protocol Safety Physician, Clinical Research Manager(s) (CRM), and OCIS representatives will serve as the PSRT. The Clinical Data Manager(s) (CDM) prepares routine AE and clinical data reports for review by the PSRT, which meets via conference call approximately once per month or more frequently as needed throughout the period of study implementation to review safety data, discuss product use management, and address any potential safety concerns.

8.2 Clinical Data and Safety Review

A multi-tiered safety review process will be followed for the duration of this study. The site IoRs/designees 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 through a series of routine reviews conducted by the PSRT and (if applicable) study sponsors. Additional reviews may be conducted at each of these levels as dictated by the occurrence of certain events.

The CDM(s) will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. To ensure prompt review of AEs of concern (e.g., serious adverse events [SAE] and Related Grade 3+ AEs), such AE reports submitted in the clinical database will be forwarded to the PSRT for review within 72 hours of entry.

The PSRT will meet approximately every month, or as needed, via conference call to review clinical data reports generated by the CDM(s). The content, format and frequency of the clinical data reports will be agreed upon by the PSRT and the CDM(s) in advance of study implementation. 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 MATRIX representing expertise in the fields of microbicides, biostatistics, HIV acquisition and medical ethics may be invited to join the PSRT safety review. A recommendation to pause or 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.

The Independent Safety Physician (ISP) will review participant safety data as part of their regular reviews (see Section 10.6.1), since no Data and Safety Monitoring Board (DSMB) oversight is planned for MATRIX-003. These reviews will take place approximately every 3 months, or as needed. The ISP will be an independent investigator(s) with no interest (financial or otherwise) in the outcomes of this study. At the time of these reviews, or at any other time, the ISP or PSRT may convene a panel (composed of the ISP, PSRT and protocol statistician[s]) to review study findings. This panel may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. If at any time a decision is made to discontinue enrollment and/or study product use in all participants, OCIS will notify USAID and (as necessary) relevant regulatory authorities, and site IoRs/designees will notify the responsible IRBs/IECs expeditiously per local guidelines.

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 administered an investigational product and which does not necessarily have a causal relationship with the investigational product. 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, whether or not considered related to the product. This definition is applied to all study participants and is applied beginning at the time of enrollment (i.e., once a participant is randomized). The term "investigational products" for this study refers to the two placebo IVRs A and B.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience. In cases of potentially life-threatening

events, participants will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where a 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 untoward medical occurrences may be obtained and required data elements will be recorded on study CRF. All participants reporting an untoward medical occurrence will be followed clinically until the occurrence resolves (returns to baseline) or stabilizes.

Study site staff will document in source documents and in the study database all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addenda 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007]). Asymptomatic BV and asymptomatic candidiasis will not be reported as AEs but will be captured on the appropriate study CRF. Bleeding at the time of speculum insertion/removal and/or cervicovaginal specimen collection that is judged by the clinician to be within the range of normally anticipated for that procedure will not be reported as an AE. Contraception related bleeding that is judged by the clinician to be within the expected range will also not be reportable as an AE.

For any SAEs that are continuing at a participant's study exit visit, the IoR/designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the SAE must be re-assessed by study staff 30 days after the participant's study exit visit; additional evaluations also may take place at the discretion of the IoR/designee.

The same approach must be taken for any AEs that are found to have increased in severity to Grade 3 or higher at the study exit visit. For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment should be re-assessed at least once within the 30 days after the study end date.

Grade 1 and Grade 2 AEs classified as "not related" to study product or procedures no longer require follow up by the study team after the participant discontinues study participation, either due to completion or withdrawal, provided the participant is given the appropriate outside referrals for follow-up.

The PSRT may advise study staff as to whether any additional follow-up may be indicated on a case-by-case basis. For AEs that are re-assessed after study exit, information on the status of the AE at the time of re-assessment will be recorded in source documents only — no updates will be made to AE CRFs based on the re-assessments.

8.3.2 Serious Adverse Events

As per the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Guidance (ICH E6; https://www.ich.org/page/efficacy-guidelines), SAEs are defined as AEs occurring at any dose that:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Per ICH SAE definition, hospitalization itself is not an AE, but is an outcome of the event. Thus, hospitalization in the absence of an AE is not regarded as an AE. The following are examples of hospitalization that are not considered to be AEs:
  - Protocol-specified admission (e.g., for procedure required by study protocol)
  - Admission for treatment of target disease of the study, or for pre-existing condition (unless it is worsening or increases in frequency of hospital admissions as judged by the clinical investigator)
  - Diagnostic admission (e.g., for a work-up of an existing condition such as persistent pretreatment lab abnormality)
  - Administrative admission (e.g., for annual physical)
  - Social admission (e.g., placement for lack of place to sleep)
  - Elective admission (e.g., for elective surgery)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.3.3 Adverse Event Relationship to Study Product

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. 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 Pregnancy and Infant Outcomes

Pregnant women are excluded from this study. A participant who becomes pregnant during the study will have study product discontinued and will be terminated from the study. Please see Section 9.7 for additional details.

8.5 Regulatory Requirements

AEs reported on CRFs will be included in reports to the applicable national drug regulatory authorities (DRA) in accordance with DRA requirements. Site IoRs/designees also will submit AE information and any other relevant safety information to their IRB/IEC in accordance with IRB/IEC requirements.

8.6 Social Harms Reporting

Although study sites will 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. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to the PSRT and responsible site IRB/IEC according to their individual requirements. 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 (CABs) in exploring the social context surrounding instances of social harm. To mitigate one possible source of social harms, each site will carefully explain to eligible participants the potential consequences of enrolling their sexual partner (e.g., disclosure of study involvement and/or IVR use) prior to contacting the partner.

9 CLINICAL MANAGEMENT

Guidelines for clinical management and permanent discontinuation of study product are outlined in this section. In general, the IoR/designee has the discretion to hold study product at any time if s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. Unless otherwise specified below, the IoR/designee should immediately consult the PSRT for further guidance on resuming study product during the second product use period (if product discontinuation occurs during the first product use period) or progressing to permanent discontinuation of study product and early study termination. The IoR/designee will document all permanent discontinuations on applicable CRFs.

9.1 Grading System

AE severity grading is described in Section 8.3.1.

9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

9.3 General Criteria for Permanent Discontinuation of Study Product

A participant will be permanently discontinued from product use by the IoR/designee for any of the following reasons:

- A reactive rapid HIV test.
- Pregnancy or breastfeeding.
- Allergic reaction to the study product(s)/drug(s).
- Reported use of or need for PrEP or PEP. Participants who experience a known or potential HIV exposure during study participation or have a recognized risk of exposure and thus need PEP or PrEP will have study product permanently discontinued and will be referred for PEP or PrEP initiation. Those who need PEP will be encouraged to start it as quickly as

possible and within 72 hours of potential exposure. Since continued study follow-up would be of no benefit following permanent discontinuation of study product use, these participants will be exited from the study.
- Non-therapeutic injection drug use.
- Participant develops a Grade 3 Related or any Grade 4 AE.
- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee.

The IoR/designee must consult the PSRT on all discontinuations instituted at their discretion for further guidance on resuming product use or progressing to permanent discontinuation of study product and early study termination.

9.4 Permanent Discontinuation in Response to Observed Adverse Events

Grades 1-3 Unrelated
Unless specifically addressed in Section 9.5 below, a participant who develops a Grade 1-2 AE, regardless of relationship to study product, may continue product use. Participants who develop a Grade 3 AE that is judged by the IoR/designee to be unrelated to study product may also continue product use. If the IoR/designee opts to discontinue study product, the PSRT must be notified.

Grade 3 Related and Any Grade 4
Study product must be permanently discontinued and the PSRT notified for participants who develop a Grade 3 Related AE or a Grade 4 AE.

9.5 Other Clinical Findings

A thorough evaluation of genital complaints is expected in the context of this study; however, syndromic management of genital symptoms is acceptable while awaiting laboratory results if such practice is in line with the local standards of care. Observed single dose treatment should be provided whenever possible, per clinician discretion. When clinically appropriate, investigators should use oral or parenteral medications when at all possible.

Product use need not be held in the event of an STI/RTI requiring treatment, unless other permanent discontinuation guidelines apply. Should the IoR/designee determine that a permanent discontinuation is warranted due to an STI or RTI, consultation with the PSRT is required. The IoR/designee should manage STI/RTI per local guidelines or current WHO guidelines, available at http://www.who.int/en/. Test for cure is not required after treatment of asymptomatic STIs.

If a suspected finding is reported by the participant between scheduled visits, an interim visit may be scheduled at the discretion of the site investigator.

9.6 HIV Infection

HIV testing will be performed at designated study visits. Potential participants who test positive for HIV during Screening or Enrollment will not be enrolled in the study but will be referred to

HIV care and management. Enrolled participants who test positive for HIV will have study product and all follow-up visits discontinued, and will be considered terminated from the study as per Section 7.4.1. Participants identified as infected with HIV are managed or referred for management according to the local standard of care. Guidance regarding management and referral for participants confirmed to be HIV-positive can be found in Section 13.10. Sites will not be responsible for paying for HIV-related care.

9.7 Pregnancy

Pregnancy testing will be performed at designated study visits and participants will be encouraged to report all signs or symptoms of pregnancy to study staff. The IoR/designee will counsel any participant who becomes pregnant according to site SOPs. A participant who becomes pregnant during the course of the study will have study product and all follow-up visits discontinued, and will be considered terminated from the study as per Section 7.4.2. The IoR/designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

9.8 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. IoRs/designees also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Sites must notify the PSRT immediately of any such instances. Participants also may be withdrawn if OCIS, USAID, MATRIX, government or regulatory authorities, including the Office for Human Research Protections (OHRP), or site IRB/IEC/DRA terminate the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up (see details regarding the Early Termination Visit in Section 7.3.4). Study staff members will record the reason(s) for all withdrawals in participants' study records.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

MATRIX-003 is a randomized, partially blinded, crossover trial with 2 arms, each assigned a different sequence of placebo IVR (A then B or B then A) to use for approximately 28 days each, with 7-21 days between the two product use periods. The primary objective of MATRIX-003 is to compare the acceptability of two placebo IVRs (A and B) with the overall goal of drawing on findings across primary, secondary and exploratory endpoints to inform design of a future drug-loaded IVR.

10.2 Study Endpoints

Primary endpoints

Acceptability

- Proportion of participants preferring each placebo IVR (A or B).

- Mean rating of overall satisfaction with using each placebo IVR.

Secondary endpoint

Safety

- Proportion of participants with genitourinary Grade 2 or higher Adverse Events deemed related to each study product.

Exploratory endpoints

Participant acceptability, attitudes and experiences

- Participant responses to quantitative (i.e., questionnaires) and qualitative (i.e., IDI) assessments. Multiple dimensions will be explored, including:
    - Past experience with IVRs, if any (e.g., Nuvaring, dapivirine IVR)
    - Insertion/removal techniques
    - Ease of insertion/removal
    - Comfort during use
    - Experience with/awareness of inserted IVR
    - Spontaneous expulsions and voluntary removals
    - Experience of IVR use during vaginal sex or menses
    - Perceived benefits and concerns/challenges with the IVR as a future HIV and/or dual purpose (HIV and pregnancy) prevention option
    - Perceptions of sexual partner(s)

Sexual partner attitudes and experiences

- Sexual partner responses during IDI related to:
    - IVR attributes, including acceptability and preferences
    - Perception of participant's experience using the IVR during the study
    - Physical sensation of the participant's IVR use during sex (as relevant)
    - Perceived benefits and concerns/challenges with the IVR as a future HIV and/or dual purpose (HIV and pregnancy) prevention option

Vaginal microbiota

- Change from baseline in composition of vaginal microbiome following each placebo IVR use.
- Change from baseline in Nugent score following each placebo IVR use.

Social harms and social benefits

- Participant or sexual partner self-report of social harms (i.e., non-clinical adverse consequences of study participation or product use that may manifest in social, psychological, or physical ways).
- Participant or sexual partner self-report of social benefits (e.g., positive consequences of product use disclosure, self-confidence, improved communication with intimate partner) resulting from IVR use and/or study participation.

10.3 Sample Size and Power Calculations

MATRIX-003 will enroll approximately 100 participants, with approximately 20 participants per site. Participants will be randomized to the 2 crossover sequences in a 1:1 ratio, allocating 50 women per IVR sequence. In light of the short study duration and the teams' previous experiences conducting similar research with the study's target population, we anticipate 5-10% LTFU. Therefore, we expect approximately 90 participants will complete the study. A subset of up to 30 study participants will complete an IDI after the 2nd period of IVR use. We will enroll up to 30 sexual partners to complete an IDI after the participant completes the 2nd period of IVR use.

Note: Replacement participants will be considered in consultation with study leadership if LTFU is higher than expected (i.e., >10%).

Table 8 presents the range of potential detectable effect sizes reflecting differences in primary and secondary endpoints of the two study products assuming 90% power, two-sided α=0.05, varying standard deviations or marginal probabilities, a sample size of 100, and 10% LTFU.

The primary acceptability endpoints will be measured at Visits 5 (satisfaction) and 9 (satisfaction and preference). Secondary endpoints will be assessed cumulatively to calculate an overall proportion experiencing the outcome (e.g., AE). Exploratory acceptability endpoints will be collected at Visits 5 and 9. In addition, interim data on experience using the placebo IVR will be collected 1 and 2 weeks after each ring insertion.

Table 8: Range of potential effect sizes for each endpoint

Continuous outcomes: effect size is difference in means (satisfaction) and difference in proportion (preference)			
Endpoint	Endpoint type	Standard deviation	Minimum detectable difference
Overall satisfaction (Likert scale 1-10)	Primary: Acceptability	4.3-5.75	1.5-2.0
Preference between Ring A and Ring B	Primary: Acceptability	p_a: 0.40-0.50	p_b: 0.23-0.33
Binary outcomes: effect size is risk difference			
Endpoint	Endpoint type	Prevalence	Minimum detectable difference
Adverse events	Secondary: Safety	0.10 – 0.30	0.20 - 0.25

Qualitative data collection

Participant experiences: Up to 30 study participants will be purposively selected and invited to complete an IDI ideally at or within 1 week of Visit 9 but no later than 3 weeks after Visit 9.

Sexual partner attitudes and experiences: Up to 30 sexual partners will be invited to provide insights into their attitudes and experiences through IDIs.

An overall sample of 30 IDIs per group is estimated to provide sufficient opportunity to reach saturation in the qualitative data on key topics. An estimated 6 IDIs per group per site is expected to provide sufficient opportunity for any variation on key topics based on geographic location. Participants will be purposively selected for invitation to an IDI based on IVR sequence assignment (A then B or vice versa) and other characteristics or experiences while using the study

product. Sexual partners will be purposively selected for invitation to the IDI based on permission provided by the clinical study participant, key experiences reported by the clinical study participant, and partner interest/availability.

10.4 Randomization Procedures

Participants will be randomized in a 1:1 ratio to the two IVR sequences (IVR A followed by IVR B or IVR B followed by IVR A), stratified by study site. The randomization scheme and procedures will be generated and maintained by the MWRI statistical team that will conduct and coordinate the randomization procedures.

10.5 Blinding and Unblinding

Only the site behavioral team and the participants will be blinded. Clinical site staff will be allowed to know the participant's study assignment. Blinding will be maintained until behavioral assessments have been completed.

10.6 Participant Accrual, Follow-up and Retention

We anticipate participant accrual to take place over a period of approximately 3-5 months. Each participant enrolled will be followed for a period of approximately 9-11 weeks.

10.7 Data and Safety Monitoring and Analysis

10.7.1 Study Monitoring

No DSMB oversight is planned for this study. The MATRIX Clinical Trials Hub will conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and secondary endpoint assessments, and study or laboratory issues. The ISP will conduct interim review of incident AEs. These reviews will take place approximately every 3 months, or as needed. At the time of these reviews, or at any other time, the ISP or PSRT may convene a panel (composed of the ISP, PSRT and protocol statistician[s]) to review study findings. This panel may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. Safety monitoring will be done by the PSRT.

10.7.2 Primary Analysis(es)

All participants randomized into the study who complete Visit 5 will be included in the 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). Overall and within-treatment group 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 using formal testing to assess endpoint differences between users of Ring A or Ring B, the following methods will be used: for binomial response variables, chi-square tests and

logistic regression (or exact testing methods); for continuous variables, t-tests and linear regression or nonparametric methods if data are non-Normal.

To assess the adequacy of the randomization, participants in each arm will be compared for baseline characteristics including demographics and laboratory measurements using descriptive statistics. Due to the small sample size, formal comparisons will not be done.

We will calculate overall estimates for mean satisfaction rating at Visits 5 and 9 (Likert 10-point scale) to permit comparisons between Ring A and Ring B. We will test for difference in mean overall satisfaction rating (Likert 10-point scale) between Ring A and Ring B using a two-sided t-test (primary endpoint), adjusting for randomization sequence. A nonparametric test will be used if normality assumptions are not met. Analyses will examine sociodemographic and behavioral correlates of acceptability rating (i.e., satisfaction) using linear regression models with robust standard errors. We will calculate the proportion preferring each ring and explore properties and usability characteristics associated with preferences.

10.7.3 Secondary and Exploratory Analyses

Safety

All visits in which participants have been exposed to the study products will be included in the analysis of safety. To assess genitourinary safety, the number and percentages of participants experiencing each safety endpoint (see Section 10.2) will be tabulated by study product A vs. B as well as the total number of safety endpoints experienced in each arm. Each participant will contribute once in each category (i.e., only for the highest severity AE for each participant) for the calculation of event rates. Exact binomial confidence intervals will be calculated for each safety endpoint for each arm.

Exploratory Acceptability Assessment

In addressing the exploratory acceptability objective, we will compare ratings of acceptability measures between rings A and B that reflect distinct components of the acceptability framework and related dimensions. Acceptability endpoints will be summarized by assessment time point (Visits 2, 5, and 9) using descriptive statistics (e.g., frequencies, means), as appropriate. For example, we will examine the level of interest in future use of the ring as an HIV prevention option overall and by each ring type, adjusting for randomization sequence. We will also examine responses over time (e.g., ratings of anticipated comfort prior to initial ring insertion, after first month of ring use, and after second month of ring use), assessing whether they changed with increased experience with product insertion. In addition, analyses will examine sociodemographic and behavioral correlates of acceptability endpoints using linear regression models with robust standard errors (for rating outcomes) and using multivariable logistic regression for dichotomous outcomes such as willingness to use (e.g., disinterest in future use).

Participant and Sexual Partner Attitudes and Experiences

Qualitative data will be audio-recorded, processed, and coded for qualitative analyses, using Dedoose or a similar qualitative software. Data coding will be used as a primary analytical approach for data reduction, that is, to summarize, extract meaning, and condense the data.[10, 11] Transcripts will be coded first through descriptive coding for key themes and topics, using a preliminary codebook.[12] Additional codes will be identified through an iterative process of reading the textual data to identify emergent themes, and the codebook will be modified

accordingly. In addition to descriptive codes, inductive codes, which achieve a greater level of abstraction, will be used to start linking themes and topics together in order to explore the relationship between socio-contextual factors and product use experiences.[11] Whenever possible, we will also compare study sites and explore differences or similarities due to different socioeconomic, cultural and geographical contexts. The analysis will be done by the investigative team, working interactively through emails, and regular videoconference or face-to-face meetings. The findings and interpretations of the data will be critically discussed until there is group consensus on the dominant themes and meanings contained in the data.[13]

10.7.4 Missing Data

In any situation with missing data, appropriate secondary analyses will be performed to adjust for variables that may be related to the missingness mechanism. If missing data rates are higher than 10%, covariates that are related to missingness in likelihood-based regression models will be included. Sensitivity analyses to assess the potential impact of the missing data will also be performed. These analyses will include imputing the data under the most extreme scenarios of information missingness, such as assuming everyone missing has an extreme value of the missing variable, and less informative imputation approaches.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Data collection tools will be developed by the CDM(s) in conjunction with the protocol team. Quality control and data integrity are managed manually and systematically with reports and queries routinely generated and provided by the CDM(s) to the study sites for verification and resolution. As part of the study activation process, each study site will identify all CRFs to be used as source documents. Study CRF data will be entered and managed using REDCap, a data management system compliant with the International Council on Harmonization (ICH) Good Clinical Practices (GCP) and US CFR guidelines for electronic data capture.

Transcriptions of interviews will be generated in the field and electronically transferred to RTI International using a secure File Transfer Protocol site, where they will be uploaded and managed using a qualitative software package. RTI International will act as a hub and manage all qualitative data for the study. A convention for file naming will be developed, and all data will be labeled according to this process. RTI International will save all versions of all files on a secure, password-protected server in the US.

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with MATRIX's Good Documentation Practice (GDP) guidelines (www.matrix4prevention.org).

Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations, IoRs/designees will maintain all study

documentation for at least three years after completion of the study. IoRs/designees may need to maintain study documentation for longer if required by their local or country regulations.

Study records must be maintained on site for the entire period of study implementation. Thereafter, instructions for record storage will be provided by OCIS. No study records may be moved to an off-site location or destroyed prior to receiving approval from OCIS.

11.3 Quality Control and Quality Assurance

Study sites will conduct quality control and quality assurance procedures in accordance with MATRIX's Quality Management Plan (www.matrix4prevention.org).

12 CLINICAL SITE MONITORING

Study monitoring will be carried out by the African Clinical Research Organisation (ACRO) for the African sites and by the University of Pittsburgh Education and Compliance Support for Human Subject Research (ECS-HSR) for the US site. Study monitors will do the following:

- Review informed consent forms, procedures, and documentation.
- Assess compliance with the study protocol, Good Clinical Practices (GCP) guidelines, and applicable regulatory requirements (US and non-US), including US Code of Federal Regulations (CFR) Title 45 Part 46 and Title 2 Parts 200 and 225.
- Perform source document verification to ensure the accuracy and completeness of study data.
- Verify proper collection and storage of biological specimens.
- Verify proper storage, dispensing, and accountability of investigational study products.
- Assess implementation and documentation of internal site quality management procedures.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose. Remote monitoring visits may be performed in place of or in addition to onsite visits to ensure the safety of study participants and data integrity.

For on-site visits, the IoR/designee will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of MATRIX, OCIS, USAID, OHRP, IRB/IEC and other local, US, or international regulatory authorities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

Site investigators will make efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, IoRs/designees will have obtained IRB/IEC approval. IoRs/designees will permit audits by USAID, OHRP, MATRIX, IRB/IEC, and other local, US, or international regulatory authorities or any of their appointed agents.

Changes to this protocol may be implemented by investigators prior to IRB/IEC approval, if those changes are required to eliminate apparent immediate hazards to the study participant; see 45 CFR 46.108(a)(3)(iii) under the 2018 Requirements (https://www.ecfr.gov). These changes must be documented as Protocol Deviations and reported to the Protocol Team and IRB/IEC as soon as possible; see ICH E6(R2), Good Clinical Practice, Section 4.5.4 (https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/ich-guidance-documents). In the event of a public health emergency, investigators should adhere to the recommendations of their local institutions, IRB/IEC and local health departments. When conflicts exist between local directives, MATRIX, Protocol Team and/or USAID policies or guidance, sites should follow the requirement that is most protective of study participants and site staff.

13.1 Institutional Review Boards/Ethics Committees

Each participating institution will be responsible for assuring that this protocol, the associated site-specific informed consent forms (ICF), and study-related documents (such as participant education and recruitment materials) are reviewed by the IRB/IEC responsible for oversight of research conducted at their study site and applicable national DRA. Any amendments to the protocol must be approved by the responsible IRBs/IECs and (if applicable) national DRA prior to implementation.

Subsequent to the initial review and approval, the responsible IRBs/IECs must review the study at least annually. Each IoR/designee will make safety and progress reports to their IRB/IEC and (if applicable) to their national DRA at least annually and within 3 months after study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. In addition, the results of all safety reviews of the study will be provided to the IRBs/IECs and (if applicable) national DRA.

13.2 Protocol Implementation

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent forms approved, as appropriate, by their local IRB/IEC and any other applicable regulatory entities. Upon receiving final approval, sites will submit copies of all relevant protocol/amendment documents (i.e., IRB/IEC approval letters with a detailed list of approved documents, approved ICF documents, etc.) to the MATRIX Clinical Trials Hub Regulatory team.

The MATRIX CRM(s) will review the submitted document packet to ensure receipt of all required protocol/amendment documents prior to study activation at the sites. Sites will receive a Study Activation Notification from the MATRIX CRM(s) that indicates successful completion of the

protocol readiness process. A copy of the Study Activation Notification should be retained in the site's regulatory files.

Upon receiving final IRB/IEC and any other applicable approval(s) for an amendment, activated sites should implement the amendment immediately but are still required to submit copies of all relevant amendment documents to the MATRIX Clinical Trials Hub Regulatory team.

13.3 Study Coordination

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chair(s) and Protocol Team representatives from MATRIX, OCIS, and USAID. Study implementation will also be guided by a common SSP Manual that provides further instructions and operational guidance on conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management, and reporting; dispensing study products and documenting product accountability; and other study operations. Standardized study-specific training will be provided to sites by the MATRIX CRM(s) and other designated members of the Protocol Team.

Close coordination between protocol team members is necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. The PSRT will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team as well as the ISP and the MATRIX Clinical Trials Hub.

13.4 Risk Benefit Statement

13.4.1 Risks

General

HIV and STI testing may make the participant feel anxious regardless of the test results. Counseling and testing for HIV and other STIs may cause worry and discomfort by learning more about risk for those conditions. A participant may become worried, sad or depressed after finding out that they have HIV or an STI. Trained study staff will be available to help participants deal with these feelings.

Finding out their HIV status could also cause problems between participants and their partners, family, or friends. Participants also could have problems in their partner relationships associated with study-required abstinence. The study staff will provide counselling and referral for support and/or care where required.

Participation in clinical research includes the risk of loss of confidentiality and discomfort with the personal nature of questions when discussing sexual behaviors. Study staff will make every effort to protect participant privacy and confidentiality during the study visits. Visits will take place in private, however, it is possible that others may learn of an individual’s study participation and, because of this, may treat them unfairly or discriminate against them.

Phlebotomy
Participants may feel discomfort or pain when their blood is drawn. They may feel dizzy or faint or develop a bruise, swelling, small clot, or in rare cases, an infection where the needle goes into their arm.

Pelvic Examination and Procedures
Participants may feel discomfort, pain or pressure during the exam and when specimens are collected. They may have a small amount of vaginal bleeding or spotting which should stop shortly after the exam.

CVF Collection
Collection of CVF may cause discomfort or pressure in the vagina or genital area.

Risks Associated with Vaginal Rings
Use of the study product is minimal risk given that the ring does not release any drug. Even so, some participants may experience discomfort while the ring is in place. It is possible that a participant could have an allergic reaction to the study product. Symptoms of an allergic reaction include rash or other irritation, itching, joint pain, or difficulty in breathing.

Social Harms
Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that involvement in the study could become known to others and that social harms – non-medical adverse consequences – may result. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities.

13.4.2 Benefits

Participants in this study may experience no direct benefit. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of safe and effective interventions to prevent HIV acquisition and transmission. Participants also may appreciate the opportunity to contribute to the field of HIV prevention.

Participants will receive HIV and STI risk reduction counseling, HIV and STI testing, and physical and pelvic exams. Participants will be provided STI treatment free of charge, and referrals may be provided if needed. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Some participants may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations, and referrals.

13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to screening. Written informed consent also will be obtained for the IDI and for long-term specimen storage and possible future testing, although consent for either the IDI or for specimen storage is not required for study participation. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to

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 MATRIX's GDP guidelines (www.matrix4prevention.org). Participants will be provided with copies of the ICF if they are willing to receive them.

In addition to the ICF, the Protocol Team will work with study staff and community representatives to develop appropriate materials about the study and a standardized approach to the informed consent process to be implemented at study sites, which will be detailed in the MATRIX-003 SSP Manual.

The informed consent process will cover all elements of informed consent required by research regulations. In addition, the process specifically will address the following topics of importance to this study:

- Both study products are placebos that provide no protection against HIV acquisition or pregnancy.
- The importance of adherence to the study visit and procedures schedule.
- The potential medical risks of study participation (and what to do if such risks are experienced).
- The potential social harms associated with study participation (and what to do if such harms are experienced).
- The limited benefits of study participation.
- The distinction between research and clinical care.
- The right to withdraw from the study at any time.

Furthermore, participants who agree to have their sexual partner contacted while in MATRIX-003 will be asked to read and sign an additional "Permission to Contact" form before the partner is invited to enroll. This form will explain that the participant gives the study staff permission to contact their sexual partner with the understanding that the partner will be invited to discuss their views on the IVR and its attributes and the participant's experiences using the IVR. This means the sexual partner will be aware of the participant's study involvement and use of the IVR. Sites will contact sexual partners according to site SOP and/or local IRB/IEC guidelines. Sexual partners who agree to enroll will provide written informed consent prior to completing the IDI.

13.6 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. Study sites will implement confidentiality protections that reflect the local study implementation plan and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them.

All study-related information will be stored securely at the study site. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded participant number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and ICFs, will be stored separately from study records identified by code number. All local databases will be secured with password protected access systems. Forms, lists,

logbooks, appointment books, and any other listings that link participants' ID numbers to 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 review, monitoring, and/or auditing by the following:

- Representatives of the US Federal Government, including the US OHRP, USAID, and/or contractors of USAID, and other local, US, or international regulatory authorities
- ACRO and ECS-HSR
- Representatives of OCIS
- MATRIX designees/representatives
- Study staff
- Site IRBs/IECs

13.7 Special Populations

13.7.1 Pregnant Women

Women who test positive for pregnancy at the Screening or Enrollment Visit will not be eligible to participate in this study. Should a participant test positive for pregnancy after Enrollment, a product discontinuation will be implemented. Follow-up visits and procedures will be discontinued, and the participant will be considered terminated from the study. An Early Termination Visit may be completed and data collected per Section 7.4.2. During the informed consent process, participants will be informed that the placebo IVRs are not a method of contraception and the effects of the placebo IVRs on a developing human fetus are unknown.

13.7.2 Children

The US NIH has mandated that children, defined as younger than 18 years old, 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"). As such, this study does not plan to enroll children.

13.8 Compensation

Pending IRB/IEC approval, participants will be compensated for time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Site-specific reimbursement amounts will be determined per local IRB/IEC/DRA guidelines and will be specified in the study ICFs of each individual site.

If a participant becomes ill or injured as a result of participation in this trial, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer the participant for ongoing treatment for the injury, if needed. Where required, clinical trial insurance purchased by sites will be responsible for compensating the study participant for appropriate medical expenses for treatment of any such illness or injury. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation.

13.9 Reporting

13.9.1 Communicable Disease Reporting

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

13.9.2 Other Reporting

Study staff will comply with local requirements to report cases of sexual assault or of sexual activity involving a person below the age of consent identified in the study.

13.10 Access to HIV-related Care

13.10.1 HIV Counseling and Testing

HIV test-related counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV testing time point. Testing will be performed in accordance with the algorithm in Appendix II. Counseling will be provided in accordance with standard HIV counseling policies and methods at each site and additionally will emphasize the study products are placebos and will not prevent HIV infection. Participants must receive their HIV test results to take part in this study. Condoms will be available to participants as part of standard risk reduction counseling.

13.10.2 Care for Participants Identified as HIV-Positive

An individual who has been identified as infected with HIV will be referred for management according to the local standard of care. Should a participant test positive for HIV after Enrollment Visit, follow-up procedures will be performed as per Section 7.4.1.

13.11 Study Discontinuation

This study may be discontinued at any time by USAID, MATRIX, OCIS, the OHRP, other local, US or international regulatory authorities, or site IRB/IEC.

14 PUBLICATION POLICY

USAID and MATRIX policies will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to USAID, MATRIX and OCIS for review prior to submission.

15 APPENDICES

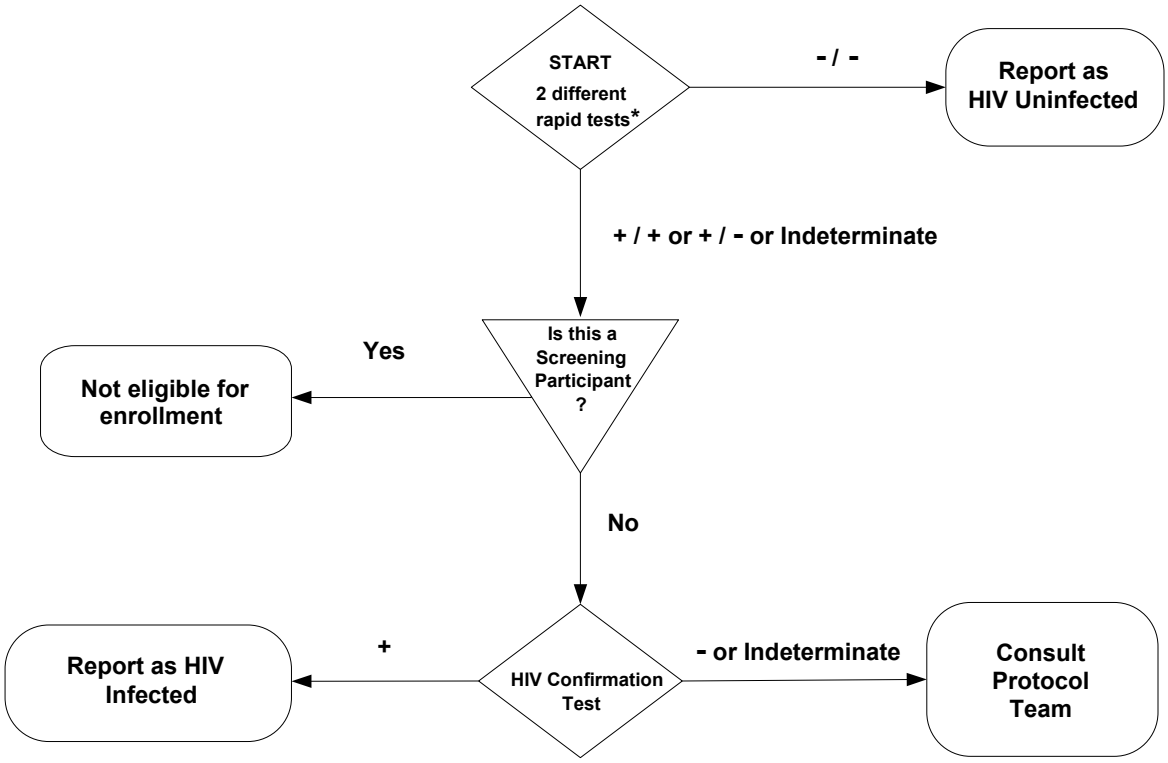
APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

STUDY PROCEDURES	SCR	Stage 1					Stage 2			
	V1	V2	V3	V4	V5		V6	V7	V8	V9
Day	-45	0	7	14	28		0	7	14	28
Clinic Visit	X	X		X	X		X		X	X
Phone Contact			X					X		
ADMINISTRATIVE AND REGULATORY										
Obtain/review informed consent for screening and enrollment (sites may split screening and enrollment consent if requested/ required by IRB/IEC)	X	*				7- to 21-day period of no IVR use				
Assign a unique PTID	X									
Collect/update/review contact/locator information	X	X	X	X	X		X	X	X	X
Collect demographic information	X									
Assess/confirm eligibility	X	X								
Randomization		X								
Confirm permission to contact sexual partner for IDI (subset)										X
Provide reimbursement	X	X	X	X	X		X	X	X	X
Schedule next visit/contact	*	*	X	X	X		X	X	X	
COUNSELING										
HIV pre- and post-test counseling	X	X		*	*		X		*	X
HIV and STI risk reduction counseling	X	X	*	*	*		X	*	*	X
Protocol counseling	X	X	X	X	X		X	X	X	
Abstinence										
BEHAVIORAL										
Review instructional materials		X					X			
Baseline behavioral questionnaire		X								
Post-insertion behavioral questionnaire		X					X			
Telephone-based brief questionnaire			X					X		
Mid-point behavioral questionnaire				X					X	
Follow-up behavioral questionnaire					X					X
Social harms assessment		X		X	X		X		X	X
Social benefits assessment					X					X
Participant IDI (subset) (ideally at or within 1 week of V9/SEV but no later than 3 weeks after V9/SEV)										X
Sexual partner IDI (subset) (within 1 month of V9/SEV)										X
CLINICAL										
Collect/update/review medical and menstrual history	X	X	X	X	X		X	X	X	X
Collect/update/review concomitant medications	X	X	X	X	X		X	X	X	X
Physical exam (symptom-directed after Screening)	X	*		*	*		*		*	*
Pelvic exam with speculum (bimanual exam at Screening)	X	X		X	X		X		X	X
Digital exam by clinical team member to confirm IVR placement		X					X			

STUDY PROCEDURES		SCR	Stage 1					Stage 2			
		V1	V2	V3	V4	V5		V6	V7	V8	V9
Day		-45	0	7	14	28		0	7	14	28
Clinic Visit		X	X		X	X		X		X	X
Phone Contact				X					X		
Clinician assessment of ring insertion or removal experience (# attempts, comfort)			X			X		X			X
Provide available test results		X	X	X	X	X		X	X	X	X
AE assessment			X	X	X	X		X	X	X	X
Treat or prescribe treatment for RTI/UTI/STI		*	*		*	*		*		*	*
LABORATORY											
Saliva	HIV test(s) (only at sites with CLIA certification)	X	X		*	*		X		*	X
Urine	Urine pregnancy test	X	X		*	*		X		*	X
	Urine dipstick/culture	*	*		*	*		*		*	*
Blood	HIV test(s) (not necessary for sites that perform saliva testing)	X	X		*	*		X		*	X
	CBC	X	*		*	*		*		*	*
	AST/ALT	X	*		*	*		*		*	*
	Serum creatinine	X	*		*	*		*		*	*
	Syphilis serology	X									
	Plasma for archive		X								
Pelvic	Pap test	^									
	KOH wet mount for candidiasis and/or BV	*	*		*	*		*		*	*
	Vaginal Gram Stain		X		X	X		X		X	X
	Vaginal swab(s) for microbiota		X		X	X		X		X	X
	Vaginal pH		X		X	X		X		X	X
	NAAT for GC/CT/TV	X	*		*	*		*		*	*
	Vaginal swab(s) for archive		X								
STUDY PRODUCT SUPPLY											
Provide IVR for self-insertion at clinic			X					X			
Collect assigned IVR after removal at clinic						X					X
Clinical team member insertion or removal of IVR at clinic (only if participant fails 2 attempts)			*			*		*			*
Offer male condoms					X	X				X	X

X = Required
* = If indicated and/or per local standard of care
^ = if indicated (if participant is unable to provide documentation of a normal Pap test within 3 years prior to enrollment)

APPENDIX II: ALGORITHM FOR HIV TESTING – SCREENING/ENROLLING/FOLLOW-UP



*CLIA certified labs may perform 1 rapid test

APPENDIX III: SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, LONG-TERM STORAGE AND FUTURE TESTING)

SAMPLE INFORMED CONSENT FORM

MATRIX-003
Trial to Assess Acceptability and Safety of Two Placebo Intravaginal Ring (IVR) Designs

USAID

Version 1.0
29 June 2023

PRINCIPAL INVESTIGATOR: *[SITES TO INSERT]*
INSTITUTION: *[SITES TO INSERT]*
AFTER HOURS CONTACT DETAILS: *[SITES TO INSERT]*
STUDY SITE CONTACT DETAILS: *[SITES TO INSERT]*
SHORT TITLE: OCIS Placebo Ring Study

INFORMED CONSENT
[*SITES TO INSERT APPROPRIATE GREETING*] You are being invited to take part in this research study because you are an 18-45-year-old woman in good health. Approximately 100 women will take part in this study across sites in the United States (US), South Africa, and Zimbabwe. This study is looking at two placebo vaginal rings.

This study is sponsored by the US Agency for International Development (USAID) and conducted by the Oak Crest Institute of Science (OCIS) as part of MATRIX: A USAID Project to Advance the Research and Development of Innovative HIV Prevention Products for Women. The placebo vaginal rings are supplied by OCIS. At this site, the person in charge of this study is [*SITES TO INSERT*].

KEY INFORMATION
- The study will assess the acceptability and safety of the two placebo vaginal rings. The placebo rings do not contain any active medication, and do not prevent HIV.
- You would be asked to try two different placebo rings, each for approximately 28 days (4 weeks). You would be randomly assigned which of the two rings to use first. The study involves answering questions, undergoing examinations of your vagina and cervix, and collecting blood, urine and vaginal fluid samples.
- You would be in the study for approximately 9-11 weeks once you are enrolled.
- The study involves a total of 9 visits/contacts, including in person visits and telephone calls.
- There may be no benefit to participating.
- You cannot join this research study if you are living with HIV, pregnant, or breastfeeding. You also may not be able to join this research study if you are already taking part in another research study.

- Taking part in this research study is voluntary. You do not have to participate, and you can stop your participation in the study at any time.

Please take the time to read this entire form and ask questions before deciding to join the study. If you are willing to take part in the study, you will sign this form. A copy of this form will be offered to you. Signing this form does not mean you will be able to join the study. You must first complete the screening tests and exams to see if you are eligible. It is important to know that your participation in this research study is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

WHY IS THIS RESEARCH BEING DONE?
This research study is being conducted to find out how easy and comfortable the vaginal rings are for women to use. The rings used in this study do not dispense any medications and will not prevent pregnancy, HIV, nor other sexually transmitted infections. We want to know what you like and dislike about these rings to help us design future products and research studies. Although the vaginal rings in this study do not dispense any medications, we also want to make sure the ring itself is safe when used by women for 28 days.

WHO WILL BE IN THIS RESEARCH STUDY?
Approximately 100 women who are 18-45 years old will be enrolled in the study across various sites in the United States (US), South Africa, and Zimbabwe.

DO I HAVE TO BE IN THIS STUDY?
You do not have to be in this study. You can still get the care you need even if you do not join the study. If you join today, you can change your mind later.

WHAT WILL I BE ASKED TO DO IF I JOIN THIS RESEARCH STUDY?
You will undergo a screening visit to be sure you are eligible and interested. If you are eligible and decide to enroll in this study, you will be asked to try two different placebo vaginal rings, each for approximately 4 weeks (28 days). You will be randomly assigned which of the two rings to use first. Randomly means by chance, like flipping a coin or throwing dice. Neither you nor investigators can choose the ring you will use first. Both placebo vaginal rings are important to the study.

You must be using an effective method of birth control for at least 2 weeks before screening and agree to continue to use the method throughout the duration of the study to qualify.

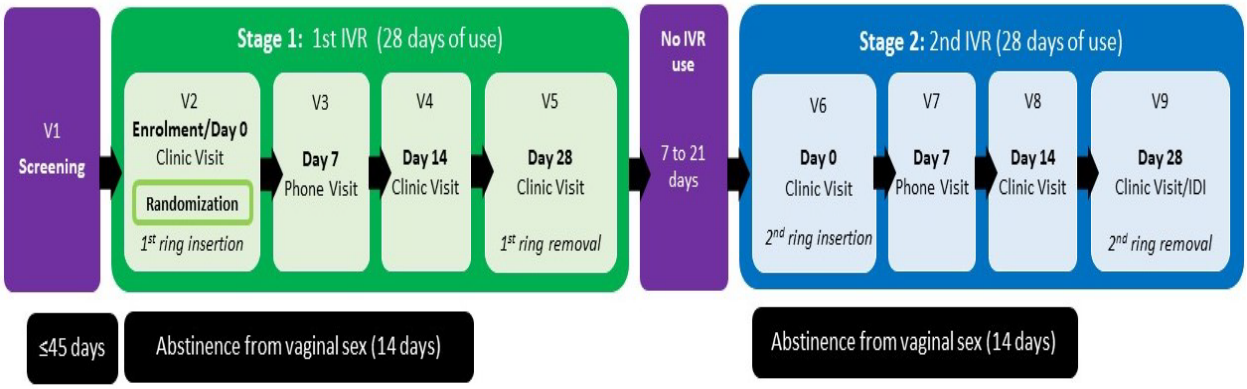
At the Enrollment Visit (V2) you will be asked to insert the first placebo vaginal ring, undergo evaluations, and answer questions about your experience. While the ring is in place you will have one phone visit about a week later to see how you are doing and then come back to clinic after about 2 weeks of ring use. After about 4 weeks of ring use, you will return to the clinic (V5) to remove the ring and return it to the study team, undergo evaluations, and answer questions about your experience. After a break of about 1 to 3 weeks, you will be asked to return to the clinic (V6) to insert the second ring and undergo similar evaluations as you did in Visit 2. You will then repeat the same visits over the next 4 weeks until study exit (V9).

You will be asked to not have vaginal sex for the first 2 weeks of each ring use period. You will be asked to abstain from using anything in the vagina during the entire study. For example, this

means no tampons, menstrual cups, toys, douches, herbal preparations, or vaginal medications. If you do not think you can agree to this, you should not participate.

WHAT WILL HAPPEN DURING THE STUDY VISITS?
The study includes a total of nine (9) scheduled clinic visits or telephone contacts. Seven (7) visits, including the Screening Visit today, will take place at this clinic. Two (2) visits will be telephone contacts, which may be done through a phone call or via text message. Participants who prefer to complete the telephone contacts in-person may elect to do so.

Study Visit Schedule:



Screening Visit (Visit 1) Procedures:
The procedures done at this visit will let us know if you can join this study and will take about *[SITES TO SPECIFY TIMEFRAME]*.

At the Screening Visit, you will:

- Answer questions related to
  - Demographics: date of birth, race, contact information, etc.
  - Medical and menstrual history: review of any medical problems you may have
  - Medication use: review any medication you take, including start date, dose, etc.
  - Birth control method: you must be using and agree to continue to use an acceptable, reliable method throughout the study to qualify
  - Visit/background questionnaire
- Undergo counseling
  - HIV and STI (sexually transmitted infection) counseling and how to reduce your risk
  - Abstinence (no vaginal sex and no vaginal product) counseling will be reviewed. For vaginal sex, this would be for the first 2 weeks of each ring use period. For vaginal products, this would be for the duration of the study.
    - **It is important that you know if you are not currently using an acceptable method of contraception, or if you do not think you can abstain from vaginal sex for the first 2 weeks of each ring use period or from use of vaginal products for the duration of the study, you will not be eligible to participate in this study.**
- Have examinations
  - Physical exam

    - Pelvic exam: To examine your vagina and cervix, the doctor may use a speculum (plastic or metal instrument inserted into the vagina)
- Have baseline testing:
    - Urine pregnancy test: If you are pregnant, you will not be able to join
    - HIV test: [*SITES TO INSERT TYPE OF HIV TEST and LOCAL REQUIRED LANGUAGE*]
    - Blood test: Approximately [*SITES TO INSERT VOLUME*] will be collected to look at the general health of your blood, basic kidney and liver function, and to screen for syphilis
    - STI test for gonorrhea, chlamydia and trichomonas by collecting vaginal fluid using a Q-tip like swab(s)
    - Pap smear: If you have not had a normal result within the required period and/or the report is not available, you will have a Pap smear performed by using a soft brush to collect a sample from your cervix [*SITES TO MODIFY/ADD AS NEEDED*: to screen for cervical cancer]
    - Additional tests of your urine and/or vaginal fluid may be done to check for infections if you are having symptoms and as clinically indicated
- Receive test results
    - Results of the tests listed above will be reviewed with you once available. Some tests results may be available while you are at today's visit (urine pregnancy test) while others may take up to a week to result (STI testing). The results of these tests will help to determine if you are eligible to participate.
    - If you are diagnosed with a urinary, vaginal (i.e., yeast or BV) or an STI at Screening, you will be offered/prescribed treatment
    - If there are other clinically significant findings, for example on your blood test or Pap smear, you will be referred for additional evaluations and treatment as needed
- In addition
    - Be provided reimbursement
    - May be scheduled for an Enrollment Visit within 45 days of Screening

It may be necessary to conduct more than one clinic visit to complete all required screening procedures or if a test needs to be repeated.

If you do not join the study, blood and other samples collected at the Screening visit will not be kept or used for any tests other than those listed above.

If you are eligible and decide to enroll in the study, there are common study procedures that will happen at every in person visit (V2, V4, V5, V6, V8, V9), including:

- Review/update your contact information, including address and phone number*
- Review/update your medical and menstrual history*
- Review/update any medications you are taking/using*
- Review/update any sexual activity or intravaginal product use*
- HIV and STI testing and counseling as needed [*SITES TO MODIFY/ADD BELOW LANGUAGE AS NEEDED*]
    - You will be told your test results as soon as they are available. You will talk with the study staff about the meaning of your results, how you feel about them, and learn about ways to prevent HIV and other STIs. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we are sure of your status. To participate in the study, you must receive the results of your

HIV test. If the test shows you have HIV, you cannot join the study. We will refer you to available sources of medical care and other services you may need.
- Review of any new complaints or side effects once you start using the ring*
- Directed physical exam, as clinically indicated based on symptoms/complaints
- Urine pregnancy test
- Pelvic exam with collection of vaginal fluid using a Q-tip like swab(s) to look at the bacteria in the vagina
- As needed tests:
  - Repeat blood tests (general health of blood, kidney and liver function)
  - Microscope exam of vaginal fluid to look for yeast or bacteria
  - Urine tests to check for infections
- Review of test results*
- Treatment or referral for abnormal test results as needed
- Protocol counseling, including HIV and STI risk reduction and contraceptive counseling, as needed*
- Reimbursement for the study visit/contact*
- Schedule next visit/contacts*

*These procedures will also be done at the scheduled Telephone Contacts (V3, V7)

Insertion Visit (Visits 2 and 6) Procedures:
The Insertion clinic visits (the visits where you are given a ring to use) will take about *[SITES TO SPECIFY TIMEFRAME]*. Visit 2 is the Enrollment Visit, which will take place up to 45 days after the Screening Visit. You will be randomly assigned which of the two rings (A or B) to use first at the Enrollment visit, and you will insert the first assigned ring at the clinic. At Visit 6, you will insert the second ring at the clinic.

In addition to the common study procedures listed above, at these visits you will:
- Answer questions
  - About the vaginal ring
  - About sexual behaviors and risk factors
  - About the vaginal ring following insertion
- Undergo counseling
  - Abstinence (not have vaginal sex or use vaginal products) counseling
- Have HIV testing and counseling
- Be assigned to the group using Ring A first or to the group using Ring B first
- Have a blood sample taken at Visit 2 [*SITES TO INSERT VOLUME*] in case there is a question about your test results at a later time
- Have examinations
  - Pelvic exam before inserting the ring
    - Vaginal fluid will be collected using a Q-tip like swab(s) at Visit 2 in case there is a question about your test results at a later time
  - Digital genital exam (clinician places finger inside vagina) after insertion of the ring to check ring position
  - You will be asked to walk around the room after insertion of the ring to make sure the ring is comfortable. If you experience any discomfort while walking, the digital genital exam may be repeated.
- Review instructional materials

    - You will be provided with vaginal ring instruction materials to review before inserting the ring. Study staff will be available to answer any questions you may have.
- Insert the vaginal ring given to you by the study team
    - You will have 2 attempts to insert the vaginal ring
    - If after 2 attempts, you are having difficulty, a clinical team member can insert the ring for you

Telephone Contact (Visits 3 and 7) Procedures:
Visits 3 and 7 will take place approximately 7 days (1 week) following the Insertion Visits. These telephone contacts will take approximately *[SITES TO SPECIFY TIMEFRAME]* to complete.

In addition to the common study procedures with Telephone Contacts listed earlier, you will be asked about concerns and comfort with ring use.

Mid-point Clinic Visit (Visits 4 and 8) Procedures:
The Mid-point clinic visits will occur approximately 14 days (2 weeks) after the Insertion Visits and will take between *[SITES TO SPECIFY TIMEFRAME]* to complete.

In addition to the common study procedures listed earlier, at these visits you will be asked about concerns and comfort with ring use, and you will have a pelvic exam. You will also be reminded there are no restrictions on sex for the second 14 days of ring use and be offered male condoms.

Removal Visit (Visits 5 and 9) Procedures:
The Removal clinic visits (the visits where you remove the vaginal ring in the clinic) will occur approximately 28 days (4 weeks) after the Insertion Visits. These visits will take between *[SITES TO SPECIFY TIMEFRAME]* to complete. Your participation in this study will end after Visit 9.

In addition to the common study procedures listed earlier, at these visits you will:
- Answer questions
    - About your experiences using the vaginal ring
    - About sexual behaviors and use of vaginal products
    - Up to 30 participants (of the total 100) will be chosen to do an in-depth interview ideally at or within 1 week of Visit 9 but no later than 3 weeks after Visit 9
        - If chosen, the interview will be performed [*SITES TO SPECIFY MECHANISM:* in the presence of one or more MATRIX-003 behavioral research staff members / remotely by a behavioral researcher]
        - Study staff will make every effort to ensure your privacy and confidentiality, and information you provide during the interview will not be shared with your partner
        - The interviewer may take notes, and interviews will be audio-recorded to make sure we record your words exactly how you said them
        - The interview will be focused on your experiences using the ring and behaviors during the study and could take up to an hour to complete
- Have examinations
    - Pelvic exam
- Remove the vaginal ring. It is important that you return the ring to the study team.
    - You will have 2 attempts to remove the vaginal ring
    - If after 2 attempts, you are having difficulty, a clinical team member can remove the ring for you

- Offer male condoms
- In addition
  - Investigators will ask you to confirm if you are willing to have your partner contacted to participate in an in-depth interview about your partner's experience while you were in the study.
    - This is optional and you should only agree if you (and your partner) feel comfortable. If you don't feel comfortable including or asking your partner to participate, you will not be disqualified.
  - If you agree and feel comfortable, you will be asked to [*SITES TO SPECIFY CONTACT METHOD:* provide your partner's current contact information / provide our contact information to your partner so they can call us if interested in participating]
    - You will be given information to share with your partner to see if your partner would be comfortable participating in an interview
    - Your partner would need to sign a separate consent

Additional Visits and Procedures

In addition to the procedures listed above, it is possible that study clinicians may need to perform additional exams or tests, if necessary. For example, you may be asked to make additional clinic visits to perform these exams/tests if you report having symptoms and/or other issues, if there are abnormal test results, or due to mistakes during the collection, processing and/or shipping of your samples. These exams/tests might include the following:

- Physical and/or pelvic exam
- Test vaginal fluid for STIs
- Test your urine for STIs or other infections
- Test your blood for STIs
- Test your blood to check the health of your blood, liver and kidneys
- Give you treatment or refer you for treatment of STIs or other issues, if needed.

It is important for you to complete every study visit/contact. If you cannot make a scheduled visit/contact, please tell the study staff as soon as possible so that the visit/contact can be rescheduled.

It is important that you remember that at any time during the study, study staff can answer any questions you may have about the procedures mentioned above or any other aspect of this study.

WHAT IF I BECOME INFECTED WITH HIV?

The placebo vaginal rings do not contain medications and will not prevent HIV infection. Persons living with HIV will not be included in this study. Being in this study will not cause HIV infection. However, there is always a chance that you can get HIV through sex or other activities. If you become HIV-positive, you will stop using the study product and will stop taking part in this study. The study staff will refer you for medical care and other available services. [*SITES TO INCLUDE/AMMEND THE FOLLOWING IF APPLICABLE:* If you are interested, study staff will inform you of other available research studies you may be eligible for.]

Depending on local and national health requirements, the study staff may need to report certain diseases, including HIV. The reportable diseases at this site are [*SITES TO INSERT*]. We must inform the following [*SITES TO INSERT MORE DETAILED INFORMATION REGARDING WHO WILL BE INFORMED OF THE REPORTABLE DISEASES*]. [*SITES TO INCLUDE/AMMEND THE*

FOLLOWING]: Outreach workers from the [*LOCAL HEALTH AUTHORITY*] may then contact you about informing your partner/s, since they also should be tested. If you do not want to inform your partner/s yourself, the outreach workers may contact them, according to the confidentiality guidelines of the [*LOCAL HEALTH AUTHORITY*].

WHAT IF I BECOME PREGNANT?
The placebo vaginal rings are not family planning methods and will not prevent pregnancy. We do not know what effect the study product(s) have on pregnancy, including any effect on the unborn babies. Because of this, pregnant women may not join this study. Also, you must use an effective family planning method (e.g., birth control pills, hormonal-based methods, intrauterine device [IUD], the patch) other than a vaginal ring for at least 2 weeks before screening and for the study duration.

If you become pregnant during the study, study staff will refer you to available medical care and other services. The study does not pay for this care. You will stop using the study product and will stop taking part in this study. [*SITES TO INCLUDE/AMMEND THE FOLLOWING IF APPLICABLE:* If you are interested, study staff will inform you of other available research studies you may be eligible for.]

RISKS AND/OR DISCOMFORTS

Risks of Blood Draws
You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, small clot, or infection where the needle goes into your hand or arm.

Risks of Pelvic Exams
You may feel discomfort or pressure during the pelvic exam and vaginal fluid collection. You may have a small amount of vaginal bleeding or spotting which should stop shortly after the exam.

Risks of Vaginal Rings
The ring is a placebo and does not contain any medications. You may experience discomfort when inserting or removing the ring, or while the ring is in place. It is possible that you may have an allergic reaction to the ring itself. Symptoms of an allergic reaction include rash or other irritation, itching, joint pain, or difficulty in breathing.

Risks of HIV and Sexually Transmitted Infection (STI) Testing
HIV and STI testing may make you feel anxious regardless of the test results. Finding out your HIV status may also cause problems with your family, friends, or partner.

Other Possible Risks
You may feel embarrassed and/or worried when talking about sexual activities (if you are currently sexually active), your living situation, ways to protect against HIV and STIs, and your test results. You can choose not to answer questions at any time. Trained study staff will help you with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality during the study visits. Your visits will take place in private. Reports via computer will be stored in computers that are password-protected and will not include personal information that could identify or link

information to you; only your study ID number will be recorded. However, it is possible that others may learn of your participation in this study, and because of this, may treat you unfairly or discriminate against you. If you have any problems, study staff will talk with you and try to help you.

The in-depth interviews with study staff may be performed [*SITES TO SPECIFY MECHANISM:* at the clinic / remotely]. The interviews will be audio recorded and questions of a personal nature may be asked. Responding to these questions may make you uncomfortable. The audio files will be put into writing by the person conducting the interview or by another person who does not know you and does not have your personal information. You should NOT identify anyone in the interviews and any names that might be mentioned on the recording will only be noted in the transcript using a generic description. The audio files will be stored in computers that are password protected.

BENEFITS

Though you may not experience any direct benefit from participation in this study, information learned from this study may help us learn ways to prevent the spread of HIV in the future. Your opinions about the ring are important to scientists working to develop this new prevention option. You will receive medical exams and counseling and testing for HIV and STIs. You will also have tests to check your overall health.

This study does not replace your clinical care and cannot give you general medical care, but study staff will refer you to another medical provider for care, if needed. Male condoms will be available at no cost, if you need them. If you are diagnosed with an STI during the study, you will receive medicine and/or a referral, if you need it.

NEW INFORMATION

You will be told about any new information learned during this study that may affect your willingness to stay in the study. For example, we will let you know if we learn that the study product may be causing bad side-effects. We will also tell you when study results may be available, and how to learn about them.

WHY YOU MAY STOP USING THE STUDY PRODUCT EARLY OR BE ASKED TO LEAVE THE STUDY

You may need to leave the study early without your permission if:

- The study is cancelled by USAID, OCIS, the US Office for Human Research Protections (OHRP), MATRIX, the local government or regulatory agency, or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). An IRB/IEC is a committee that watches over the safety and rights of study participants.
- You are not able to keep appointments.
- Other reasons that may prevent you from completing the study successfully.

The study doctor will ask you to stop using the study products if:

- You acquire an HIV infection (see "If You Become Infected With HIV" section).
- You become pregnant or are breastfeeding (see "If You Become Pregnant" section).
- You use drugs for HIV prevention or to prevent infection after HIV exposure.
- You use injectable drugs for reasons other than treating disease.
- You experience a serious adverse event while on study.

- You fail to follow study requirements in a manner judged by the study doctor to significantly put you at risk of an adverse reaction or otherwise affect study outcomes.
- A study clinician decides that using the study product would be harmful to you, for example, you have a bad reaction to the vaginal ring(s).

If a study doctor asks you to stop using study product, we will ask you to come in for an interim visit during which some/all of the procedures scheduled to occur on Visit 9 will be completed. You will then exit the study, unless otherwise informed by study staff.

If you are removed from the study or choose to leave, we will ask you to come back for one final clinic visit. It is important that you come to the clinic to remove the ring if you are still using it. If you do not have the study products with you when you come to the clinic, staff members will make every effort to assist you in returning them as soon as possible. [*SITES TO SPECIFY ALLOWANCES FOR SPECIAL CIRCUMSTANCES*]

ALTERNATIVES TO BEING IN THE STUDY
This is a placebo study enrolling healthy, adult women. You can choose not to participate in this study without affecting your care at this or other facilities or your ability to participate in other studies.

[*SITES TO INCLUDE/AMEND THE FOLLOWING, IF APPLICABLE*: You may be able to join other studies here or in the community. There may be other places where you can go for HIV counseling and testing and family planning. We will tell you about those studies and those places if you wish.]

COSTS TO YOU
[*SITES TO COMPLETE ACCORDING TO SITE CAPACITY*] There is no cost to you for study visits, study products, physical/clinical exams, laboratory tests or other procedures. We can give you treatments for STIs (other than HIV) at no cost while you are in the study, or we can refer you for available treatment.

REIMBURSEMENT
[*SITES TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT:*] You will receive [*SITES TO INSERT AMOUNT $XX*] for your time, effort, and travel to and from the clinic for each scheduled study visit. You may receive [*SITES TO INSERT AMOUNT $XX*] for any extra study visits. For responding to phone calls and text messages, you will receive up to [*SITES TO INSERT AMOUNT $XX*]. If you are selected and agree to take part in the in-depth interview, you will receive [*SITES TO INSERT AMOUNT $XX*].

CONFIDENTIALITY
We will make every effort to keep your information private and confidential. But we cannot guarantee it.

Study visits will take place in private. We will keep the information about your study visits in a secure place that only certain people can access for the purposes of this study. We will only enter your information into computers protected by passwords and will not include information that could identify you. Your identity on these records will be indicated by a number rather than by your name, and the information linking these numbers with your name will be kept separate from

the research records. You can choose not to answer questions at any time. We will keep the audio recordings and materials from all interviews and discussions confidential and will only use study numbers or fake names. We will store the original records, including the audio recordings, for at least three years after completion of the study. These records will be stored in a secure, locked location.

Your personal information may be disclosed if required by law. For example, if we learn something that would immediately put you or others in danger, the study staff must take steps to keep you and others safe. This means that we have to share any information with the authorities (hospital, police, or social services) that tells us you may be in danger. For example, if you tell us that you plan to hurt or kill yourself, hurt or kill someone else, or if you tell us that someone is abusing or neglecting you.

The study staff may use your personal information to verify that you are not in any other research studies. This study will not use your name or identify you personally in any publication.

[*SITES TO INSERT INFORMATION ABOUT SYSTEMS CURRENTLY IN PLACE TO ENSURE PARTICIPANTS ARE NOT PART OF OTHER CONFLICTING STUDIES, INCLUDING BIOMETRIC IDENTIFICATION SYSTEMS; SEE EXAMPLE BELOW FOR SOUTH AFRICAN SITES:*

In clinical studies where study products or other medical devices are being assessed, it is important that volunteers are enrolled in only one clinical study at a time. Using more than one study product may lead to drug interactions and side effects that could potentially be harmful to your health. In addition to compromising the health of the study participant, this can affect the outcome of the study.

The Biometric Co-Enrollment Prevention System (BCEPS) is a web-based system developed by the South African Medical Research Council IT (Information Technology) department, for the prevention of co-enrolment (being enrolled in more than one study at a time). It is a secure system that is used to ensure participant safety and study integrity, in studies where co-enrolment could impact both.

Authorized study staff enters the South African Identify number (SA ID) or SA/foreign Passport Number of the participant into the system to check if they are enrolled in any study within any of the organizations using BCEPS in South Africa. During screening for a study at an Aurum Institute clinic/site, the SA ID number or SA/foreign Passport Number and all fingerprints are captured onto the system. At every study follow-up visit thereafter, their SA ID number or SA/foreign Passport Number and fingerprints will be checked.

In the long term, after study completion, it is important that study staff can verify what studies a participant has volunteered in, in order to ensure that the participant's safety is not compromised in future study participation. The SA ID number or SA/foreign Passport Number and fingerprints will remain in the database on an ongoing basis for a period of up to 15 years after the end of a study. If the participant has not participated in any additional studies for the 15-year period, their SA ID number or SA/foreign Passport Number and fingerprints will be removed from the system.

If a participant refuses for the system to be used at the initial visit or requests to be removed from the system while using a study product, the study investigator will decide if it is safe for the

participant to be enrolled into the study or if it is safe to continue using study product without regularly checking for co-enrolment. The study that the potential participant is screening for may also prohibit co-enrolment in which case we will not be able to screen you.]

Your records may be reviewed by:

- Representatives of the US Federal Government, including US OHRP, USAID and/or USAID contractors, and other US, local or international regulatory authorities
- [*SITES TO INSERT APPLICABLE LOCAL AND NATIONAL AUTHORITIES*]
- Representatives of OCIS
- MATRIX representatives
- Study monitors
- Site IRB/IEC
- Study staff

[*US SITE TO INCLUDE/AMEND THE FOLLOWING:* Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form, you provide your authorization for the use and disclosure of information protected by the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. This includes things learned from the procedures described in this consent form. Study staff may also collect other information including your name, address, date of birth, and information from your medical records.]

[*NON-US SITES TO INCLUDE/AMEND THE FOLLOWING:* As part of your participation in this research study, your personal information may be sent to the United States for analysis or storage. This includes things learned from the procedures described in this consent form. Study staff may also collect other information including your name, address, date of birth, and information from your medical records. There are laws in the U.S. to protect your personal information when in that country.]

[*SOUTH AFRICA SITES TO INCLUDE/AMEND THE FOLLOWING:* The Protection of Personal Information Act (POPIA) ensures that all South African institutions collect, process, store, and share your personal information in a responsible manner and that they will be held accountable should they abuse or compromise your personal information.]

People outside the study team may need to see or receive your information for this study, such as those listed above. We cannot do this study without your authorization to use and give out your information to them. You do not have to give us this authorization. If you do not, then you may not join this study.

The use and disclosure of your information has no time limit. You may cancel your authorization to use and disclose your information at any time by notifying the Principal Investigator of this study in writing. If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

RESEARCH-RELATED INJURY

[*SITES TO INCLUDE/AMEND PER THEIR INSTITUTIONAL POLICY:* It is unlikely that you will be injured by being in this study. If you are injured or get sick from being in this study, please tell study staff immediately.

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. If you become ill or injured as a result of participation in this study, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer you for ongoing treatment for the injury, if needed. Clinical trial insurance purchased by the site will be responsible for compensating you for appropriate medical expenses for treatment of any such illness or injury. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation. The research center or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:

- Any injury that happens because you used other medicine during the study that you did not tell us about.
- Any injury that happens because you did not follow instructions given by the study doctor or nurse.
- Any injury that happens because of negligence on your part.]

[*SITES TO SPECIFY ANY ADDITIONAL POLICY RELATED TO EMERGENCY MEDICAL ATTENTION*]

[*US SITE TO INCLUDE/AMEND PER THEIR INSTITUTIONAL POLICY:* To pay these medical expenses, the site will need to know some information about you, like your name, date of birth, and social security number or Medicare Health Insurance Claim Number. This is because they have to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.]

You are not giving up any legal rights by signing this form.

CLINICALTRIALS.GOV

A description of this research study will be available on https://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

[*SOUTH AFRICA SITES TO INCLUDE LANGUAGE RELATED TO SOUTH AFRICAN NATIONAL CLINICAL TRIALS REGISTER*]

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER

[*SITES TO INCLUDE/AMEND PER THEIR INSTITUTIONAL POLICY:* Being in this study is completely voluntary. You may choose not to join this study or leave this study at any time. If you choose not to join or to leave the study, you can still join other studies and you can still access non-study services you would normally get at this or another clinic. If you leave the study, your specimens will be destroyed when all protocol-specified testing has been completed and your study records may be kept for at least three years after study completion. If you want the results of the study after it is over, let the study staff members know.]

PROBLEMS OR QUESTIONS

If you ever have any questions about the study, or if you have a research-related injury, you should contact [*INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF*] at [*INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS*].

If you have questions about your rights as a research participant, you should contact [*INSERT NAME OR TITLE OF PERSON ON THE IRB/EC OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE*] at [*INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER*].

[SITES TO OMIT THE FOLLOWING IF A SEPARATE CONSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS IS REQUIRED]

CONSENT FOR LONG-TERM STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION

There might be a small amount of blood or vaginal fluid left over after we have done all of the study-related testing. We would like to ask your permission to store these leftover samples and related health information for use in future studies, such as future research to fight HIV and other related diseases. This health information may include personal facts about you such as your race, ethnicity, sex, medical conditions and your age range. This health information will not include your name or any other personal identifying information. The samples will be stored by your participant number only.

If you enroll in the study and agree, your samples and related health data will be stored safely and securely at facilities that are designed so that only approved researchers will have access to the samples. Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you.

There is no time limit on how long your samples will be stored. Your samples may be shipped and/or stored outside of the country. The type of testing planned for your leftover specimens is not yet known. However, samples may be used by OCIS to complete additional quality assurance testing, ensuring that the tests work correctly and supply accurate data. No genetic testing on either a limited set or the full set of genes is planned for leftover samples that are stored for the purposes of future research. It is important that you know that any future testing or studies planned for these specimens must be approved by an Institutional Review Board before they can be done. You will not receive the results from any future testing of these specimens.

You can still enroll in this study if you decide not to have leftover samples stored for future studies. If you do not want the leftover samples stored, we will destroy them when all protocol-specified testing has been completed. You can withdraw your consent for the storage and future testing of specimens at any time by providing your request in writing to the person in charge of this study. However, researchers will not be able to destroy samples or information from research that is already underway.

_____ Initials and Date — I DO agree to allow my biological specimens and health data to be stored and used in future research studies. I understand my biological specimens may be shipped and stored outside of the country.

_____ Initials and Date — I DO NOT agree to allow my biological specimens and health data to be stored and used in future research studies.

[SITES TO OMIT THE FOLLOWING IF A SEPARATE CONSENT IS REQUIRED FOR PARTICIPANT IDI]

CONSENT TO PARTICIPATE IN AN IN-DEPTH INTERVIEW

We would like to ask your permission to participate in a conversation-style interview (in-depth interview or IDI) at the end of the study to gather more feedback about the placebo vaginal ring. If you agree and are selected to participate in the IDI, trained study staff will ask you questions about your experiences using the product, about product design, packaging and delivery, and other topics related to product use. Information you provide during the IDI will not be shared with your partner. The IDI may be conducted at the study site, over a secure digital platform, or an agreed upon location.

The IDI is anticipated to last approximately 45-60 minutes. Study staff will take notes and record the interview. You can choose not to answer questions at any time. We will keep the audio recordings and materials from all interviews and discussions confidential and will only use study numbers or fake names to identify them. These materials will be stored in a secure, locked location for at least three years after completion of the study.

We will reconfirm the decision you make today at later study visits should you change your mind about participating in the IDI.

You can still enroll in this study if you decide not to participate in the IDI. You can withdraw your consent to participate in the IDI at any time.

_____ Initials and Date — I DO agree to participate in an in-depth interview. I understand the interview will be recorded and notes will be taken.

_____ Initials and Date — I DO NOT agree to participate in an in-depth interview.

[SITES TO OMIT THE FOLLOWING IF A SEPARATE CONSENT IS REQUIRED FOR PERMISSION TO CONTACT SEXUAL PARTNER]

PERMISSION TO CONTACT SEXUAL PARTNER

We would like to ask your permission to contact your sexual partner to participate in a conversation-style interview (in-depth interview or IDI) at the end of the study to gather more feedback about the vaginal ring.

If both of you agree and your partner is selected to participate in the IDI, trained study staff will ask your partner questions about their views on the vaginal ring and its characteristics and about your experiences using the vaginal ring. This means that your partner will be aware of your participation in this study and your use of the vaginal ring but no other information will be shared with your partner.

If you give us permission to talk to your sexual partner, you will be asked to [*SITES TO SPECIFY CONTACT METHOD*: provide their current contact information at this time / provide our contact information to your partner so they can call us if interested in participating].

We will reconfirm the decision you make today at later study visits should you change your mind about us contacting your sexual partner.

You can still enroll in this study if you decide not to give us permission to contact your sexual partner. You can withdraw your permission for us to contact your sexual partner at any time.

_____
Initials and Date

I DO give permission for study staff to talk to my sexual partner. I agree to [*SITES TO SPECIFY CONTACT METHOD*: provide current contact information for my sexual partner / provide my partner with your contact information so they can call you for more information].

_____
Initials and Date

I DO NOT give permission for study staff to talk to my sexual partner.

[SITES TO OMIT THE FOLLOWING IF NOT APPLICABLE]

CONSENT FOR OFF-SITE VISITS

If the site determines that an off-site visit is appropriate and with your permission, members of the research team at this clinic may be able to schedule off-site visits with you at your home or at another location as part of the study. Some of the scheduled study visits and some of the study procedures may take place at your home or other location outside of the research clinic. For example, if you need to receive study product or to have a urine or blood sample collected but you are unable to come into the clinic. The study personnel will explain in greater detail the requirements of these visits (like the conditions of the place, the type of visit and the time it will take) and the procedures in-place to maintain your information in a confidential manner. However, it is important that you know that off-site visits may eventually affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

We will only conduct visits outside of the clinic if you give us permission to do so. Please read carefully the following statement and initial and date one option. Choosing not to have study visit procedures outside of the study clinic will not affect your participation in this study. Even if you agree today, you can withdraw your consent for off-site visits at any time by providing your request in writing to the person in charge of this study. In addition, before each off-site visit, we will confirm with you that you still agree and remember today's discussion.

PARTICIPANT INITIALS		
_____		I DO agree to have study visit procedures at a location other than the study clinic by clinic staff, when necessary.
Initials	Date	
_____		I DO NOT agree to have study visit procedures at a location other than the study clinic by clinic staff, when necessary.
Initials	Date	

SIGNATURE PAGE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/IEC:]
All of the above has been explained to me and all of my current questions have been answered. I understand that I can ask questions about any aspect of this research study during the course of this study, and that future questions will be answered by the researchers listed on the first page of this form or their representatives.

Any questions I have about my rights as a research participant will be answered by *[INSERT LOCAL IRB/IEC INFORMATION].*

I voluntarily agree to be in this research study. A copy of this permission form will be given to me.

_____
Participant's Name (Print)

_____ _____
Participant's Signature Date

_____
Study Staff's Name Conducting
Consent Discussion (Print)

_____ _____
Study Staff Conducting Date
Consent Discussion (Signature)

_____
Witness Name (Print)

_____ _____
Witness Signature Date

APPENDIX IV: SAMPLE INFORMED CONSENT FORM (SEXUAL PARTNER SUBSET)

SAMPLE INFORMED CONSENT FORM

MATRIX-003
Trial to Assess Acceptability and Safety of Two Placebo Intravaginal Ring (IVR) Designs

USAID

Version 1.0
29 June 2023

PRINCIPAL INVESTIGATOR: *[SITES TO INSERT]*
INSTITUTION: *[SITES TO INSERT]*
AFTER HOURS CONTACT DETAILS: *[SITES TO INSERT]*
STUDY SITE CONTACT DETAILS: *[SITES TO INSERT]*
SHORT TITLE: OCIS Placebo Ring Study

INFORMED CONSENT
[*SITES TO INSERT APPROPRIATE GREETING*] You are being invited to take part in this research study because you were identified by a MATRIX-003 study participant as their sexual partner. MATRIX-003 is looking at two placebo vaginal rings. Up to 30 sexual partners of MATRIX-003 participants like you will take part in this study across sites in the United States (US), South Africa, and Zimbabwe.

This study is sponsored by the US Agency for International Development (USAID) and conducted by the University of Pittsburgh/Magee-Womens Research Institute and Foundation (Pitt/MWRIF) as part of MATRIX: A USAID Project to Advance the Research and Development of Innovative HIV Prevention Products for Women. At this site, the person in charge of this study is [*SITES TO INSERT*].

KEY INFORMATION
- There are no study products (investigational drugs or other products) for you to use in this research study.
- The purpose of including sexual partners in this study is to better understand your views about the vaginal ring and its characteristics, and your views on your partner's experiences using the vaginal ring.
- If you qualify and choose to participate, you will be enrolled in the study and asked to answer questions and complete one conversation-style interview (in-depth interview) with trained study staff. The total length of your participation in the study will be one visit of approximately [*SITES TO SPECIFY TIMEFRAME*].
- Some risks or discomforts from participating in this study include:
  - Feeling uncomfortable with some of the questions study staff may ask about your sexual behaviors and relationships.

- Risk of conflict in your relationship if you or your partner are upset by discussions of sex, contraceptive choice, or HIV prevention.
- There may be no benefit to participating.
- Taking part in this research study is voluntary. You do not have to participate, and you can stop your participation in the study at any time.

Please take the time to read this entire form and ask questions before deciding to join the study. If you are willing to take part in the study, you will sign this form. A copy of this form will be offered to you. Signing this form does not mean you will be able to join the study. You must first complete the screening assessment to see if you are eligible. It is important to know that your participation in this research study is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

WHY IS THIS RESEARCH BEING DONE?
Investigators are studying products that women can use for HIV prevention and also for contraception. Vaginal rings are being evaluated as one potential way to deliver anti-HIV drugs and contraceptives into the vagina (in future studies). Both vaginal rings being used in the MATRIX-003 study are placebo vaginal rings (containing no medication). They are "prototype" rings for future studies.

The main goal of including sexual partners like you in this study is to better understand your views about the vaginal ring and its characteristics, and about your partner's experiences using the vaginal ring during the study.

WHO WILL BE IN THIS RESEARCH STUDY?
Up to 30 sexual partners of MATRIX-003 participants will be enrolled in the study across various sites in the United States (US), South Africa, and Zimbabwe.

WHAT WILL I BE ASKED TO DO IF I JOIN THIS RESEARCH STUDY?
You will be asked to answer questions and participate in an in-depth interview (IDI) with trained study staff. You will be asked about your attitudes towards and experiences with the vaginal ring, and your perspective of your partner's attitudes and experiences with the vaginal ring.

DO I HAVE TO BE IN THIS STUDY?
You do not have to be in this study. You can still get the care you need even if you do not join the study.

WHAT WILL HAPPEN DURING THE STUDY VISIT?
The study consists of one study visit, which will take place after you sign this informed consent form. If you agree and are eligible to participate, the IDI may take place today. If scheduling does not allow, it may take place on a different day that is convenient for you. Additional visit(s) may be conducted to complete all required procedures, if necessary. The visit will take place at a place agreed upon by you and the study staff, which may be the study clinic, your home, or another convenient location *[SITE TO INCLUDE ALTERNATE LOCATION]*.

The procedures done at this visit will take about *[SITES TO SPECIFY TIMEFRAME]*.

- Study staff will ask you where you live and other questions about you, and your understanding of the study requirements.

- You will be asked questions and have an IDI about:
  - Your age, education level, health, relationship status, and employment status.
  - Your views about HIV risk and prevention, sexual history, existing prevention methods, and aspects of your relationship.
  - Your views about the vaginal ring and your partner's experiences using the vaginal ring.
- The IDI will be performed [*SITES TO SPECIFY MECHANISM:* in the presence of one or more MATRIX-003 research staff members / remotely by a behavioral researcher]. The IDI will take approximately [*SITES TO SPECIFY TIMEFRAME*].
  - Study staff will make every effort to ensure your privacy and confidentiality. Information you provide during the IDI will not be shared with your partner.
  - During the IDI, the interviewer may take notes. Interviews will be audio-recorded to make sure we record your words exactly how you said them.
- In addition, study staff will:
  - Reimburse you for your visit.
  - Inform you about other available health and social services, if needed.
  - Schedule your next visit, if necessary.

RISKS AND/OR DISCOMFORTS

You may feel embarrassed and/or worried when talking about sexual activities, your living situation, or your opinions about HIV prevention strategies. You can choose not to answer questions at any time. Trained study staff will help you with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality during the study visit. Your visit will take place in private. Reports via computer will be stored in computers that are password-protected and will not include personal information that could identify or link information to you; only your study ID number will be recorded. However, it is possible that others may learn of your participation in this study, and because of this, may treat you unfairly or discriminate against you. If you have any problems, study staff will talk with you and try to help you.

The interviews with study staff will be audio recorded and questions of a personal nature may be asked. Responding to these questions may make you uncomfortable. The audio files will be put into writing by the person conducting the interview or by another person who does not know you and does not have your personal information. You should NOT identify anyone in the interviews and any names that might be mentioned on the recording will only be noted in the transcript using a generic description. The audio files will be stored in computers that are password protected.

BENEFITS

Though you may not experience any direct benefit from participation in this study, information learned from this study may help us learn ways to prevent the spread of HIV in the future. Your opinions about the ring are important to scientists working to develop this new prevention option.

Medical care for HIV infection and other health conditions will not be part of this study. This study cannot provide you with general medical care, but study staff will refer you to other available sources of care, if needed.

NEW INFORMATION
You will be told when study results may be available, and how to learn about them.

COSTS TO YOU
There is no cost to you for study-related visits.

REIMBURSEMENT
[*SITES TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT:*] You will receive [*SITES TO INSERT AMOUNT $XX*] for your time, effort, and travel to and from the clinic to take part in the in-depth interview.

CONFIDENTIALITY
We will make every effort to keep your information private and confidential. But we cannot guarantee it.

The study visit will take place in private. We will keep the information about your study visit in a secure place that only certain people can access for the purposes of this study. We will only enter your information into computers protected by passwords and will not include information that could identify you. Your identity on these records will be indicated by a number rather than by your name, and the information linking these numbers with your name will be kept separate from the research records. You can choose not to answer questions at any time. We will keep the audio recordings and materials from all interviews and discussions confidential and will only use study numbers or fake names. We will store the original records, including the audio recordings, for at least three years after completion of the study. These records will be stored in a secure, locked location.

Your personal information may be disclosed if required by law. For example, if we learn something that would immediately put you or others in danger, the study staff must take steps to keep you and others safe. This means that we have to share any information with the authorities (hospital, police, or social services) that tells us you may be in danger. For example, if you tell us that you plan to hurt or kill yourself, hurt or kill someone else, or if you tell us that someone is abusing or neglecting you.

This study will not use your name or identify you personally in any publication.

Your records may be reviewed by:
- Representatives of the US Federal Government, including US OHRP, USAID and/or USAID contractors, and other US, local or international regulatory authorities
- [*SITES TO INSERT APPLICABLE LOCAL AND NATIONAL AUTHORITIES*]
- Representatives of Pitt/MWRIF
- MATRIX representatives
- Study monitors
- Site IRB/IEC
- Study staff

[*US SITE TO INCLUDE/AMEND THE FOLLOWING:* Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form, you provide your authorization for the use and disclosure of information protected by the Health Insurance Portability and

Accountability Act (HIPAA) Privacy Rule. This includes things learned from the procedures described in this consent form. Study staff may also collect other information including your name, address, date of birth, and information from your medical records.]

[*NON-US SITES TO INCLUDE/AMEND THE FOLLOWING:* As part of your participation in this research study, your personal information may be sent to the United States for analysis or storage. This includes things learned from the procedures described in this consent form. Study staff may also collect other information including your name, address, date of birth, and information from your medical records. There are laws in the U.S. to protect your personal information when in that country.]

[*SOUTH AFRICA SITES TO INCLUDE/AMEND THE FOLLOWING:* The Protection of Personal Information Act (POPIA) ensures that all South African institutions collect, process, store, and share your personal information in a responsible manner and that they will be held accountable should they abuse or compromise your personal information.]

People outside the study team may need to see or receive your information for this study, such as those listed above. We cannot do this study without your authorization to use and give out your information to them. You do not have to give us this authorization. If you do not, then you may not join this study.

The use and disclosure of your information has no time limit. You may cancel your authorization to use and disclose your information at any time by notifying the Principal Investigator of this study in writing. If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

RESEARCH-RELATED INJURY

[*SITES TO INCLUDE/AMEND PER THEIR INSTITUTIONAL POLICY:* It is unlikely that you will be injured by being in this study. If you are injured or get sick from being in this study, please tell study staff immediately.

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. If you become ill or injured as a result of participation in this study, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer you for ongoing treatment for the injury, if needed. Clinical trial insurance purchased by the site will be responsible for compensating you for appropriate medical expenses for treatment of any such illness or injury. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation. The research center or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:

- Any injury that happens because you used other medicine during the study that you did not tell us about.
- Any injury that happens because you did not follow instructions given by the study doctor or nurse.
- Any injury that happens because of negligence on your part.]

[*SITES TO SPECIFY ANY ADDITIONAL POLICY RELATED TO EMERGENCY MEDICAL ATTENTION*]

[*US SITE TO INCLUDE/AMEND PER THEIR INSTITUTIONAL POLICY:* To pay these medical expenses, the site will need to know some information about you, like your name, date of birth, and social security number or Medicare Health Insurance Claim Number. This is because they have to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.]

You are not giving up any legal rights by signing this form.

CLINICALTRIALS.GOV
A description of this research study will be available on https://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

[*SOUTH AFRICA SITES TO INCLUDE LANGUAGE RELATED TO SOUTH AFRICAN NATIONAL CLINICAL TRIALS REGISTER*]

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER
[*SITES TO INCLUDE/AMEND PER THEIR INSTITUTIONAL POLICY:* Being in this study is completely voluntary. You may choose not to join this study or leave this study at any time. If you choose not to join or to leave the study, you can still join other studies and you can still access non-study services you would normally get at this clinic. If you leave the study, your study records may be kept for at least three years after study completion. If you want the results of the study after it is over, let the study staff members know.]

PROBLEMS OR QUESTIONS
If you ever have any questions about the study, or if you have a research-related injury, you should contact [*INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF*] at [*INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS*].

If you have questions about your rights as a research participant, you should contact [*INSERT NAME OR TITLE OF PERSON ON THE IRB/EC OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE*] at [*INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER*].

SIGNATURE PAGE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/IEC:]
All of the above has been explained to me and all of my current questions have been answered. I understand that I can ask questions about any aspect of this research study during the course of this study, and that future questions will be answered by the researchers listed on the first page of this form or their representatives.

Any questions I have about my rights as a research participant will be answered by *[INSERT LOCAL IRB/IEC INFORMATION].*

I voluntarily agree to be in this research study. A copy of this permission form will be given to me.

_____
Participant's Name (Print)

_____ _____
Participant's Signature Date

_____
Study Staff's Name Conducting
Consent Discussion (Print)

_____ _____
Study Staff Conducting Date
Consent Discussion (Signature)

_____
Witness Name (Print)

_____ _____
Witness Signature Date

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