MTN-032

Assessment of ASPIRE and HOPE Adherence

Microbicide Trials Network

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Division of AIDS, US National Institute of Allergy and Infectious Diseases
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LIST OF ABBREVIATIONS AND ACRONYMS

ACASI	Audio Computer-Assisted Self-Interviewing
AIDS	Acquired Immunodeficiency Syndrome
ARV	antiretroviral
BRWG	Behavioral Research Working Group
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CAB	community advisory board
CFR	Code of Federal Regulations
CRF	case report form
CRS	clinical research site
CSPRO	Census and Survey Processing System
CWG	Community Working Group
DAIDS	Division of AIDS
DLV	Delavirdine
EC	Ethics Committee
EFV	Efavirenz
FGD	focus group discussion
FHCRC	Fred Hutchinson Cancer Research Center
FTC	Emtricitabine
FTP	File Transfer Protocol
GCP	Good Clinical Practices
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
IDI	in-depth interview
IND	investigational new drug
IoR	Investigator of Record
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
LOC	Leadership and Operations Center
MTD	maximum tolerated dose
MTN	Microbicide Trials Network
MO	Medical Officer
NIH	National Institutes of Health
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIMH	National Institute of Mental Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OHRP	Office for Human Research Protections
PK	pharmacokinetics
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
PTID	Participant Identification
QC	quality control
RSC	Regulatory Support Center

RTI	Research Triangle Institute
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SOP	standard operating procedure
SSP	study specific procedures
STI	sexually transmitted infection
TDF	Tenofovir Disoproxil Fumarate
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
VR	vaginal ring

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INVESTIGATOR SIGNATURE FORM

Version 1.0

August 20, 2015

A Study of the Microbicide Trials Network

Funded by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US Eunice Kennedy Shriver National Institute of
Child Health and Human Development
US National Institute of Mental Health
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I, the Investigator of Record (IoR), agree to conduct this study in full accordance with the provisions of this protocol. I agree to maintain all study documentation for a minimum of three years after submission of the site's final Financial Status Report to the US Division of Acquired Immunodeficiency Syndrome (DAIDS), unless otherwise specified by DAIDS or the Microbicide Trials Network (MTN) Leadership and Operations Center (LOC). Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, DAIDS and other entities for review prior to submission, as required by the MTN Publication Policy.

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

_____
Name of Investigator of Record

_____ _____
Signature of Investigator of Record Date

MTN-032

Assessment of ASPIRE and HOPE Adherence

PROTOCOL SUMMARY

Short Title:	Assessment of ASPIRE and HOPE Adherence
Funders:	Division of AIDS, NIAID, NIMH, NICHD, US NIH
Protocol Chair:	Elizabeth Montgomery, PhD, MHS
Protocol Co-Chairs:	Sarita Naidoo, PhD Jonathan Stadler, PhD, MA
Sample Size:	Phase 1: Up to 224 former ASPIRE participants Phase 2: Approximately 84 former HOPE participants who have completed Phase 1
Study Population:	Former ASPIRE and HOPE participants
Study Sites:	ASPIRE and HOPE site(s) selected by the MTN Executive Committee
Study Design:	Exploratory sub-study of the ASPIRE and HOPE trials that will utilize qualitative In-Depth Interviews (IDIs) and Focus-Group Discussions (FGDs)
Study Duration:	Approximately 4-6 months for recruitment and follow-up for each phase at each site

Primary Objective:

- To explore socio-contextual and trial specific issues, which affected participants' adherence to the dapivirine vaginal ring (VR)

Secondary Objectives:

- To explore participants' HIV risk and perceptions of HIV risk, in general and specific to:
  - motivation to participate in ASPIRE and/or HOPE
  - product use (or lack of) in ASPIRE and/or HOPE

- To explore factors influencing product initiation and patterns of use during ASPIRE and/or HOPE

- To explore participants' perceptions of various adherence support interventions and engagement activities implemented (or not implemented) during ASPIRE and/or HOPE

- To explore participants' understanding of the ASPIRE results and ring efficacy, and the impact of this understanding on
  - participants' intention and/or ability to join HOPE and continue in follow-up

- adherence to the dapivirine VR as part of an open label extension trial as compared to adherence in a Phase 3 safety and effectiveness trial

Exploratory Objective:

- To explore participants' preference regarding drug delivery modalities and attributes that might encourage end-user uptake

1 KEY ROLES

1.1 Protocol Identification

Protocol Title: Assessment of ASPIRE and HOPE Adherence

Protocol Number: MTN-032

Date: August 20, 2015

1.2 Sponsor and Monitor Identification

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2 INTRODUCTION

2.1 Microbicides and Human Immunodeficiency Virus (HIV) Prevention

In 2012, 2.3 million people became newly infected with HIV and 1.6 million people lost their lives to acquired immunodeficiency syndrome (AIDS). Every 60 seconds, a young woman is infected with HIV.[1] According to the Joint United Nations Programme on Human Immunodeficiency Virus (HIV)/AIDS (UNAIDS) Global Report, the estimated number of individuals living with HIV is 35.3 million globally. Women and girls continue to be disproportionately affected by HIV in sub-Saharan Africa, where women account for approximately 60% of people living with HIV. Given the high rates of HIV infection among women, female controlled prevention options remain a global priority. The ongoing development of safe and effective HIV prevention technologies that can be made easily accessible to developing countries remains a public health priority.

Unprotected heterosexual intercourse is currently the leading mode of HIV acquisition among women. Condoms, as the most widely available HIV prevention methods require the consent of the male partnerCorrect and consistent use of latex condoms is one proven method of preventing HIV acquisition; however, condoms are widely regarded as inadequate prevention options for women, because many women are unable to negotiate condom use with their partners. Thus, developing HIV prevention options that women can use remains a global concern. Vaginal microbicides, which are self-initiated and controlled, offer women a critically needed biomedical prevention tool that will complement existing HIV prevention strategies as well as future products that are being developed.

With successful proof-of-concept that antiretroviral (ARV)-based microbicides reduce the risk of HIV-1 acquisition, confirmatory work and further trials involving different ARV compounds, of various formulations and differing dosing strategies are required to provide further options to end-users.

2.2 HIV Prevention Product Adherence

Results from VOICE, a multi-site randomized placebo-controlled trial of three different formulations of tenofovir among women in sub-Saharan Africa, indicated that drug was detected in less than a third of blood samples from participants assigned to the Truvada and oral tenofovir arms, and in less than a quarter of samples from participants assigned to the tenofovir gel arm.[2] If trial participants do not consistently use products, demonstration of effectiveness is undermined even if the product is efficacious. The link between product adherence and the likelihood of infection has been demonstrated in several microbicide trials. The CAPRISA 004 trial of tenofovir gel indicated that: 1) HIV incidence was significantly higher among participants who used the product less frequently, and 2) greater protection was conferred with higher drug concentration in the cervico-vaginal fluids of participants who received the active gel.[3] Similarly in the iPrEx trial of oral prophylaxis with Truvada, the odds of infection among men and transgender women were substantially lower among those with detectable drug level, a biomarker of adherence to product use.[4] Partners PrEP, which tested both daily dosing of tenofovir and Truvada, found that the estimated protective effect of pre-exposure prophylaxis (PrEP) against HIV, based on concentrations of tenofovir consistent with daily dosing, was 88% for individuals receiving Tenofovir Disoproxil Fumarate (TDF) and 91% for individuals receiving emtricitabine (FTC)/TDF.[5]

Adherence to a trial product is required to determine a product's effectiveness, and accurate measurement of product adherence is critical to help explain why a product may or may not be

effective. It is unknown what level of participant adherence is needed in order to achieve sufficient levels of drug to provide efficacy. Even with adherence levels as high as 60%, the effectiveness of a product can be reduced to less than half of its true biological efficacy, resulting in a significant decrease in a trial's ability to detect efficacy.[6] Accurate measurement also plays an important role in estimating product effectiveness. If participants' actual use of a product does not match what is measured through self-report or other methods, a trial will be unable to determine whether lack of effectiveness is due to inefficacy of the drug or simply lack of use by participants.[7]

For a microbicide to be effective, it is essential that it is used correctly and consistently, and importantly, is acceptable to the user. In addition, a product used independently of sex could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse. Higher adherence to a product may translate into higher effectiveness of the product. It is likely that products that can be applied less frequently or products that can remain *in situ* for an extended duration will be more acceptable and will achieve better adherence. Vaginal rings (VRs) that need to be replaced monthly may have benefits over dosage forms that need to be used more frequently.

2.3 Dapivirine Vaginal Ring

2.3.1 Description

Dapivirine, a non-nucleoside reverse-transcriptase inhibitor (NNRTI), is a substituted di-amino-pyrimidine (DAPY) derivative with potent antiviral activity against HIV-1. Dapivirine is chemically described as 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile.[8] The dapivirine matrix VR is a flexible ring containing 25 mg of drug substance dispersed in a platinum-catalyzed cured silicone matrix. When delivered via VR, dapivirine has demonstrated favorable safety and pharmacokinetic profiles as described in Section 2.3.2.

Dapivirine was originally developed by Janssen Research and Development (formerly Tibotec Pharmaceuticals Ltd.), a subsidiary of Johnson & Johnson, as an oral ARV compound for treatment of HIV/AIDS and was tested in Phase 1 and 2 clinical trials in more than 200 participants.[9] However, dapivirine is also a promising topical microbicide candidate due to its proven *in vitro* and *in vivo* efficacy and favorable safety profile as well as its physical and chemical properties. Dapivirine has potent activity against wild-type HIV-1 strains and strains harboring different resistance-inducing mutations. Dapivirine's ARV profile is superior to that of several other NNRTI drugs, including nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV). Like other NNRTIs, *in vitro* tests have also shown that dapivirine is not active against HIV-2 and has little or no activity against common sexually transmitted infections (STI), therefore, it is not intended for use against HIV-2 or other STIs. Dapivirine does not have any contraceptive properties.[10] Detailed information on dapivirine is available in the Dapivirine VR Investigator's Brochure (IB).[11]

The International Partnership for Microbicides (IPM) has investigated a wide range of dosage forms for the development of topical microbicide products, including vaginal gels, rings, films, tablets and soft gel capsules. The vaginal gel was the initial dosage form chosen for a dapivirine-based microbicide because the majority of previous microbicides to have entered clinical trials were also vaginal gels and therefore a wealth of information was available on that dosage form. However, the dapivirine silicone elastomer VR has now been prioritized over all other dosage forms for the following reasons:

- Clinical trials have demonstrated sustained delivery of high levels of dapivirine for up to 1 month;
- Since the ring is able to deliver drug for at least 1 month, the burden of user-dependent adherence is lower than for once daily products;
- Product acceptability studies and the experience gained from marketed VR products have established a high level of acceptance and adherence from women using VR with similar physical characteristics;
- The overall cost for the VR is relatively low;
- Minimal storage space is required for the VR when compared with once daily products

Summaries of the safety and tolerability of dapivirine delivered orally and vaginally as evaluated in clinical studies by IPM and Tibotec Pharmaceuticals can be found in the following section.

2.3.2 Clinical Studies

Multiple clinical trials have evaluated the safety of dapivirine in VRs, gels and oral formulation. These clinical trials support the favorable safety profile and tolerability of dapivirine in general and specifically in vaginal delivery formulations.

To date, 27 Phase 1 and Phase 1/2 clinical trials of dapivirine have been conducted: [11]

- Eight trials of dapivirine VRs (25 mg and 200 mg loads) in which 469 participants were assigned to dapivirine VRs,
- Eight trials of dapivirine vaginal gel in which 491 participants used dapivirine vaginal gel,
- And, eleven trials of oral dapivirine among 211 participants.[8]

Clinical Pharmacokinetics of Dapivirine Vaginal Rings

In all clinical trials of dapivirine VRs and gels to date, dapivirine concentrations in plasma have been very low (less than 2 ng/mL) or undetectable after up to 84 days exposure. Plasma levels of dapivirine after vaginal exposure in clinical trials are 1000-fold lower than maximum plasma concentrations after oral administration of dapivirine (e.g., C_{max} after 300 mg b.i.d. for 14 days was 2286 ng/mL).[11]

The clinical pharmacokinetic profile of Ring-004 in IPM 013 showed a rapid increase in plasma and vaginal fluid concentrations of dapivirine after ring insertion, resulting in maximum concentrations in plasma by Day 7 and in vaginal fluids between Day 1 and Day 14, after which concentrations decreased steadily over the remainder of a 28-day or 35-day ring use period. Plasma dapivirine concentrations did not exceed 1 ng/mL, and were therefore well below concentrations at the maximum tolerated dose (MTD) for multiple oral doses (300 mg b.i.d. for 14 days; plasma C_{max} of 2286 ng/mL). For dapivirine in vaginal fluids, the highest concentration was observed in the area where the ring was placed, followed by the cervix, with the lowest concentrations near the introitus.

Data from post-use analysis of residual levels of dapivirine in Ring-004 (IPM 015, in which a ring was inserted once every 28 days over a 12-week period) indicate that, on average, 4 mg of dapivirine were released over approximately one month of ring use. The mean amounts of dapivirine remaining in the used rings were similar for Weeks 4, 8 and 12 (post-insertion), at 21.09 mg, 21.54 mg and 21.84 mg, respectively.[11] No clear relationship (neither linear nor exponential) was observed between the residual amount of dapivirine and corresponding

plasma concentrations (i.e., at scheduled ring removal). It would appear that plasma concentrations below approximately 200 pg/mL were generally associated with above-average ring residual amounts, while the residual amounts appeared relatively constant (at levels between approximately 20 and 22 mg) for plasma concentrations above this value (200 pg/mL).[11]

Safety of Dapivirine Vaginal Rings

Table 1: Clinical Phase I/II Trials of Dapivirine Vaginal Rings

Trial Details			**Number of Participants**				
Trial Number	**Description**	**Country**	**Ring-001 reservoir (200 mg)**	**Ring-002 reservoir (25 mg)**	**Ring-003 matrix* (25 mg)**	**Ring-004 matrix** (25 mg)**	**Placebo Ring**
IPM 001	Safety and pharmacokinetics (PK) in women; 7 days	Belgium	12	--	--	--	12 (crossover)
IPM 008	Safety and PK in women; 7 days	Belgium	--	10	--	--	3
IPM 013	Safety and PK in women; 56/57 days	Belgium	--	--	--	36	12
IPM 015	Safety and PK in women; 84 days	Multiple Countries in Sub-Saharan Africa	--	--	--	140	140
IPM 018	Safety and PK in women; 28 days	Belgium	--	8	8	--	8
IPM 024	Safety and PK in women; 28 days	Belgium	--	--	--	8	8
MTN-013/ IPM 026***	Safety and PK in women	United States	--	--	--	12	12
IPM 028	Drug-drug Interaction (miconazole nitrate); 28 days	Belgium				36	0
IPM 034	Safety and PK in women; 7, 14, 28, 56, or 84 days	Belgium				40	0
TOTAL			**12**	**18**	**8**	**272**	**195**

*Tin-catalyzed matrix ring.
**Platinum-catalyzed matrix ring
***MTN-013/ IPM 026 was the first in human clinical trial of a VR containing maraviroc alone, dapivirine alone or a combination of the two (dapivirine/maraviroc) compared to placebo. The dapivirine VR arm included 12 participants. It should be noted, however, that the dapivirine VR was similar to Ring-004, but of slightly different composition.

Across all clinical trials with multiple ring configurations in healthy participants, the dapivirine VR was generally safe and well-tolerated.[11]

MTN-020, A Study to Prevent Infection with a Ring for Extended Use (ASPIRE), was a Phase 3 clinical trial designed to assess the efficacy and safety of a ring containing 25 mg of dapivirine for the prevention of HIV-1 acquisition in women. The double-blind, randomized controlled trial enrolled HIV-uninfected women, between the ages 18 – 45. A total of 2629 women from Malawi, South Africa, Uganda, and Zimbabwe enrolled in the trial. Participants replaced the ring monthly for a minimum of one year. MTN-020 aimed to determine the safety and efficacy of the dapivirine ring in preventing HIV-1 infection among healthy sexually active HIV-uninfected women when inserted vaginally once every 4 weeks. Additional goals of MTN-020 included the assessment of participant acceptability and adherence to the investigational product, HIV-1 drug resistance mutations among participants who acquire HIV-1 infection and establishing steady state drug concentrations in the study population. Results from this study are anticipated Q1 2016.

MTN-025, the HIV Open-label Prevention Extension (HOPE) trial, is a multi-site, open-label, randomized, Phase 3B trial that will be implemented if the dapivirine VR is found to be a safe and effective HIV prevention method in the MTN-020 (ASPIRE) trial. Eligible HIV-uninfected ASPIRE participants will receive the same VR used in MTN-020, a silicone elastomer VR containing 25 mg of dapivirine, to be replaced monthly, for a total period of 12 months of use. Study follow-up visits will occur monthly for the first 3 months and quarterly thereafter, reflecting a transition to a more real-world type of follow-up (versus a clinical trial approach). The study will compare the safety of and participant adherence to dapivirine (25 mg) in a silicone elastomer VR. The HOPE sample size will be contingent upon how many former ASPIRE participants are interested in enrolling, are HIV-negative and otherwise eligible to enroll.

2.3.3 Behavioral Studies

Acceptability of Dapivirine VR

IPM 011 assessed the acceptability of the dapivirine VR and the placebo VR in 170 women. The trial was conducted across multiple sites in Tanzania and South Africa. The study participants found the ring to be very comfortable (95%), very easy to insert (94%) and remove (92%), and rarely were the rings felt during daily activities. All questionnaire respondents, when asked if they would be willing to use the VR if shown to be effective for HIV prevention, replied that they would use the VR.[12]

In IPM 015, at Week 12, 97% of African women reported that the dapivirine VR was comfortable and that they were willing to use the VR if it was found to be effective. Women preferred to wear the VR every day (97%) and reported that the ring did not interfere with their daily activities (89%). In terms of the male partner acceptability, 63% of women reported that their partner did not feel the ring during sex. Of those participants who reported that their partner felt the ring, only 1% reported that this might be or definitely was a problem.[13]

Adherence to Dapivirine VR Use

In IPM 011, 11% of the women experienced expulsions/removal, with the most common reason being ‘menses related’. In the majority of cases (64%), the VR was washed and re-inserted.[12]

In IPM 015, perfect adherence, defined as never having the VR out for more than an entire day, was reported by 92% of the female participants. Of the women who reported that the ring was out, the most common activity for expulsion was urination/defecation. The most common reason reported by participants for VR removal was cleaning. As the study progressed, more

women reported removing the VR prior to sexual intercourse, 17% at week 2 and 36% by week 12.[13]

2.4 HIV Risk Perception and Motivation for Trial Participation

One possible factor that may contribute to low adherence is participants' varying perceptions of HIV risk, as well as reasons for joining the trial. A woman's perception of HIV risk is influenced by her individual level behaviors, such as engagement in high-risk sex, as well as the social-cultural context in which she lives. This perception of risk has often been linked to willingness to participate in hypothetical HIV prevention trials [14-25] and occasionally to interest in and acceptance of an HIV prevention product.[26]

Despite these linkages, the question remains: how does one's perception of HIV risk contribute to product adherence once enrolled in a trial? One might expect that a higher perception of risk would lead to more consistent product use due to a greater desire for protection. However, a recent study in India found that contrary to this hypothesis, increased HIV risk perception was negatively associated with consistent gel use. Indeed, women who perceive themselves at higher risk may be less able to adhere to product use for a host of contextual reasons.[27] Further, it is not well understood how regular (e.g., monthly) HIV testing may change individual risk perception and adherence behavior over time. By investigating how the socio-cultural environment influences perception of risk and ultimately product use among ASPIRE and HOPE participants, this study hopes to contribute to a greater understanding of the relationship between these issues.

Other motivations for joining an HIV prevention trial, such as increased access to quality health care and altruism, and their contribution to product adherence will also be explored.

2.5 Rationale for Study Design

MTN-032, an exploratory study, is primarily designed to identify factors that may have affected participant adherence to study product in ASPIRE and HOPE. MTN-032 will also elicit perceptions about various participant engagement and adherence promotion interventions implemented in ASPIRE and may also explore the potential use of incentives to promote adherence to VR use. There are few published studies investigating whether adherence interventions facilitate or maintain microbicide use in general and dapivirine VR use in particular.

There is little known about what works to encourage uptake and sustain product use in microbicide trials. MTN-032 will use study product adherence results from ASPIRE and HOPE, qualitative in-depth interviews (IDI) and focus group discussions (FGD) to explore study product adherence behaviors and strategies used to overcome adherence challenges. An in-depth understanding of the various socio-behavioral factors that contribute to product use adherence may assist in the interpretation of past and ongoing study results and inform implementation of future studies.

In the absence of a "gold standard," it is recommended that HIV prevention trials use multiple measures to capture adherence.[28] However, the use of multiple adherence measures often results in some level of discrepancy between measures.[29] Any potential difference in reported adherence across measures raises questions around true levels of product adherence as well as the measures themselves. It is for these reasons that the adherence measures utilized in this study will be derived from biological, objective markers of adherence.[30]

This study will examine the role of the contextual environment on adherence. Generally, trials attempt to discourage behaviors that may have a detrimental effect on outcomes through participant-focused counseling. For example, they may provide guidance and support to participants to maintain high levels of product use. However, despite a trial's best efforts to support adherence and/or discourage sexual behaviors that may contribute to dilution of efficacy, the socio-cultural context,[31] including the trial context, organization of the participant's social environment (i.e., living arrangements, importance and role of partners, family members, and the larger social network), and individual beliefs and attitudes about HIV risk and/or the trial may influence these behaviors. Furthermore, a trial's efforts to discourage non-adherence to study product through ongoing counseling and messaging may promote social desirability bias in participant responses about these behaviors. MTN-032 will explore the impact of adherence support interventions, including the potential effects of this support on the dynamic between trial participants and trial staff.

3 OBJECTIVES

3.1 Primary Objective

- To explore socio-contextual and trial specific issues which affected participants' adherence to the dapivirine VR

3.2 Secondary Objectives

- To explore participants' HIV risk and perceptions of HIV risk, in general and specific to:
    - motivation to participate in ASPIRE and/or HOPE
    - product use (or lack of) in ASPIRE and/or HOPE

- To explore factors influencing product initiation and patterns of use during ASPIRE and/or HOPE

- To explore participants' perceptions of various adherence support interventions and engagement activities implemented (or not implemented) during ASPIRE and/or HOPE

- To explore participants' understanding of the ASPIRE results and ring efficacy, and the impact of this understanding on
    - participants' intention and/or ability to join HOPE and continue in follow-up
    - adherence to the dapivirine VR as part of an open label extension trial as compared to adherence in a Phase 3 safety and effectiveness trial

3.3 Exploratory Objective

- To explore participants' preference regarding drug delivery modalities and attributes that might encourage end-user uptake

4 STUDY DESIGN

4.1 Identification of Study Design

The MTN-032 trial is a two-phase exploratory sub-study of the ASPIRE and HOPE trials. MTN-032 will utilize qualitative in-depth interviews (IDIs) and focus-group discussions (FGDs) to explore the socio-contextual and trial specific issues which affected ASPIRE and HOPE trial participants' adherence to the dapivirine VR.

4.2 Description of Study Population

- Phase 1: The MTN-032 study population will consist of former ASPIRE participants who meet eligibility criteria as described in Sections 5.3.1 and 5.4.

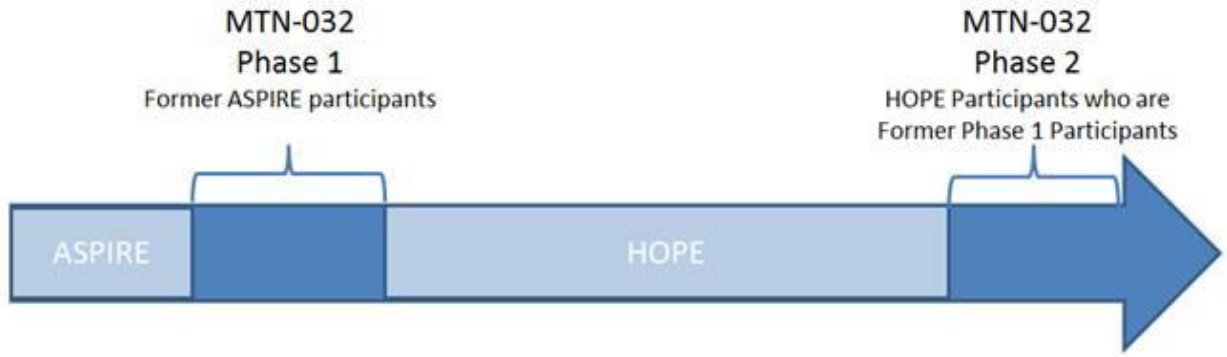
- Phase 2: The MTN-032 study population will consist of HOPE participants who meet eligibility criteria as described in Sections 5.3.2 and 5.4.

4.3 Time to Complete Accrual

- Phase 1: Approximately 4-6 months for recruitment and follow-up at each site. See Section 10.4 for additional details.

- Phase 2: Approximately 4-6 months for recruitment and follow-up at each site. See Section 10.4 for additional details.

Figure 1: MTN-032 Study Timeline in Relation to the ASPIRE and HOPE Timelines



4.4 Expected Duration of Participation

The total duration of study participation for each participant is not anticipated to exceed 6 hours for each phase, including administrative and data collection procedures. However, the duration of participation is dependent upon the scheduling of IDIs or FGDs. Each IDI is not anticipated to exceed 2 hours and each FGD is expected to take up to 4 hours. Multiple visits may be conducted to complete all required procedures, if necessary.

4.5 Sites

MTN-032 participants will be recruited from former ASPIRE and current HOPE clinical research sites (CRS) selected by the MTN Executive Committee.

5 STUDY POPULATION

5.1 Selection of the Study Population

A sample of up to 224 women who participated in ASPIRE will be selected for participation in Phase 1 of this study. Approximately 84 former Phase 1 participants who participated in HOPE will be selected for participation in Phase 2. Inclusion and Exclusion Criteria, Sections 5.3 and 5.4, respectively, are used to ensure the appropriate selection of study participants for MTN-032.

5.2 Recruitment

Participants will be recruited from ASPIRE and HOPE study sites in Africa. Recruitment materials will be approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs) prior to use. Site community representatives should advise on these materials before they are submitted to the IRB/EC for review. Community education strategies, including group sessions, may be employed as part of participant/partner outreach.

5.3 Inclusion Criteria

5.3.1 Phase 1: Former ASPIRE participants

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

1. Participated in the ASPIRE protocol, randomized to active product and informed of their randomization assignment.

2. Able and willing to provide written informed consent in one of the study languages.

3. Able and willing to complete the required study procedures.

For participants who did not acquire an HIV infection while taking part in ASPIRE:

4. Evidence of study product dispensation at a minimum of three consecutive ASPIRE scheduled clinic visits.

5. Have a minimum of three ASPIRE PK data measurement points available.

For participants who acquired HIV infection while taking part in ASPIRE:

6. Evidence of study product dispensation in the month prior to the participant's acquisition of HIV infection.

7. Have a minimum of one ASPIRE PK data measurement available.

5.3.2 Phase 2: HOPE participants

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

1. Participated in the HOPE protocol.

2. Completed Phase 1 of MTN-032.

3. Able and willing to provide written informed consent in one of the study languages.

4. Able and willing to complete the required study procedures.

For participants who did not acquire an HIV infection while taking part in HOPE:

5. Evidence of study product dispensation for a minimum of three consecutive months.

For participants who acquired an HIV infection while taking part in HOPE:

6. Evidence of study product dispensation in the month prior to the participant's acquisition of an HIV infection.

5.4 Exclusion Criteria: Phase 1 & 2

Potential participants who meet the following criteria will be excluded from both phases of the study:

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

6 STUDY PRODUCT

MTN-032 will not involve the administration of any study product.

7 STUDY PROCEDURES

7.1 Phase 1

In Phase 1 of the MTN-032 study, up to 224 ASPIRE participants who had varying levels of adherence to the dapivirine VR will be enrolled (see Section 10.3 for sample composition details). Based upon objective measures of adherence, participants will be pre-designated into groups and then randomly selected and approached for study participation. Final group designation will be dependent on adequate sample size and ability to determine level and pattern of adherence, but is likely to resemble the following:

- Consistently low adherence
- Inconsistent adherence
- Consistently high adherence

Note: Specific information regarding group designation will be specified in the MTN-032 study-specific procedures (SSP) Manual, available at http://www.mtnstopshiv.org/studies.

After being presented and explained their ASPIRE adherence results, enrolled participants will be asked to complete a single IDI or a FGD (with other participants in the same adherence group) where factors influencing adherence, as well as strategies used to overcome adherence challenges, will be explored. Intermittent and strategic use of the ring around study visits will also be discussed.

7.1.1 Screening and Enrollment – Administrative, Behavioral and Regulatory Procedures

Table 2: Screening and Enrollment Procedures

Screening and Enrollment	
Component	**Procedures**
Administrative and Regulatory	• Confirm eligibility • Obtain written informed consent for screening and enrollment • Assign a unique Participant Identification (PTID) Number • Collect demographic data • Collect locator information • Provide reimbursement for study visit
Behavioral	• Administer behavioral questionnaire(s) • Conduct in-depth interview (IDI) or Focus Group Discussion (FGD)

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

7.2 Phase 2

Approximately 84 former Phase 1 participants who completed HOPE will be enrolled into Phase 2 (see Section 10.3 for sample composition details). Prior to being consented to Phase 2, participants from Phase 1 will be designated into groups based upon objective measures of adherence (during ASPIRE and HOPE) similar to Phase 1, and randomly selected for Phase 2 participation from among that adherence group.

The second phase will examine the effect of known VR efficacy on adherence to study product in HOPE. In particular, this phase will focus on:

- Motivations for participants with varying levels of adherence in ASPIRE to enroll into HOPE
- What effect, if any, knowledge of the ring's efficacy had on adherence behavior
- Motivation for continued study participation among those participants who were inconsistently or not adherent
- VR uptake, marketing and other product roll-out issues

A single IDI will be conducted with each enrolled participant. Whenever possible, effort will be made to enroll eligible former HOPE participants who took part in the HOPE qualitative component.

7.2.1 Screening and Enrollment – Administrative, Behavioral and Regulatory Procedures

Table 3: Screening and Enrollment Procedures

Screening and Enrollment	
Component	**Procedures**
Administrative and Regulatory	• Confirm eligibility • Obtain written informed consent for Phase 2 screening and enrollment • Collect demographic data • Collect locator information • Provide reimbursement for study visit
Behavioral	• Administer behavioral questionnaire(s) • Conduct in-depth interview (IDI)

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

7.3 Behavioral Evaluations

The study will address questions related to the primary and secondary objectives of product adherence facilitators and challenges experienced by ASPIRE and HOPE participants. The study will also explore participants' views on acceptable approaches to support study product adherence (e.g., financial incentives). These questions will be assessed via behavioral questionnaires and either IDIs or FGDs conducted by trained interviewers/facilitators. In addition, the study aims to gain further insight on:

- Attitudes and understanding of VR efficacy and the concept of partial efficacy
- Product storage and use, including facilitators and barriers
- Motivations to join the trial
- Socio-cultural context of risk behaviors and risk perceptions over time
- Perceived feasibility of continued study product use with and without adherence support interventions
- Attitudes towards other types of adherence support interventions (e.g., financial incentives)

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

7.3.1 Behavioral Questionnaires

Behavioral questionnaires will be used to inform different dimensions of data collected during the IDIs and FGDs.

7.3.2 In-Depth Interviews (IDIs) and Focus Group Discussions (FGDs)

Both IDIs and FGDs will include, but not be limited to, topics such as:

- Reactions to and explanation of longitudinal adherence data
- Descriptions of ring use practices (e.g., unorthodox use, sharing, disposal, removal, etc.)
- Main challenge(s) encountered with ring use

- Other reasons for nonuse or removal (e.g., wanting to get pregnant, menses, etc.)
- Main facilitator(s) to ring use
- Participant engagement activities influencing ring use patterns (e.g., ring uptake, sustained use) during ASPIRE and/or HOPE
- Other factors (e.g., situational, relationship, trial-specific, social/cultural/economic, sex and menstruation related, etc.) influencing ring use patterns (e.g., ring uptake, sustained use) during ASPIRE and/or HOPE
- Understanding of (partial) efficacy and simultaneous use of various methods of prevention (e.g., ring, condoms, contraceptives)
- Recommendations for "real world" implementation (e.g., overcoming financial barriers)
- Factors that affect decision to join HOPE (e.g., situational, relationship, trial-specific, social/cultural/economic, sex and menstruation related, fertility intentions, etc.)

IDI and FGD guides will be developed by qualified social scientists and administered by qualified 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 and translated into English (if applicable).

Various tools will be used to facilitate interviews and discussion of sensitive topics with both IDI and FGD participants. These may include, but not be limited to, visual displays of objective adherence marker data/results and drug use patterns over time, study visit timelines, show-cards listing topics and themes previously elicited in other studies, and newspaper clippings of other study results when appropriate.

8 ASSESSMENT OF SAFETY

MTN-032 is a minimum-risk research study. It does not involve a study product nor involve clinical, laboratory or other procedures associated with significant risk to participants. Therefore, few safety concerns are expected as a result of study participation, see Section 13.4.1 for expected risks of trial participation. The study site IoR is responsible for continuous monitoring of all study participants and for alerting the protocol team if unexpected safety events arise. Study sites will have written procedures for ensuring prompt reporting to the IRB/EC, of any unanticipated problem involving risks to subjects or others. No safety events will be captured in the study database.

8.1 Safety Monitoring

Site IoRs are responsible for continuous close safety monitoring of all study participants, and for alerting the protocol team if unexpected concerns arise. Since the safety risks are minimal in this study, if any such unexpected concerns arise, site study staff must make the site IoR aware. The site IoR will provide follow-up guidance to the appropriate on-site staff member (e.g., site clinician, counselor, nurse, etc.).

The Manual for Expedited Reporting of Adverse Events to Division of AIDS (DAIDS) will not be used for this study for the following reasons: 1) this study does not involve a study drug and is non-invasive; and, 2) adverse events are not primary or secondary objectives of the study. Untoward clinical or medical occurrences reported by study participants to have been experienced during study participation will be recorded in participant file notes.

8.2 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 – 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. Social harms that are judged by the IoR/designee to be related to study participation will be reported to the DAIDS Medical Officer (MO), Protocol Chairs, and responsible site ECs/IRBs according to their individual requirements beginning at the time of enrollment (i.e., after a participant signs the informed consent and eligibility is confirmed) until study participation is complete. 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. Each site will provide such care and counseling in accordance with standardized guidance provided in the MTN-032 SSP Manual. While maintaining participant confidentiality, study sites may engage their community advisory boards (CABs) in exploring the social context surrounding instances of social harm. Additionally, a Standard Operating Procedure (SOP) for emergency procedures will be developed for the MTN-032 site staff to be used in situations of social harm and when situations that require immediate attention are identified, including domestic violence, and suicidal ideation or behavior. The SOP will provide clear guidelines for site staff to refer participants in these situations to the relevant institution/body and to provide feedback to the protocol team.

9 CLINICAL MANAGEMENT

There are no additional clinical management considerations for participants enrolled in this study. Participants who express concerns with social, psychological or clinical issues will be referred for appropriate care to services available at the CRS, or at nearby partnering facilities.

9.1 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The IoR 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. Participants also may be withdrawn if the study sponsors, government or regulatory authorities, including the Office for Human Research Protections (OHRP), or site IRBs/ECs terminate the study prior to its planned end date. Study staff members will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may do so if the accrual target has not yet been met for that Phase.

10 ANALYTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

MTN-032 is an exploratory sub-study of the ASPIRE and HOPE trials that will utilize qualitative research methods, specifically IDIs and FGDs.

The main goal of the study is to explore the socio-contextual and trial specific issues which affected ASPIRE and HOPE participants' adherence to the dapivirine VR as captured via objective marker data.

Secondary objectives of the study include:

- To explore participants' HIV risk and perceptions of HIV risk, in general and specific to their motivation to participate in ASPIRE and/or HOPE as well as their product use (or lack of) during ASPIRE and/or HOPE
- To explore factors influencing product initiation and patterns of use during ASPIRE and/or HOPE
- To explore participants' perceptions of various adherence support interventions and engagement activities implemented (or not implemented) during ASPIRE and/or HOPE
- To explore participants' understanding of the ASPIRE results and ring efficacy, and the impact of this understanding on their intention and/or ability to join HOPE and continue in follow-up, as well as their adherence to the dapivirine VR as part of an open label extension trial as compared to adherence in a Phase 3 safety and effectiveness trial

10.2 Study Endpoints

After being presented and explained their ASPIRE adherence results, Phase 1 participants will be asked to complete a single IDI or FGD (with other participants in the same designated adherence group) to explore:

- Factors influencing adherence
- Strategies used to overcome adherence challenges
- Intermittent and strategic use around study visits

Phase 2 will examine the effect of known ring efficacy level on adherence in participants who take part in HOPE, an open label extension trial to ASPIRE. A single IDI will be conducted. In particular, this phase will focus on:

- Motivations for participant enrollment into HOPE among participants with varying levels of adherence in ASPIRE
- What effect, if any, knowledge of the ring's efficacy had on adherence behavior
- Motivation for continued study participation among those participants who were inconsistently or not adherent
- VR uptake, marketing and other product roll-out issues

10.3 Sample Size and Composition

A sample size of up to 224 ASPIRE participants will be selected to take part in Phase 1 of the study, and approximately 84 Phase 1 participants who then enroll in HOPE will be selected to take part in Phase 2. Two items thought to be of significance were factored into the sample size: the number of sites and the required number of participants for Phase 2 of MTN-032. First, it is important to have at least one site from each country represented, with at least three sites from South Africa in order to have a somewhat representative country sample. Therefore, seven (7) sites were thought to be ideal. Second, a minimum of twelve (12) participants per site were thought to be necessary in order to achieve a meaningful sample size for Phase 2 of the study. Thus, given loss-to-follow-up between Phase 1 and 2 and other issues that may arise, a sample size of 224 ASPIRE participants (in order to re-interview 84 who later go on to enroll in HOPE) was thought to be necessary.

In Phase 1, up to 224 ASPIRE participants who had varying levels of adherence to the dapivirine VR will be enrolled. Similarly, approximately 84 of those women who then go on to take part in HOPE will be identified and enrolled in Phase 2. Based upon participants' ASPIRE or HOPE objective adherence marker results, participants will be pre-selected for study participation in Phase 1 or 2, respectively. Participants will be categorized into one of the following groups (with final group designation dependent on adequate sample size and ability to determine pattern of product use):

- Consistently low adherence
- Inconsistent adherence
- Consistently high adherence

While the number of participants in each group at a given site is relatively small, we anticipate they will still be sufficient to reach theoretical saturation.[32] Furthermore, it is anticipated that participants will be representative of the overall ASPIRE and HOPE trials by enrolling participants from each of the participating ASPIRE and HOPE countries.

10.4 Participant Selection

Participant selection will be based upon objective measures of adherence in ASPIRE and HOPE (see Section 7.1 and 7.2 for likely group categorization parameters). The pre-determined method for group designation (i.e., consistently non-adherent, consistently adherent or inconsistently adherent) is available in the MTN-032 SSP.

10.5 Data and Study Monitoring Procedures

Demographic and behavioral data will be captured by case report form (CRF) and entered in an electronic database (e.g., CSPRO). Qualitative data will be audio-recorded, transcribed, translated and coded for thematic analyses, using NVivo or a similar qualitative software. Research Triangle Institutue (RTI) International will function as the overall data coordinating center for quantitative and qualitative data and will lead all analyses.

No Study Monitoring Committee (SMC) review will be performed for MTN-032 given the short study timeline and the nature of the study. Protocol team members from MTN, including RTI International and FHI 360, will provide oversight of study operations and ensure the study is implemented in accordance with MTN standards, as defined in the MTN Manual of Operating Procedures.

10.6 Data Analysis

10.6.1 Quantitative Analysis

Demographic and behavioral data will be captured by CRF and entered in an electronic database (e.g., CSPRO). We will use the following descriptive statistics to assess the characteristics of MTN-032 participants: the number and percent in each category for categorical variables (e.g., marital status, employment, adherence group, self-reported product use and sexual practices per ASPIRE or HOPE CRF and audio computer-assisted self-interviewing (ACASI) data), and the mean or median and range for continuous variables (i.e., age, education).

10.6.2 Qualitative Analysis

Data Sources

The qualitative data from MTN-032 will include three main data sources:

- Original handwritten notes of IDIs and FGDs
- Debrief report summaries of IDIs and FGDs
- Transcripts from audio-recorded IDIs and FGDs

Qualitative data will be audio-recorded, transcribed, translated and coded for thematic analyses, using NVivo or a similar qualitative software. RTI International will function as the overall data coordinating center for quantitative and qualitative data and will lead all analyses.

Qualitative Analysis Overview

The following section provides a brief overview of the analysis process; however, a more detailed description of the qualitative analysis will be presented in the study analysis plan.

Qualitative analyses from the MTN-032 study will use a variety of techniques to provide an in-depth characterization of the contextual factors that affected participants' actual product use, as well as participants' reactions to adherence support interventions. The primary source of qualitative data used in the MTN-032 analysis will consist of raw textual data. Qualitative data will be audio-recorded, transcribed, translated and coded for qualitative analyses, using NVivo 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.[33, 34] MTN-032 transcripts will be coded first through descriptive coding for key themes and topics, using a preliminary codebook (see section 10.6.3).[35] 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, pattern 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 adherence, as well as between adherence support interventions and adherence.[33] Whenever possible, we will also compare study sites and explore differences or similarities related to product use adherence facilitators and challenges and participating in adherence support interventions due to different socioeconomic, cultural and geographical contexts. The analysis will be done by the investigative team, working interactively through emails, and regular phone 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.[36]

10.6.3 Codebook Development and Coding Process[37]

Coding is an essential process for data reduction necessary for the management and interpretation of large amounts of qualitative data. To ensure the quality of the coding, staff at RTI International in collaboration with site staff and other MTN-032 team representatives will develop a codebook and study procedures for coding and analysis of all of the qualitative data. Each code will be operationally-defined and refined in an iterative way, as needed. Transcripts will be coded using a qualitative software package such as Nvivo.

During the study development stage, a set of preliminary codes will be developed based on the research questions of this study. The analysis coding structure will be hierarchical, and will reflect the topics/themes covered in the interview guides. After the first 2-3 interviews are completed, each member (analyst) of the coding group will apply this initial set of thematic codes to a common transcript, discuss their coding experiences (via email, a meeting, or conference call), and agree on expanding and modifying code names and definitions when necessary. The coding team will generate substantive and conceptual categories through an iterative process of reading the data, and generating codes based on the data and on key themes or topics identified *a priori*, applying the codes to the data, and refining these as coding progresses. Thus, codes will be centered on the main topics of interest (e.g., product use adherence: facilitators influencing product initiation, persistence and implementation and challenges associated with product use) and the hypothesized contextual spheres of influence. However, by nature, the qualitative research process is iterative, and the Nvivo software allows for the generation of new codes for emergent themes that were not identified *a priori* by the research team. The software also allows for coders to insert descriptive comments and memos to themselves and others as they are working, and to code for concepts not spelled out in verbatim text, such as “contradiction,” when a participant contradicts herself.

Once finalized, the codebook will be used for coding of all of the transcripts. Comprehensive listings of all coded quotations for every code (as well as “families” of related codes) will be generated in Nvivo. The coding team will consider the coded dataset in its entirety, and “stratify” the coded quotations by the site, reported opinions of adherence facilitators/challenges, reported opinions of adherence support interventions, and group assignment (e.g., low vs. inconsistent vs. high product use) when applicable. Depending on findings from the analysis of these data clusters, the team may conduct additional grouping and stratifications of the data.

The coding process will involve a core group of at least 2-3 analysts who will frequently communicate (via email, phone or in person meetings) and discuss their use of the codebook and application of the codes during the coding process. A pre-selected number of transcripts will be double-coded by at least two coders to establish intra-coder and inter-coder reliability. These measures can be automatically generated in Nvivo. Following this process, the coding team will discuss (in person or via teleconference) the coding discrepancies, which will ultimately be resolved through consensus. This process will continue until the inter-coder reliability is sufficiently high, defined as 80% or above. Thereafter each remaining text will be coded by one analyst only within Nvivo. Regular discussions among the coding team will ensure that coding remains standardized and reliable.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study CRFs will be developed by RTI International in conjunction with the protocol team and will be manually double-entered in an electronic database. Quality control (QC) reports and queries routinely will be generated and distributed by RTI International to the study sites for verification and resolution. As part of the study activation process, each study site must identify all CRFs to be used as source documents.

IDI and FGD guides will be developed by RTI International in conjunction with the protocol team and will receive IRB/EC approval. Audio files and transcriptions of interviews and group discussions generated in the field will be electronically transferred to RTI International using a secure File Transfer Protocol (FTP) site, where they will be uploaded and managed using a qualitative software package. RTI International will act as a hub, and manage all data for the study. A convention for file naming will be developed, and all data will be labeled according to this process. Original language and translated transcripts will be transferred to RTI International as they are completed. RTI International will save all versions of all files on a secure, password-protected server.

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocpolicy.pdf) and the relevant appendix regarding source documentation (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocappndx.pdf).

For MTN-032, source documentation may include recruitment logs, enrollment records, visit checklists, CRFs, interview data, participant file notes, and electronic audio files. Essential documentation for the study also includes all versions of the protocol, informed consent forms, operating procedures and key communication with the protocol team. In accordance with U.S regulations, each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study.

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

Audio files will be transcribed and destroyed once the QC process is complete and the data coordinating center at RTI International confirms that the database is locked for analysis. The site IoR or designee will be responsible for ensuring that these files have been destroyed.

11.3 Quality Control and Quality Assurance

At the field level, designated staff will check the quality of the transcripts and translations to ensure that they reflect the content of the interview, and then send each transcript to RTI International for additional QC. CRFs will be reviewed at the site and transmitted to RTI

International where they will be reviewed and queried. All queries will be resolved through a standardized QC reporting mechanism.

All study sites will conduct QC and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported CRS (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdf).

12 CLINICAL SITE MONITORING

FHI 360 staff or designee will review study records during the course of the study, however no formal clinical monitoring will be conducted. FHI 360 staff or designee 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 21 Parts 50, 56, and 312
- Perform source document verification to ensure the accuracy and completeness of study data
- Assess implementation and documentation of internal site quality management procedures

The IoR/designee will allow inspection of study facilities and documentation (e.g., informed consent forms, clinic records, other source documents, CRFs), as well as observation of study procedures. The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of the US OHRP, NIH, NIAID, and/or contractors of the NIH, and other local or US regulatory authorities, and representatives of the MTN, as needed. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Boards/Ethics Committees

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, the IoR will have obtained IRB/EC approval. The IoR will permit audits by the NIH, local authorities, site IRBs/ECs, the MTN, OHRP, or any of their appointed agents.

Each participating institution is responsible for assuring that this protocol, the associated site-specific informed consent form, and study-related documents as required, are reviewed by an IRB/EC responsible for oversight of research conducted at the study site. Any amendments to the protocol must be approved by the responsible IRBs/ECs prior to implementation.

Each IoR/designee will make progress reports to the IRBs/ECs within three months after study termination or completion, unless specified otherwise by their IRBs/ECs. 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. More real-time or frequent reporting of one or more of these or other items may need to be furnished if so specified by their IRBs/ECs. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office (DAIDS PRO) in accordance with the most current DAIDS policies at the time of registration.

13.2 Protocol Registration

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

Site-specific informed consent forms (ICFs) *will not* be reviewed or approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

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

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

13.3 Study Coordination

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.

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chair and DAIDS MO. Study implementation will be guided by a common SSP manual that provides further instructions and operational guidance on conducting study procedures and associated data processing. Standardized study-specific training will be provided to all sites by FHI 360, RTI International, and other designated members of the Protocol Team.

13.4 Risk Benefit Statement

13.4.1 Risks

It is not expected that this trial will expose human subjects to unreasonable risk. Participation in research includes the risks of loss of confidentiality and discomfort with the personal nature of questions when discussing sexual behaviors and VR use.

Psychological Harms

MTN-032 will ask questions that may cause individuals discomfort given their personal nature. Stress and feelings of guilt or embarrassment may arise simply from thinking or talking about one's own behavior or attitudes on sensitive topics. This could result in undesired changes in thought and emotion.

While the risk of psychological harm is anticipated to be minimal, and study staff will inform participants that they can choose not to answer questions at any time, study staff will collect information on participants who report a change in mood as a result of study participation. In addition, study staff will ensure that participants have access to proper clinical resources to address psychological harms.

All FGD participants will be asked and strongly encouraged to respect each other's confidentiality, but participants who participate in the FGDs may still disclose what other participants said during the group discussion. Furthermore, all FGD participants will be asked to use pseudonyms for themselves and for anyone they may talk about during the course of the FGD.

Social Harms

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-positive or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

Data on the occurrence of potential social harms will be collected from all participants. These data will be captured via CRF and analyzed on an ongoing basis. The protocol team will monitor, evaluate and adjust operations to reduce the potential for such occurrences.

13.4.2 Benefits

There are no direct benefits to participating in this study. However, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may help to understand issues important for broader implementation of the dapivirine ring. Participants may also appreciate the opportunity to contribute to the field of HIV prevention research.

Lastly, the information that participants provide may help health professionals develop better ways to improve communication and understanding between researchers and participants in HIV prevention studies.

13.5 Informed Consent Process

Each study participant will provide written informed consent prior to completing any study procedures. 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 the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (http://rsc.tech-res.com/policiesandregulations/). Participants will be provided with copies of the informed consent forms if they are willing to receive them.

In addition to informed consent forms, 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 all study sites, which will be detailed in the study-specific procedures manual.

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

- The purpose of the study
- The potential social harms associated with study participation (and what to do if such harms are experienced)
- There is no benefits to taking part in this study
- The right to withdraw from the study at any time

13.6 Participant Confidentiality

All study procedures will be conducted in a location agreed upon by the participant, and every effort will be made to protect participant privacy and confidentiality. Each study site 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. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked areas with access limited to study staff. All study data collection and administrative forms will be identified solely by PTID number to maintain participant confidentiality. All records that contain names or other personal identifiers, such as informed consent forms, will be stored securely. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link PTID numbers to identifying information will be stored in a locked file in an area with limited access. All digital audio files will be stored on password-protected computers. Audio files will be transcribed. Please see SSP for guidance regarding audio file destruction. 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, NIH, and/or contractors of the NIH, and other local and US regulatory authorities
- Study staff
- Site IRBs/ ECs

13.7 Special Populations

13.7.1 Pregnant Women

Pregnancy is not exclusionary. Due to the nonclinical nature of this study, no pregnancy-related risks are anticipated in MTN-032.

13.7.2 Children

MTN-032 will enroll former ASPIRE and HOPE participants who were age 18 through 45 years (inclusive) at the time of screening for ASPIRE, as verified per site SOPs, thus children will not be considered eligible for this trial.

13.8 Compensation

Pending IRB/EC 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 specified in the study informed consent forms.

13.9 Study Discontinuation

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

14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies will govern publication of the results of this study.

15 APPENDICES

APPENDIX I: SCREENING AND ENROLLMENT SAMPLE INFORMED CONSENT FORM - PHASE I (ASPIRE) PARTICIPANTS

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-032

Assessment of ASPIRE and HOPE Adherence

Version 1.0

PHASE I (ASPIRE) PARTICIPANTS

August 20, 2015

PRINCIPAL INVESTIGATOR: ***[Site to insert]***
PHONE: ***[Site to insert]***
Short Title for the Study: Assessment of ASPIRE and HOPE Adherence

INFORMED CONSENT

You are being asked to take part in this research study because you are a woman who took part in the MTN-020 (ASPIRE) trial and received the dapivirine vaginal ring during your trial participation. Up to 224 women will take part in the first study phase of this study at multiple ASPIRE research sites in Africa. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). At this site, the person in charge of this study is ***[INSERT NAME OF PRINCIPAL INVESTIGATOR]***.

Before you decide if you want to join this study, we want you to learn more about it. This consent form gives you information about the study. Study staff will talk with you and answer any questions you may have. Once you read and understand the study and its requirements, you can decide if you want to join. If you do decide to take part in the trial, you will sign your name or make your mark on this form. A copy of this document will be offered to you.

Your eligibility to participate in this study will then be assessed, and once confirmed, you will be considered enrolled in the MTN-032 study.

It is important to know that your participation in this research is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

WHAT IS THE PURPOSE OF THIS STUDY?

You are being asked today to take part in Phase 1 of MTN-032. The main goal of the first phase of this study is to better understand ASPIRE participants' use of study product (vaginal rings) when they were in the ASPIRE trial. If you are eligible for and

complete Phase 1, and afterwards decide to enroll and participate in the HOPE trial, you then may be eligible to participate in MTN-032 Phase 2.

Some Phase 1 participants will be asked to participate in an in-depth interview (IDI), and some will be asked to participate in a focus group discussion (FGD) with other participants. Participants will be asked questions individually or in a group setting. Study staff will tell you if you are going to take part in an IDI or FGD.

To obtain information about your participation in ASPIRE, the MTN-032 study team will need to review your ASPIRE research records. By signing this form, you are giving the MTN-032 study team permission to access your research records.

STUDY PRODUCTS
There are no study products (investigational drugs or other products) involved in this research study.

STUDY PROCEDURES
Phase 1 of the MTN-032 study consists of one study visit, including the Screening/Enrollment Visit which is taking place today after you sign this informed consent form. Additional visit(s) may be conducted to complete all required procedures, if necessary. Visit(s) will take place here at this study clinic or at a place agreed upon by you and the study staff, which may be your home or another convenient location ***[SITE TO INCLUDE ALTERNATE LOCATION]*****.**

The procedures done at this visit will take about ***[SITE TO INSERT TIME]****.*

- Study staff will ask you where you live and other questions about you, and your understanding of the study requirements.
- You will complete one or more questionnaires that will help researchers better understand your interview responses.
- You may be asked to have an in-depth interview (IDI). If asked to complete an IDI:
    - You will have an IDI in the presence of one or two MTN-032 research staff members. The IDI will take approximately ***[SITE TO INSERT TIME]***. Clinic staff will make every effort to ensure your privacy and confidentiality.
    - Before the IDI begins, the interviewer will talk with you about your ASPIRE adherence results.
        - Adherence refers to whether ASPIRE participants correctly used the dapivirine vaginal ring as instructed by trial staff.
        - In ASPIRE, a participant's adherence levels were measured by the amount of study drug (dapivirine) that remained in returned vaginal rings, the amount of study drug in your blood, and adherence was discussed during counseling and interview sessions.
    - The interviewer will then ask more questions, and may take notes and will audio-record your conversation. Interviews will be audio-recorded to make sure we record your words exactly how you said them.
    - You will be asked some general questions, such as your age, education,

living situation, relationship status, and health.
    - The interviewer will also ask you questions about:
        - Your experience with ring use and ASPIRE trial participation.
        - Your understanding of the results of the ASPIRE trial.
        - Your perception of your sexual health risk, how this understanding may have affected your decision to use vaginal rings, and what impact it may have on your use of HIV prevention products that may become available in the future.
- You may be asked to participate in a focus group discussion (FGD). If you're asked to join a FGD:
    - The FGD will take approximately ***[SITE TO INSERT TIME]***. Study interviewers/facilitators will lead the discussion, fully explain the process, and answer any questions you have.
    - Before the FGD begins, the interviewer will talk with you in private about your ASPIRE adherence results.
        - Adherence refers to whether ASPIRE participants correctly used the dapivirine vaginal ring as instructed by trial staff.
        - In ASPIRE, a participant's adherence levels were measured by the amount of study drug (dapivirine) that remained in returned vaginal rings, the amount of study drug in your blood, and adherence was discussed during counseling and interview sessions.
    - In a small group setting with other study participants, an interviewer will encourage discussion of various topics similar to those discussed during the IDIs.
    - Like the IDIs, FGDs will be audio-recorded and later transcribed.
    - A study staff member will take notes during the discussion as a backup to the audio-recording.
    - You will be asked to use fake names for yourself and anyone you talk about.
- If you have either an IDI or FGD, study staff will also:
    - Inform you about other services, if needed
    - Schedule your next visit, if necessary
    - Reimburse you for your visit(s)

RISKS AND/OR DISCOMFORTS

During the interview or focus group discussion, you may be asked some questions that cause you to feel embarrassed or uncomfortable. You may become embarrassed and/or worried when discussing sexual practices or your use of the vaginal ring. Trained study interviewers will help you deal with any feelings or questions you have. You can choose not to answer questions in the interview at any time.

Another possible risk of this study is loss of confidentiality of the information you give. Every effort will be made to protect your confidential information, but this cannot be guaranteed. To reduce this risk, IDIs will take place in private, and the information recorded during your interview will be strictly protected. The audio recording, notes, and analyses from these materials will be kept confidential and will only use study numbers

or fake names. This means that no one other than the MTN-032 interview team will be able to link your responses to you personally. The information that links you to the research materials will be kept in a secure location that will be accessed only by members of the MTN-032 study team for the purposes of this research. Your voice recordings will also be kept in a secure location and only people involved with the study will have access to these recordings. The voice recordings will be destroyed as soon as the audio recording has been typed and all responses are verified. Study leaders will make sure this happens.

If you participate in a focus group discussion, other participants will hear what you say. Although we will not reveal your full name to other participants, it is possible that others may know you from previous interactions. We will also ask every participant not to tell anyone outside of the group what any person said during the FGD. While it is not at all likely that your discussion will be made public, we cannot guarantee that everyone will keep the discussion private.

However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

BENEFITS

There are no direct benefits to participating in this study. However, you and others may benefit in the future from information learned in this study. Participants in this study may also appreciate the opportunity to contribute to HIV prevention research efforts. Information participants provide may help researchers improve counseling materials about product use and sexual behavior. Lastly, the information provided in this study may help health professionals develop ways to improve communication and understanding between researchers and participants in HIV prevention studies.

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 of any new information learned during this study that might affect your willingness to stay in the study. You will also be told when study results may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You may be removed from the study early without your permission if:

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

- You are unwilling or unable to comply with required study procedures, including study visit attendance.
- Other reasons that may prevent you from completing the study successfully

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 at each scheduled visit.

CONFIDENTIALITY
Efforts will be made to keep your information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. The study staff may use your personal information to verify that you are not in any other research studies. This includes studies conducted by other researchers that study staff may know about. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:
- The Research Triangle Institute
- Site IRBs/ECs
- FHI 360
- Representatives of the US Federal Government, including the US OHRP, NIH and/or contractors of NIH, and other local and US regulatory authorities
- Study monitors
- Study staff

The researchers will do everything they can to protect your privacy.

RESEARCH-RELATED INJURY
[SITE TO SPECIFY INSTITUTIONAL POLICY]: It is unlikely that you will be injured as a result of study participation. If you are injured, the ***[INSTITUTION]*** will give you immediate necessary treatment for your injuries. You ***[WILL/WILL NOT]*** have to pay for this treatment. You will be told where you can receive additional treatment for your injuries. The U.S. NIH does not have a mechanism to pay money or give other forms of compensation for research related injuries. You do not give up any legal rights by signing this consent form.

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER
[SITE TO SPECIFY INSTITUTIONAL POLICY]: Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. If you choose not to participate or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled at this clinic. If you want the results of the study after the study 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]***.

SIGNATURES- VOLUNTARY CONSENT

[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/EC]:

If you have read this consent form (or had it read and explained to you) and if you understand the information and voluntarily agree to take part in the study, please sign your name or make your mark below.

Participant Name (print)	Participant Signature/Mark	Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

APPENDIX II: SCREENING AND ENROLLMENT SAMPLE INFORMED CONSENT FORM - PHASE 2 (HOPE) PARTICIPANTS

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-032

Assessment of ASPIRE and HOPE Adherence

Version 1.0

PHASE 2 (HOPE) PARTICIPANTS

August 20, 2015

PRINCIPAL INVESTIGATOR: ***[Site to insert]***
PHONE: ***[Site to insert]***
Short Title for the Study: Assessment of ASPIRE and HOPE Adherence

INFORMED CONSENT
You are being asked to take part in this phase of the research study because you are a woman who participated in the MTN-025 (HOPE) trial, received the dapivirine vaginal ring during your trial participation and completed Phase 1 of the MTN-032 trial. Approximately 84 women will participate in this second study phase at multiple HOPE research sites in Africa. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). At this site, the person in charge of this study is ***[INSERT NAME OF PRINCIPAL INVESTIGATOR]***.

Before you decide if you want to continue in this study, we want you to learn more about Phase 2 of the MTN-032 study. This consent form gives you information about Phase 2 of this study. Study staff will talk with you and answer any questions you may have. Once you read and understand Phase 2 and its requirements, you can decide if you want to take part in the second phase of this trial. If you do decide to continue in this study and take part in Phase 2, you will sign your name or make your mark on this form. A copy of this document will be offered to you.

Your eligibility to participate in Phase 2 of this study will then be assessed, and once confirmed, you will be considered enrolled in Phase 2 of the MTN-032 study.

It is important to know that your participation in this research is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

WHAT IS THE PURPOSE OF THIS STUDY?
You are being asked today to take part in Phase 2 of MTN-032. The main goal of the second phase of this study is to better understand HOPE participants' use of study product (vaginal rings) while participating in both the ASPIRE and HOPE trials. Women who completed MTN-032 Phase 1 as well as participated in the HOPE trial may be eligible to participate in MTN-032 Phase 2.

All Phase 2 participants will be asked to participate in an in-depth interview (IDI). Participants will be asked questions individually.

To obtain information about your participation in ASPIRE or HOPE, the MTN-032 study team will need to review your ASPIRE or HOPE research records. By signing this form, you are giving the MTN-032 study team permission to access your research records.

STUDY PRODUCTS
There are no study products (investigational drugs or other products) involved in this research study.

STUDY PROCEDURES
Phase 2 of the MTN-032 study consists of one study visit, including the Screening/Enrollment Visit which is taking place today after you sign this informed consent form. Additional visit(s) may be conducted to complete all required procedures, if necessary. Visits will take place here at this study clinic or at a place agreed upon by you and the study staff, which may be your home or another convenient location ***[SITE TO INCLUDE ALTERNATE LOCATION].***

The procedures done at this visit will take about ***[SITE TO INSERT TIME].***

- Study staff will ask you where you live and other questions about you, and your understanding of the study requirements.
- You will complete one or more questionnaires that will help researchers better understand your interview responses.
- You may be asked to have an in-depth interview (IDI):
    - You will have an IDI in the presence of one or two MTN-032 research staff members. The IDI will take approximately ***[SITE TO INSERT TIME]***. Clinic staff will make every effort to ensure your privacy and confidentiality.
    - Before the IDI begins, the interviewer will talk with you about your HOPE adherence results.
        - Adherence refers to whether HOPE study participants used the dapivirine vaginal ring as instructed by trial staff.
        - In HOPE, a participant's adherence levels were measured by the amount of study drug (dapivirine) that remained in returned vaginal rings, the amount of study drug in your blood, and adherence was discussed during counseling and interview sessions.
    - The interviewer will then ask more questions, and may take notes and will audio-record your conversation. Interviews will be audio-recorded to make sure we record your words exactly how you said them.

    - You will be asked some general questions, such as your age, education, living situation, relationship status, and health.
    - The interviewer will also ask you questions about:
        - Your experience with ring use and HOPE trial participation.
        - Your understanding of the results of the ASPIRE trial and how those results effected your participation in HOPE.
        - Your perception of your sexual health risk, how this understanding may have affected your decision to use vaginal rings, and what impact it may have on your use of HIV prevention products that may become available in the future.
- Study staff will also:
    - Inform you about other services, if needed.
    - Schedule your next visit, if necessary.
    - Reimburse you for your visit(s).

RISKS AND/OR DISCOMFORTS

During the interview, you may be asked some questions that cause you to feel embarrassed or uncomfortable. You may become embarrassed and/or worried when discussing sexual practices or your use of the vaginal rings. Trained study interviewers will help you deal with any feelings or questions you have. You can choose not to answer questions during the interview at any time.

Another possible risk of this study is loss of confidentiality of the information you give. Every effort will be made to protect your confidential information, but this cannot be guaranteed. To reduce this risk, IDIs will take place in private, and the information recorded during your interview will be strictly protected. The audio recording, notes, and analyses from these materials will be kept confidential and will only use study numbers or fake names. This means that no one other than the MTN-032 interview team will be able to link your responses to you personally. The information that links you to the research materials will be kept in a secure location that will be accessed only by members of the MTN-032 study team for the purposes of this research. Your voice recordings will also be kept in a secure location and only people involved with the study will have access to these recordings. The voice recordings will be destroyed as soon as the audio recording has been typed and all responses are verified. Study leaders will make sure this happens.

However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

BENEFITS

There are no direct benefits to participating in this study. However, you and others may benefit in the future from information learned in this study. Participants in this study may also appreciate the opportunity to contribute to HIV prevention research efforts.

Information participants provide may help researchers improve counseling materials about product use and sexual behavior. Lastly, the information provided in this study may help health professionals develop ways to improve communication and understanding between researchers and participants in HIV prevention studies.

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 of any new information learned during this study that might affect your willingness to stay in the study. You will also be told when study results may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT
You may be removed from the study early without your permission if:

- The study is cancelled by the US NIH, the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB) or Ethics Committee (EC). An IRB is a committee that watches over the safety and rights of research participants
- You are unwilling or unable to comply with required study procedures, including study visit attendance.
- Other reasons that may prevent you from completing the study successfully

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

REIMBURSEMENT
[*SITE TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT*]: You will receive ***[SITE TO INSERT AMOUNT $XX]*** for your time, effort, and travel to and from the clinic at each scheduled visit.

CONFIDENTIALITY
Efforts will be made to keep your information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. The study staff may use your personal information to verify that you are not in any other research studies. This includes studies conducted by other researchers that study staff may know about. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- The Research Triangle Institute
- Site IRBs/ECs
- FHI 360
- Representatives of the US Federal Government, including the US OHRP, NIH and/or contractors of NIH, and other local and US regulatory authorities

- Study monitors
- Study staff

The researchers will do everything they can to protect your privacy.

RESEARCH-RELATED INJURY

[SITE TO SPECIFY INSTITUTIONAL POLICY]: It is unlikely that you will be injured as a result of study participation. If you are injured, the ***[INSTITUTION]*** will give you immediate necessary treatment for your injuries. You ***[WILL/WILL NOT]*** have to pay for this treatment. You will be told where you can receive additional treatment for your injuries. The U.S. NIH does not have a mechanism to pay money or give other forms of compensation for research related injuries. You do not give up any legal rights by signing this consent form.

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. If you choose not to participate or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled at this clinic. If you want the results of the study after the study 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]***.

SIGNATURES- VOLUNTARY CONSENT

[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/EC]:

If you have read this consent form (or had it read and explained to you) and if you understand the information and voluntarily agree to take part in the study, please sign your name or make your mark below.

Participant Name (print)	Participant Signature/Mark	Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

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