NCT02862171

IPM 032

A FOLLOW-ON, OPEN-LABEL TRIAL TO ASSESS CONTINUED SAFETY OF AND ADHERENCE TO THE DAPIVIRINE (25 mg) VAGINAL RING-004 IN HEALTHY, HIV-NEGATIVE WOMEN

- **Protocol Version 2.0 Amendment 4.0 dated 17 October 2019**

IPM 032

Version 2.0 Amendment 4.0

17 October 2019

A FOLLOW-ON, OPEN-LABEL TRIAL TO ASSESS CONTINUED SAFETY OF AND ADHERENCE TO THE DAPIVIRINE (25 mg) VAGINAL RING-004 IN HEALTHY, HIV-NEGATIVE WOMEN

Phase IIIb

SPONSOR:
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I have read this protocol and appendices and agree to conduct the trial as stipulated and in compliance with the principles of the World Medical Association Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, and all applicable regulations and guidelines.

Investigator Signature

Date

Investigator Name

Research Centre Name

On behalf of the International Partnership for Microbicides, I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this trial.

17-Oct-2019 | 09:30:47 EDT

Chief Medical Officer Signature

Date

Annaléne Nel, MBChB, PhD
Chief Medical Officer Name (Printed)

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Signing Time: 17-Oct-2019 | 09:30:42 EDT
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DocuSigned by:
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B25CED25D1AB47B289F32334647B15C0

Investigator Signature

30-Oct-2019 | 07:01:56 EDT
Date

Dr. C Louw
Investigator Name

Madibeng Centre for Research
Research Centre Name

On behalf of the International Partnership for Microbicides, I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this trial.

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DocuSigned by:
Prof J Smit
Signer Name: Prof J Smit
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BA41FA569BBA4061BEC8CCCDD64CBA3C

Investigator Signature

04-Feb-2020 | 22:55:21 PST
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Prof J Smit
Investigator Name

MatCH Research Unit
Research Centre Name

On behalf of the International Partnership for Microbicides, I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this trial.

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Dr. PL Kotze

Signer Name: Dr. PL Kotze
Signing Reason: I approve this document
Signing Time: 01-Nov-2019 | 00:21:39 PDT
84B97DBB4BAF434CB2C6DBA2DD5255D8

Investigator Signature

01-Nov-2019 | 00:21:55 PDT
Date

Dr. PL Kotze
Investigator Name

Qhakaza Mbokodo Research Clinic
Research Centre Name

On behalf of the International Partnership for Microbicides, I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this trial.

17-Oct-2019 | 09:30:47 EDT
Chief Medical Officer Signature

Date

Annaléne Nel, MBChB, PhD
Chief Medical Officer Name (Printed)

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DocuSigned by:
Dr. S Kusemererwa
Signer Name: Dr. S Kusemererwa
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Signing Time: 30-Oct-2019 | 09:14:30 PDT
655BADB18DA24B9F848F96891C4A0D8B

Investigator Signature

30-Oct-2019 | 09:14:38 PDT
Date

Dr. S Kusemererwa
Investigator Name

MRC/UVRI and
LSHTM Uganda
Research Unit
Research Centre Name

On behalf of the International Partnership for Microbicides, I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this trial.

Chief Medical Officer Signature

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Dr. K Gill

Signer Name: Dr. K Gill
Signing Reason: I approve this document
Signing Time: 30-Oct-2019 | 01:36:06 PDT
3B43DA531C504637A872F8F25BBBE4F2

Investigator Signature

30-Oct-2019 | 01:36:17 PDT
Date

Dr. K Gill
Investigator Name

Desmond Tutu HIV Foundation
Research Centre Name

On behalf of the International Partnership for Microbicides, I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this trial.

Chief Medical Officer Signature

17-Oct-2019 | 09:30:47 EDT
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Chief Medical Officer Name (Printed)

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DocuSigned by:
Dr. R Moraba
Signer Name: Dr. R Moraba
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Investigator Signature

31-Oct-2019 | 08:59:41 PDT
Date

Dr. R Moraba
Investigator Name

Ndlovu Research Consortium
Research Centre Name

On behalf of the International Partnership for Microbicides, I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this trial.

Chief Medical Officer Signature

17-Oct-2019 | 09:30:47 EDT
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Annaléne Nel, MBChB, PhD
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TABLE OF CONTENTS

ACRONYMS AND ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC	Area Under Plasma Concentration-time Curve
BV	Bacterial Vaginosis
b.i.d.	"*bis in die*"/twice a day
ºC	Degree Celsius
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CT	*Chlamydia Trachomatis*
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAPY	Di-amino pyrimidine
DSMB	Data and Safety Monitoring Board
DVR	Dapivirine Vaginal Ring-004
EC_{50}	50% Effective Inhibition Concentration
FBC	Full Blood Count
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
HIV-1	Human Immunodeficiency Virus type 1
Hu-SCID	Humanized Severe Combined Immunodeficient
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDI	In-depth individual interview
IEC	Independent Ethics Committee
IB	Investigator's Brochure
IP	Investigational Product
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
IRE	Immediately Reportable Event
ITT	Intent-To-Treat
LPUV	Last Product Use Visit
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
MTN	Microbicide Trials Network
NAAT	Nucleic Acid-Amplification Testing
NG	*Neisseria Gonorrhoeae*
NGS	Next Generation Sequencing
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NOAEL	No Adverse Effect Level
PCR	Polymerase Chain Reaction
PID	Participant Identification
PMTCT	Prevention of Mother-to-Child Transmission of HIV
PEP	Post-Exposure Prophylaxis
PT	Preferred Term
RNA	Ribonucleic Acid

RPR	Rapid Plasma Reagin
RT	Reverse Transcriptase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR-ID	Screening Identification
SOC	System Organ Class
SOM	Study Operations Manual
SOP	Standard Operating Procedure
STI	Sexually Transmitted Infection
TEAE	Treatment Emergent Adverse Event
TPHA	Treponema Pallidum Haemagglutination Test
TPPA	Treponema Pallidum Particle Agglutination Assay
TV	*Trichomonas Vaginalis*
UNAIDS	Joint United Nations Programme on HIV/AIDS
USA	United States of America
WHO	World Health Organization

PROTOCOL SYNOPSIS

IPM 032

A FOLLOW-ON, OPEN-LABEL TRIAL TO ASSESS CONTINUED SAFETY OF AND ADHERENCE TO THE DAPIVIRINE (25 mg) VAGINAL RING-004 IN HEALTHY, HIV-NEGATIVE WOMEN

BACKGROUND:

The Phase III clinical program of Dapivirine Vaginal Ring-004, containing 25 mg of dapivirine, consisted of the MTN-020 and IPM 027 clinical trials. These trials were conducted in South Africa, Uganda, Zimbabwe and Malawi, to assess the safety and efficacy of the Dapivirine Vaginal Ring-004 in preventing the acquisition of HIV-1 infection through male to female transmission during vaginal sexual intercourse in healthy, HIV-negative women.

The results of the IPM 027 and MTN-020 trials demonstrated that the Dapivirine Vaginal Ring-004 is safe and reduced the risk of acquiring HIV-1 infection[1,2]. A lower HIV-1 risk reduction was observed in women ≤21 years of age in IPM 027 (the age effect was not statistically significant). Results were communicated to the relevant local and international regulatory authorities, IRBs/IECs, community representatives, participants and key stakeholders, as appropriate.

IPM 032, a Phase IIIb follow-on trial to IPM 027, has been designed as an open-label clinical trial with the monthly Dapivirine Vaginal Ring (25 mg) to collect additional safety data and assess adherence to ring use in healthy, HIV-negative women with monthly (at least one to a maximum of three months) followed by 3-monthly research centre follow-up visits over 12 months.

OBJECTIVES:

The Primary Trial Objectives are:

1. To assess the safety profile of the 25 mg Dapivirine Vaginal Ring-004, when inserted at monthly intervals, in an open-label trial
2. To assess adherence to the use of the 25 mg Dapivirine Vaginal Ring-004 inserted at monthly intervals, in an open-label trial

The Secondary Trial Objectives are:

1. To assess the incidence of HIV-1 seroconversion
2. To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection

The Exploratory Trial Objectives are:

1. To assess the feasibility of 3-monthly follow-up visits, as a possible schedule for post-licensure vaginal ring clinical follow-up
2. To explore the correlation between drug amount and results from the visual inspection of the returned vaginal rings by research staff between the monthly and 3-monthly research centre follow-up schedules
3. To determine the proportion of participants electing to undergo HIV rapid tests at the research centres between scheduled 3-monthly visits
4. To explore self-reported acceptability of and adherence to the 25 mg Dapivirine Vaginal Ring-004.

ENDPOINTS AND ASSESSMENTS:

The primary endpoints are:

1. Safety
   - All Adverse Events (AEs) assessed by the investigator to be related to the Dapivirine Vaginal Ring-004
   - All Grade 3 and 4 AEs
   - All Serious Adverse Events (SAEs)

2. Adherence
   - Residual amounts of dapivirine in returned rings; and/or dapivirine concentrations in plasma and/or dapivirine concentrations in vaginal fluid

The primary endpoints will be assessed through:

1. Safety
   - All product-related AEs, Grade 3 or 4 AEs, SAEs, physical examination, gynaecological assessments, including pelvic/speculum examination, laboratory tests and other indicated investigations

2. Adherence
   - Determined dapivirine residual amounts in returned used vaginal rings and/or
   - Measured concentrations of dapivirine in plasma and/or
   - Measured concentrations of dapivirine in vaginal fluids

The secondary endpoints are:

- The HIV-1 seroconversion rate per 100 woman-years of product use at the end of the vaginal ring use period
- HIV-1 drug resistance mutations among participants who acquire HIV-1 infection

The secondary endpoints will be assessed through:

- Rapid and specialised laboratory testing according to a pre-specified HIV testing algorithm
- Viral genotype (including NGS) and phenotype resistance testing methods which include sensitive methods to detect low frequency drug-resistant variants

The exploratory endpoints are:

- Feasibility of 3-monthly clinical follow-up schedule
- Dapivirine residual amounts in returned used vaginal rings and/or dapivirine concentrations in blood and/or vaginal fluid in correlation with results from the visual inspection of the returned used vaginal rings by research staff
- Proportion of participants opting for HIV rapid tests at the research centre between scheduled 3-monthly research centre follow-up visits
- The proportion of women who report the use of the vaginal ring as acceptable
- Participant self-reported patterns of ring use

The exploratory endpoints will be assessed through:

- Participant report of feasibility regarding a 3-monthly clinical follow-up schedule (Participant Questionnaire)
- Number of women opting not to receive two additional rings at the 3-monthly visits
- Proportion of returned rings (used and unused) during the 3-monthly clinical follow-up schedule
- Dapivirine residual amounts in returned used vaginal rings and/or dapivirine concentrations in blood and/or vaginal fluid
- Visual inspection of the returned used vaginal rings by research centre staff
- Number of participants undergoing HIV rapid tests at the research centre between scheduled 3-monthly research

centre follow-up visits

- Qualitative data regarding reasons for ring acceptability and self-reported patterns of ring use

TRIAL DESIGN: IPM 032 is a Phase IIIb, multi-centre follow-on open-label trial to evaluate the continued adherence to and safety of the Dapivirine Vaginal Ring-004 inserted at monthly intervals in healthy, HIV-negative women who have participated in the IPM 027 Phase III Dapivirine Vaginal Ring-004 trial. All women who have participated in IPM 027 and are HIV-negative at screening for IPM 032 will be eligible. An estimate of up to 1400 participants will be enrolled.

All participants will attend a research centre follow-up visit one month after enrolment. Following this visit, at the investigator's discretion, a participant can continue on a 3-monthly visit schedule. Monthly visits may however be extended up to the first three months of participation. Once the 3-monthly trial visit schedule commences, three rings will be dispensed to the participant. One ring will be self-inserted at the research centre and two additional rings will be dispensed for the participant to take home, or dispensing will take place as arranged with the participant.

TRIAL DURATION: Each participant will engage in the screening process for up to 45 days prior to enrolment and will use the Dapivirine Vaginal Ring-004 for a period of up to 12 months. IPM will have the option to extend this trial period. Accrual will take place over approximately 6 months and those participants who are enrolled more than 6 months after the onset of the trial site's accrual period may have a shortened follow-up period.

Each participant will have an exit visit approximately 1-2 months after ring discontinuation, to assess safety and identify HIV seroconversions after product discontinuation.

POPULATION AND SAMPLE SIZE:

Up to 1400 HIV-negative women who have participated in the IPM 027 Phase III Dapivirine Vaginal Ring-004 trial, who understand the trial and can provide informed consent are expected to enrol in this open-label trial.

INCLUSION CRITERIA– WOMEN PREVIOUSLY ENROLLED IN IPM 027:

Women must meet all of the following criteria to be eligible for trial enrolment:

1. Previously enrolled in the IPM 027 trial
2. Available for all visits and consent to follow all procedures scheduled for the trial
3. Using an effective method of contraception at the

Enrolment Visit, and intending to use an effective contraceptive method for the duration of trial participation, unless post-menopausal with no history of menses for one year prior to screening

4. HIV-negative as determined by the HIV algorithm applied at Screening/Pre-Enrolment
5. Willing to refrain from participation in another research trial using drugs, vaccines, medical devices and microbicides for the duration of the IPM 032 trial
6. Willing to provide adequate locator information for trial retention purposes and be reachable per local standard procedures (*e.g.* by home visit or telephone; or *via* family or close neighbour contacts); confidentiality to be maintained

EXCLUSION CRITERIA– WOMEN PREVIOUSLY ENROLLED IN IPM 027:

Women who meet any of the following criteria are NOT eligible to enrol in the trial:

1. Investigational product use permanently discontinued in response to an AE (where the AE was considered related to investigational product) or safety-related concern while taking part in the IPM 027 trial
2. Currently pregnant, intending to become pregnant, or currently breast-feeding
3. Known drug abuse or alcohol dependence in the 12 months prior to screening
4. Participated in another research trial (other than IPM 027) using drugs, medical devices, microbicides or oral pre-exposure prophylaxis agents within 30 days prior to screening
5. Any new illness or condition(s), chronic condition(s) or abnormal laboratory finding(s) that, in the opinion of the investigator, might put the participant at risk, or interfere with the trial objectives or the participant's adherence to trial requirements

METHODS:

Screening Visit:

Potential participants who are HIV-negative, who participated in IPM 027 and who provide informed consent will be invited to screen for the trial and to enrol in the open-label follow-on trial. After informed consent is obtained, a SCR-ID number will be assigned to each potential participant for identification purposes and the potential participant will be screened to assess eligibility for the trial. A comprehension checklist will be used to support the informed consent process.

At screening, potential participants will provide information on inclusion and exclusion criteria, including locator and basic menses information, demographic information, and medical and concomitant medication history. Each potential participant will receive a general physical examination and pelvic examination.

All potential participants will be provided with HIV/STI risk-reduction counselling (including provision of male and/or female condoms, should participants wish to receive them), contraceptive counselling and HIV pre- and post-test counselling. Contraceptives will be provided if necessary, as well as treatment and/or referral for sexually transmitted infections (STIs) and other findings as necessary. Safety laboratory assessments, urine dipstick analysis (microscopy only if clinically indicated), cervical sample collection for cytology and testing for pregnancy, HIV, STIs, and syphilis will be performed. Blood samples for HIV-1 RNA PCR, HIV viral genotype (including NGS) and phenotype resistance testing will be collected and stored for retrospective testing subsequent to a confirmed HIV-1 seroconversion.

Enrolment Visit:
At the Enrolment Visit, potential participants will provide information on inclusion and exclusion criteria, including locator and basic menses information, and medical and concomitant medication history. AEs (post-enrolment) and the occurrence of possible social harms will be assessed.

All potential participants will be provided with HIV/STI risk-reduction counselling (including provision of male and/or female condoms, should participants wish to receive them), contraceptive counselling and provision of contraceptives (if necessary), HIV pre- and post-test counselling and vaginal ring adherence counselling. Participants will be provided with feedback on the IPM 027 and MTN-020 trial results. Diary cards will be issued with instructions for completion.

Testing for pregnancy and HIV will be performed. Blood samples will be collected for storage, and HIV-1 RNA PCR, HIV viral genotype (including NGS) and phenotype resistance testing will be performed retrospectively subsequent to confirmed HIV-1 seroconversion.

Eligible women will be assigned a unique PID number. Each participant will be provided with vaginal ring use and storage instructions and instructed to self-insert a newly dispensed vaginal ring.

Trial Visits:
All participants will provide information on concomitant medication, locator details and menses. Participants will receive pre- and post-test HIV counselling; HIV/STI risk reduction counselling; vaginal

ring adherence counselling; HIV rapid testing and pregnancy testing. Male and/or female condoms will be provided at all visits, should participants wish to receive them, as part of HIV/STI risk reduction counselling. Contraceptive counselling and contraceptives (if needed) will be provided at all visits. Possible occurrence of social harms will be assessed during research centre visits.

Blood samples will be collected for storage at each trial visit and will be tested retrospectively by HIV-1 RNA PCR, HIV viral genotype (including NGS) and phenotype resistance testing subsequent to confirmed HIV seroconversion. At the point of HIV seroconversion, vaginal ring use will be discontinued, and in addition, blood samples for viral genotype (including NGS) and phenotype resistance will be collected at the scheduled exit visit, 1-2 months following seroconversion.

Blood and vaginal fluid samples will be collected for possible measurement of dapivirine concentrations. Returned rings will be visually inspected by research centre staff and may also be analysed for residual amounts of dapivirine. Results may be shared with participants to support ring-use adherence counselling.

Returned diary cards will be reviewed and new diary cards issued to participants as applicable. Each participant will be asked to complete a Participant Questionnaire at every trial visit. AEs will be assessed at all visits post-enrolment. In addition, if clinically indicated, safety laboratory assessments, urine dipstick analysis (microscopy only if clinically indicated), pelvic examinations, cervical sample collection for cytology, physical examinations and STI tests will be performed. Treatment and/or referral for STIs and other findings may be performed, if required.

At each trial visit, participants will return used vaginal rings and each participant will be instructed to self-insert a newly-dispensed vaginal ring and be provided with vaginal ring use and storage instructions. Two additional rings will be dispensed once participants commence with the 3-monthly trial visit schedule, which the participants should self-insert at monthly intervals, at home, until the next Trial Visit. Participants who prefer not to have additional vaginal rings in their possession may also choose to return and to collect the vaginal rings from the research centre at time intervals suitable to them, providing a new ring is inserted monthly. HIV rapid tests will be offered to participants during these interim visits.

If a participant is unable to attend the next scheduled visit, the investigator or designee could dispense additional ring(s) on a case-by-case basis. All such circumstances must be documented fully by the investigator or designee as described in the IPM 032 Study Operations Manual (SOM). If a participant requires an

additional ring at a time other than when they are scheduled to receive one, they will be required to attend the clinic for an interim visit.

Last product use visit (LPUV):
At the last product use visit, participants will return any used/unused rings; report any medical problems, social harms and concomitant medications since the last visit; provide locator and basic menses information; receive pre- and post-test HIV counselling, contraceptive counselling and HIV/STI risk-reduction counselling (including provision of male and/or female condoms, should participants wish to receive them); undergo a physical examination as well as a pelvic examination; be tested for STIs, pregnancy and HIV; and may undergo safety laboratory assessments, urine dipstick analysis (microscopy only if clinically indicated) and cervical sample collection for cytology (if no result is evident within the previous year, or abnormal at last cervical cytology). Contraception and STI treatment will be provided or participants will be referred, if needed. Blood samples will be collected for storage, and will be tested retrospectively by HIV-1 RNA PCR, HIV viral genotype (including NGS) and phenotype resistance testing subsequent to confirmed HIV seroconversion. Blood and vaginal fluid samples may be collected for measurement of dapivirine concentrations. Returned rings will be visually inspected by research centre staff and may also be analysed for residual amounts of dapivirine. Returned diary cards will be reviewed. Participants will be asked to complete a Participant Questionnaire.

Exit visit - approximately 1-2 months after ring discontinuation:
On the day of the scheduled exit visit, participants will return to the research centre to receive results from their STI testing and safety laboratory assessments performed at the last product use visit, if applicable, and receive treatment or referral as needed. AEs, concomitant medications and possible social harms will be recorded at this visit.

Participants will receive pre- and post-test counselling for HIV and undergo HIV testing. HIV/STI risk reduction counselling (including provision of male and/or female condoms, should they wish to receive them) and contraceptive counselling will also be provided at the exit visit. Contraception and STI treatment will be provided or the participant will be referred, if needed. The following procedures are not required, but may be conducted if clinically indicated: physical and pelvic examination, cervicovaginal sample collection for STI testing, provision of treatment and/or referral for STIs and other findings, laboratory testing for safety assessments, urine dipstick analysis (microscopy only if clinically indicated), and cervical sample collection for cytology (if no result is evident within the previous year, or abnormal at last cervical cytology). Blood samples will be collected for storage, and will be tested retrospectively by HIV-1 RNA PCR, HIV viral genotype (including

NGS) and phenotype resistance testing subsequent to confirmed HIV seroconversion.

Participants will then be considered to have completed trial participation.

Qualitative and Quantitative Behavioural Assessments:

In cases of interest in-depth interviews (IDIs) will be conducted; approximately three participants will be interviewed per site. These cases of interest may include, but will not be limited to participants who may have experienced social harms, may have had problems using the ring, or who HIV seroconverted.

These assessments will provide data on acceptability and influencers of ring use. The recruitment and sampling strategy will be specified in the study operations manual.

STATISTICAL CONSIDERATIONS:

Sample Size:
This is an open-label, follow-on trial to IPM 027 to evaluate the safety of and adherence to Dapivirine Vaginal Ring-004, inserted at monthly intervals in healthy, HIV-negative women who have participated in the IPM 027 trial. No formal sample size or power calculations have been performed.

It is expected that up to 70% of the participants enrolled in IPM 027 will participate in this trial. Therefore, a total sample size of up to 1400 HIV-negative women is anticipated.

Statistical Analyses:
The primary analysis will focus on safety as well as adherence assessments, performed under the intent-to-treat (ITT) principle. As it is possible that the inclusion of non-adherent participants or participants who discontinued from ring use may artificially lower the rates of safety outcomes, additional analyses will be conducted on the per-protocol population, which will include only participants who were adherent to the protocol.

A descriptive analysis of all AEs will be presented in tables and listings. AEs will be summarised by MedDRA System Organ Class (SOC) and Preferred Term (PT). The proportion of participants experiencing adverse events, including the proportion of participants experiencing product-related adverse events, Grade 3 or 4 AEs, or SAEs, will be determined, and presented with corresponding 95% confidence intervals (CIs).

Residual levels of dapivirine in returned rings, and/or plasma and/or vaginal fluid concentrations of dapivirine will be used as measures of adherence to ring use. The data will be listed, summarised and

presented graphically. The ring residual levels and/or plasma and/or vaginal fluid concentrations of dapivirine associated with non-adherence will be informed by the results from IPM 027, and will be described in detail in the SAP, which will be finalised prior to final database lock. The correlation between the amount of residual dapivirine in the used rings and the corresponding plasma and/or vaginal fluid levels of dapivirine will be explored graphically and summarised descriptively.

For the secondary analysis, the number of HIV-1 seroconversions, the incidence density rate of HIV-1 seroconversion, i.e. HIV-1 seroconversion rate per 100 woman-years of product use at the end of the ring use period, as well as a 95% confidence interval for the HIV-1 seroconversion rate per 100 woman-years based on the normal approximation of the Poisson distribution will be presented for each research centre and overall. Kaplan-Meier curves will also be presented, overall and by research centre. The analysis of HIV-1 drug resistance will be primarily descriptive in nature, and will depend on the pattern of resistance mutations observed in the HIV-1 seroconverters. A frequency tabulation of individual resistance mutations associated with the various classes of antiretrovirals, *e.g.* Protease Inhibitors, Nucleoside Reverse Transcriptase Inhibitors and Non-nucleoside Reverse Transcriptase Inhibitors, will be produced. The proportion of HIV-1 seroconverters with at least one HIV-1 drug resistant mutation will be presented, with the corresponding 95% CI.

Appropriate statistical analyses of the exploratory endpoints will be performed.

Full details of the planned statistical analyses will be provided in a Statistical Analysis Plan (SAP) that will be finalised before final database lock.

1. Introduction

1.1. Background

Women continue to be affected disproportionately by HIV in sub-Saharan Africa, where they account for 58% of people living with HIV[3]. It is estimated that every hour, around 19 young women are newly infected with HIV[4]. Unprotected heterosexual intercourse is currently the leading mode of HIV acquisition among women. Correct and consistent use of latex condoms is one proven method of preventing HIV acquisition. However, many women are unable to negotiate condom use with their partners. Physiologically, women are more likely than men to acquire HIV during heterosexual intercourse, and young girls are most vulnerable[5]. In sub-Saharan Africa, the number of new HIV infections among adolescent girls and young women aged 15-24 years remains exceptionally high, with approximately 8600 new infections per week[6]. These females are at least twice as likely to be infected with HIV as their male peers[7]. The United Nations (UN) Political Declaration on Ending AIDS adopted in June 2016 calls for reducing new HIV infections among adolescent girls and young women aged 15-24 years to fewer than 100,000 per year by 2020[8]. Achieving this target demands dramatic acceleration of action and expanding of programs for adolescent girls and young women, as gender inequities often render women unable to abstain from sex or negotiate condom use with partners, a proven method of preventing HIV acquisition. Most current HIV prevention methods require the consent (as well as some action or behaviour change) of the male partner[9]. Therefore, the ongoing development of safe and effective HIV prevention technologies that can be made easily accessible to developing countries remains a public health priority.

Developing HIV prevention options that women can use therefore remains a global challenge. Antiretroviral (ARV) approaches to prevention have the potential to transform the response to the HIV/AIDS pandemic. For women, further research is needed on microbicides that contain different ARV compounds in different formulations and dosing strategies, in order to provide various options for HIV prevention. Vaginal microbicides, which are self-initiated, could offer women a critically needed new tool to prevent HIV, especially for those women who are not able to negotiate mutual monogamy or condom use[10]. ARV-based microbicides can be formulated in a number of dosage forms that allow them to be used in a variety of ways, such as around the time of sex, or daily or monthly, independent of sexual activity.

In order for a microbicide to be most effective, it is essential that it is used correctly and consistently, and is acceptable to women and their male partners. A product used independently of sexual intercourse could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse. Vaginal rings that need monthly replacement may therefore have benefits. The Dapivirine Vaginal Ring-004 has completed Phase III clinical development.

The results from two Phase III trials of the Dapivirine Vaginal Ring-004, The Ring Study (IPM 027) and ASPIRE (MTN- 020) were announced at the Conference on Retroviruses and Opportunistic Infections (CROI in Boston, MA) in February 2016. Both trials demonstrated that the Dapivirine Vaginal Ring-004 was well-tolerated and prevented HIV-1 infection in approximately one in three women between the age of 18-45 years overall, a statistically significant result ($p<0.05$ in both trials[1,2,11,12]). Post-hoc data analyses provide supportive evidence that Dapivirine Vaginal Ring-004 risk reduction of HIV-1 increases when adherence increases. The ASPIRE trial showed that women who

appeared to use the ring more consistently (defined as at least 3 mg of dapivirine released from the ring during 4 weeks of continuous use) had at least a 65% reduction in risk, and additional subgroup analyses of women who appeared to use the ring most consistently suggest 75% or more reduction in risk[13]. Similarly, in a post-hoc analysis of The Ring Study data, 65% efficacy was seen in women who appeared to use the Dapivirine Vaginal Ring-004 more consistently[11]. A lower HIV-1 risk reduction was observed in women ≤21 years of age in IPM 027 (the age effect was not statistically significant). In ASPIRE, age was shown to be significantly related to HIV-1 protection, with no protection observed in participants aged 18-21 years, and 56% protection in participants over 21 years of age[2,12]. Further research is needed to understand younger women's unique challenges in using HIV prevention methods, as well as exploring dapivirine vaginal ring-use in the context of known safety and efficacy and if it would increase the HIV risk reduction demonstrated in the Phase III trials.

1.2. Dapivirine Vaginal Ring

1.2.1. *Dapivirine*

Dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is a di-amino-pyrimidine (DAPY) derivative with the chemical name 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino] benzonitrile. NNRTIs bind directly to the HIV reverse transcriptase (RT) enzyme, preventing viral replication. Dapivirine was originally developed by Janssen Research and Development (formerly Tibotec Pharmaceuticals) as an oral antiretroviral compound and was tested in Phase I and II clinical trials in more than 200 participants. Although first conceived as an oral therapeutic, dapivirine is a promising candidate for development as a topical microbicide due to its proven *in vitro* and *in vivo* efficacy and favourable safety profile as well as its physical and chemical properties. Dapivirine has potent activity against wild-type HIV-1 strains and strains harbouring different resistance-inducing mutations. Dapivirine's antiretroviral profile is superior to that of earlier NNRTI class compounds such as nevirapine, delavirdine, and efavirenz. *In vitro* tests have shown that dapivirine is inactive against HIV-2 and has no efficacy against common sexually transmitted infections. Dapivirine is therefore not intended to protect against HIV-2 or other sexually transmitted infections, nor does it have any contraceptive properties.

1.2.2. *Formulation of a Silicone Elastomer Matrix ring containing 25 mg of Dapivirine*

The dapivirine silicone elastomer vaginal matrix ring (Ring-004) is an off-white flexible ring containing 25 mg of dapivirine dispersed in a platinum-catalysed silicone matrix. The dimensions of the ring are 56 mm (outer diameter) and 7.7 mm (cross-sectional diameter). Details regarding the formulation and dimensions are provided in the Dapivirine Vaginal Ring-004 Investigator's Brochure (IB)[14]. The dapivirine vaginal ring is designed to provide sustained release of dapivirine for a minimum of one month.

1.3. Nonclinical Studies

The potential of dapivirine as a microbicide for prevention of sexual transmission of HIV has been assessed in a variety of *in vitro*, *ex vivo* and *in vivo* models. Furthermore, a comprehensive program of preclinical studies was used to evaluate the toxicity of dapivirine. The studies are described in the IB[14].

Virology:
The activity of dapivirine against wild-type HIV-1, African isolates of HIV-1 (including subtype C virus), and a panel of NNRTI-resistant viruses has been established using *in vitro* models, with EC_{50} values ranging from 0.3 ng/mL (0.9 nM) against laboratory isolates to < 33 ng/mL (< 100 nM) for HIV-1 isolates encoding one or more known NNRTI resistance mutations. The anti-HIV activity was also confirmed in an *ex vivo* model of human cervical explant cultures and in an *in vivo* humanized severe combined immunodeficient (hu-SCID) mouse model.

Nonclinical safety pharmacology:
In a series of preclinical safety pharmacology studies, dapivirine was generally devoid of adverse effects on overt behaviour, reflexes and other body functions. Although safety pharmacology studies revealed no cardiovascular effects, there was evidence of an increase in QT interval during the 4- and 6-month oral toxicity study in dogs. However, this was only seen at ≥ 30 mg/kg/day, at which C_{max} and AUC values were respectively more than 3800 and 2500 times the values achieved in women following use of the Dapivirine Vaginal Ring-004.

Nonclinical pharmacokinetics:
Systemic exposure to dapivirine was low following vaginal administration of dapivirine gels to rabbits. Much higher systemic exposures were obtained in single dose oral and subcutaneous toxicity studies in mice and rats, and in repeat dose oral toxicity studies in rats, dogs and monkeys. The free fraction of dapivirine in plasma was 0.19-0.34% in the male rat, 0.18-0.39% in the female rat, 0.21–0.22% in the dog and 0.15% in man. In rats, tissue to plasma AUC_{0-24} ratios following a single oral dose were 11 in liver, 7-8 in lung, kidney and adrenals, about 4 in spleen and lymph nodes, and 2-3 in brain, heart and muscle. Plasma/tissue equilibrium was rapid, and there was no undue retention of dapivirine in tissues.

For virtually all tissues, maximal concentrations after vaginal dosing were < 1% of those after oral dosing. Preliminary metabolism studies demonstrated the presence of free and conjugated metabolites in rats, dogs, monkeys and humans, but the molecular structures have not been elucidated. There was evidence of extensive cytochrome P450 (particularly CYP3A4) mediated metabolism.

Nonclinical toxicology:
Dapivirine has been investigated in single and repeat dose toxicity studies, in a range of reproductive toxicity and mutagenicity studies, and in a carcinogenicity study. In vaginal studies in rabbits there were no significant local or systemic findings following repeat administration at up to 20 mg/mL for 14 days, up to 5 mg/mL for 13 weeks or up to 2 mg/mL for 39 weeks, or in reproductive toxicity studies in rats and rabbits performed at concentrations up to 2 mg/mL (0.2%). In a 13-week study in sheep using Ring-004, there was no evidence of local or systemic toxicity.

The no adverse effect level (NOAEL) in rats and dogs following oral administration was 20 mg/kg/day. At higher dose levels, hepatotoxicity was observed in dogs and slight hematological and clinical chemistry changes were observed in rats. The NOAEL in oral reproductive toxicity studies in the rat was also 20 mg/kg/day, whereas in the rabbit no effects were seen at dosages up to 90 mg/kg/day. Dapivirine was considered to be non-genotoxic. In the guinea pig, dapivirine (2 mg/mL) did not demonstrate any potential to

cause contact sensitization. No treatment-related neoplastic or non-neoplastic findings were seen in a vaginal carcinogenicity study in rats at concentrations up to 5 mg/mL.

1.4. Clinical Trials

Multiple clinical trials have evaluated the safety of dapivirine in different formulations. Below is a summary of the data collected through these studies. More detailed information is available in the Dapivirine Vaginal Ring-004 IB[14].

Across all clinical trials with multiple ring configurations in healthy participants, the dapivirine vaginal ring was generally safe and well tolerated. No drug-related serious adverse events (SAEs) have been reported to date and no trials were stopped for safety reasons. In completed trials of Dapivirine Ring-004, one participant assigned to Dapivirine Ring-004 required permanent discontinuation of the investigational product due to a non-serious adverse event considered by the investigator as possibly related to product use. This event, a Grade 2 (moderate intensity) generalized pruritus, required action taken by the Investigator to discontinue IP use permanently as a direct result of the event. Three SAEs were reported in dapivirine ring users (Ring-004) and six SAEs in placebo ring users.

The Phase III clinical development program for the Dapivirine Vaginal Ring-004 included two pivotal trials, IPM 027 and MTN-020, which evaluated long term safety and efficacy of Dapivirine Vaginal Ring-004 compared to a placebo vaginal ring in 4588 participants (2620 enrolled to the dapivirine ring and 1968 enrolled to the placebo ring). No safety concerns or clinically relevant differences in safety parameters were observed between treatment groups. No SAEs were considered related to the use of dapivirine or placebo vaginal rings in either trial.

1.4.1. *Phase I and II*

To date (16 January 2017), 27 Phase I and Phase I/II clinical trials of dapivirine have been completed: 8 trials of dapivirine vaginal rings in 469 participants (298 using dapivirine rings and 183 using placebo rings); 8 trials of dapivirine vaginal gel in 774 participants (491 using dapivirine gel and 283 using placebo gel); and 11 trials of oral dapivirine in which a total of 211 participants used oral dapivirine. Two Phase I clinical trials that evaluated a vaginal film formulation of dapivirine in 71 women have been conducted. In addition, one Phase I clinical trial in male participants to assess the safety and tolerability of a dapivirine vaginal gel, following multiple topical penile exposures, was conducted in 48 healthy, HIV-negative, adult males, 24 of whom were circumcised and 24 uncircumcised (MTN-012/IPM 010). The dapivirine gel formulation was well tolerated by the participants. No SAEs or discontinuations due to TEAEs were reported during this trial.

Based on information in the current IB[14], across all completed Dapivirine Ring-004 trials (IPM 024, IPM 013, IPM 015, IPM 028 and IPM 034), the most commonly occurring TEAEs that were documented in at least 5% of participants in dapivirine versus placebo treated participants (n=259 using dapivirine rings and n=160 using placebo rings, respectively) were metrorrhagia (29.7% vs 24.4%), headache (15.1% vs 11.9%), gynaecological chlamydia infection (8.5% vs 13.4%), vaginal candidiasis (8.1% vs 7.5%), urinary tract infection (6.9% vs 8.8%), vaginal discharge (6.6% vs 6.3%), upper respiratory tract infection (5.8% vs 10.0%) and lower abdominal pain (5.4% vs 5.0%).

1.4.1.1. *Oral Dapivirine*

There have been 11 oral administration trials in which a total of 211 participants have been dosed with dapivirine. The maximum tolerated dose (MTD) established was 350 mg for a single dose, and for multiple doses, 300 mg b.i.d. for 14 days. There were no deaths during the clinical trials of oral dapivirine, and no trials were stopped for safety reasons. A total of 10 participants stopped dapivirine treatment prior to trial completion for safety reasons, 6 of whom stopped due to a clear dose-dependent increase in central nervous system (CNS) and gastrointestinal TEAEs, thereby establishing the MTD at 300 mg b.i.d. These TEAEs resolved within 1-2 days after discontinuation of use of oral dapivirine.

Adverse events documented in 5 or more participants (> 2%) after oral exposure to dapivirine were headache, dizziness, nausea, diarrhoea, fatigue, tremor, somnolence, flatulence, and vomiting. Most (≥ 80%) of these TEAEs were Grade 1 or 2 (mild or moderate) and most (≥ 80%) were considered to be related to dapivirine. Grade 3 (severe) TEAEs included headache, dizziness, injury, nausea, tremor, paraesthesia, disturbance in attention, abrasion, AST increased, ALT increased, polyuria, fever, diarrhoea, and vomiting. The increases in AST and ALT were transient and the Grade 3 increases in AST and ALT occurred in a single participant who received 50 mg oral dapivirine as a twice daily dose.

1.4.2. *Phase III*

The Phase III clinical program of the dapivirine vaginal ring, containing 25 mg of dapivirine (Ring-004), consisted of the MTN-020 and IPM 027 clinical trials. These trials were conducted in South Africa, Uganda, Zimbabwe and Malawi, to assess the safety and efficacy of the Dapivirine Vaginal Ring-004 in preventing the acquisition of HIV-1 infection through male to female transmission in healthy, HIV-negative women.

IPM 027 was a double-blind, multi-centre, placebo-controlled trial that was designed to assess the safety and efficacy of the Dapivirine Vaginal Ring-004, inserted once every 4 weeks over a period of 24 months, in healthy, sexually active HIV-negative women, 18 to 45 years of age, when compared to a placebo vaginal ring. It was conducted at 7 research centres, six in South Africa and one in Uganda. A total of 1959 eligible women were randomized in a 2:1 ratio to receive either the dapivirine vaginal ring or placebo vaginal ring. Of these, 1307 women were enrolled in the dapivirine ring group and 652 women in the placebo ring group. This trial was initiated in March 2012 and an early primary efficacy analysis was initiated in November 2015 to align with the publication of the MTN-020 data (see below).

MTN-020 was designed to assess the safety and effectiveness of the Dapivirine Vaginal Ring-004, inserted once every 4 weeks, in healthy, sexually active, HIV-negative women, 18 to 45 years of age, when compared to a placebo vaginal ring. It was conducted in Malawi, South Africa, Uganda and Zimbabwe. A total of 2629 women were randomized. Each participant was to use the investigational product until 120 events (HIV-1 seroconversions) were observed in the trial. All participants were to use the investigational product for a minimum of 12 months. The trial was initiated in August 2012 and clinical conduct completed in June 2015.

The results from two Phase III trials of the Dapivirine Vaginal Ring-004, The Ring Study

(IPM 027) and ASPIRE (MTN-020) were announced at the Conference on Retroviruses and Opportunistic Infections (CROI in Boston, MA) in February 2016. Both trials demonstrated that the Dapivirine Vaginal Ring-004 was well-tolerated and prevented HIV-1 infection in approximately one in three women between the age of 18-45 years overall, a statistically significant result ($p<0.05$ in both trials[1,2,11,12]). Post-hoc data analyses provide supportive evidence that Dapivirine Vaginal Ring-004 risk reduction of HIV-1 increases when adherence increases. The ASPIRE trial showed that women who appeared to use the ring more consistently (defined as at least 3 mg of dapivirine released from the ring during 4 weeks of continuous use) had at least a 65% reduction in risk, and additional subgroup analyses of women who appeared to use the ring most consistently suggest 75% or more reduction in risk[13]. Similarly, in a post-hoc analysis of The Ring Study data, 65% efficacy was seen in women who appeared to use the Dapivirine Vaginal Ring-004 more consistently[11]. A lower HIV-1 risk reduction was observed in women ≤21 years of age in IPM 027 (the age effect was not statistically significant). In ASPIRE, age was shown to be significantly related to HIV-1 protection, with no protection observed in participants aged 18-21 years, and 56% protection in participants over 21 years of age[2,12].

1.4.3. *Adherence to and Acceptability of the Dapivirine Vaginal Ring*

IPM 011 was an open-label, crossover trial conducted in South Africa and Tanzania among sexually active women to assess the safety and acceptability of a silicone elastomer placebo vaginal ring (containing no active ingredient), intended as a microbicide delivery method for the prevention of HIV infection. Participants were randomly assigned in a 1:1 ratio to one of two trial groups. Both groups participated in two regimens: a placebo vaginal ring regimen and an observational safety regimen (with no placebo vaginal ring). Each regimen had 12-week duration. Eighty-two percent (82%) of women in this trial reported no ring removals at all for the entire duration of the trial, across trial groups and visits, and 99% of participants reported wearing the ring for at least 80% of the days they were meant to. Eighteen percent (18%) of women self-reported at least one ring removal or expulsion during the course of trial participation. This proportion increased to 22% when pharmacy records were incorporated. Many of the reported expulsions and removals were related to menses, *e.g.* heavy blood flow or concern about the ring becoming dirty or retaining odour, leading to removal. Ninety-five percent (95%) of women found the ring to be very comfortable. All questionnaire responders were willing to use the vaginal ring if shown to be effective for HIV prevention[15].

IPM 015 was a Phase I/II randomized, double-blind, placebo-controlled trial conducted at 10 research centres in Kenya, Malawi, Tanzania and South Africa. The trial was performed in 280 HIV-negative, sexually active women, 18 to 40 years of age, to assess and compare the safety of 28-day use of Dapivirine Vaginal Ring-004, and a placebo vaginal ring, containing no dapivirine. Eligible women were randomly assigned in a 1:1 ratio to the dapivirine ring or placebo ring, inserted once every 28 days over a 12-week period. In IPM 015, “perfect adherence” was reported by 92% of the female participants. Perfect adherence was defined as never having the ring out for more than an entire day. The most frequent activity associated with ring expulsion was urination/defecation and the most common reason reported by participants for removing the ring themselves was cleaning. At the end of the trial, 96% of participants reported that the ring was usually comfortable to wear, and 97% reported that they would be willing to use it in the future if it were proven effective and they thought they were at risk for HIV infection. Just over 60% of the participants in both arms reported that their male partners did not feel the ring at Visit 5 (trial week 12). A further 22% reported that their partner felt the ring during sex, but that it

was not a problem. Only a small number (3%) at Visit 3 (trial week 4) and (1%) at Visit 5 (trial week 12) reported that her male partner felt the ring and it might be, or definitely was a problem for her to continue ring use[16].

1.4.4. *Condom Compatibility*

Two clinical condom functionality studies (one with male condoms [IPM 029] and one with female condoms [IPM 033]) were conducted with a placebo vaginal ring (silicone elastomer ring containing no active ingredient). Results from both studies showed that the difference between the total clinical failure rate between condom use with the vaginal ring and condom use without the vaginal ring was less than the pre-defined non-inferiority margins (3% for the male condom study and 8% for the female condom study). Condom use was safe and well tolerated with vaginal ring use.

Studies with dapivirine-containing vaginal gel formulations (0.05%, 2.5 g) were conducted on the following types of male and female condoms:

- Non-lubricated latex condoms (male condom)
- Silicone lubricated latex condoms (male and female condoms)
- Aqueous lubricated latex condoms (male condom)
- Polyurethane condoms with silicone lubricant (male and female condoms)
- Nitrile condoms with silicone lubricant (female condom)

All types of condoms met the acceptance criteria established in the protocol for the mean values of the treated samples after treatment with dapivirine gels. The results of condom compatibility testing indicate that dapivirine-containing vaginal gel formulations (0.05%, 2.5 g) have no deleterious effects on the integrity of male or female condoms[14].

1.5. Rationale for Protocol IPM 032

The potential of dapivirine as a safe and efficacious microbicide for prevention of sexual transmission of HIV-1 has been evaluated in nonclinical studies (virology studies, secondary/safety pharmacology, pharmacokinetics, toxicology) using different *in vitro*, *ex vivo and in vivo* models, as well as Phase I-II and III clinical trials. Results were communicated to the relevant local and international regulatory authorities, IRBs/IECs, community representatives, participants and key stakeholders, as appropriate, before activation of IPM 032. IPM is pursuing regulatory approval for the product.

IPM 032, a Phase IIIb follow-on trial to IPM 027, has been designed as an open-label clinical trial with the Dapivirine Vaginal Ring (25 mg) to collect additional safety data and assess adherence to ring use in healthy, HIV-negative women with monthly (at least one to a maximum of three months) followed by 3-monthly research centre follow-up visits over 12 months. Further, IPM 032 will examine incidence of HIV-1 seroconversion and monitor HIV-1 resistance in women who acquire HIV-1 infection. The assessment of the monthly visits (first one to three months) followed by 3-monthly research centre follow-up visits will provide insight into the feasibility of a 3-monthly scheduling strategy that would be less costly and time-consuming in a resource-limited environment such as sub-Saharan Africa.

IPM 032 will collect behavioral data needed to support the potential introduction of a microbicide as the dapivirine vaginal ring as a public health intervention and to assist with future program development.

2. Trial Objectives

2.1. Trial Objectives

The primary trial objectives are:

1. To assess the safety profile of the 25 mg Dapivirine Vaginal Ring-004, when inserted at monthly intervals, in an open-label trial
2. To assess adherence to the use of the 25 mg Dapivirine Vaginal Ring-004 inserted at monthly intervals, in an open-label trial

The secondary trial objectives are:

1. To assess the incidence of HIV-1 seroconversion
2. To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection

The exploratory trial objectives are:

1. To assess the feasibility of 3-monthly follow-up visits, as a possible schedule for post-licensure vaginal ring clinical follow-up
2. To explore the correlation between drug amount and results from the visual inspection of the returned vaginal rings by research staff between the monthly and 3-monthly research centre follow-up schedules
3. To determine the proportion of participants electing to undergo HIV rapid tests at the research centres between scheduled 3-monthly visits
4. To explore self-reported acceptability of and adherence to the 25 mg Dapivirine Vaginal Ring-004.

2.2. Trial Endpoints and Assessments

The primary endpoints are:

1. Safety
    - All Adverse Events (AEs) assessed by the investigator to be related to the Dapivirine Vaginal Ring-004
    - All Grade 3 and 4 AEs
    - All Serious Adverse Events (SAEs)

2. Adherence
    - Residual amounts of dapivirine in returned rings; and/or dapivirine concentrations in plasma and/or dapivirine concentrations in vaginal fluid

The primary endpoints will be assessed through:

1. Safety
    - All product-related AEs, Grade 3 or 4 AEs, SAEs, physical examination, gynaecological assessments, including pelvic/speculum examination, laboratory tests and other indicated investigations
2. Adherence
    - Determined dapivirine residual amounts in returned used vaginal rings and/or
    - Measured concentrations of dapivirine in plasma and/or
    - Measured concentrations of dapivirine in vaginal fluids

The secondary endpoints are:

- The HIV-1 seroconversion rate per 100 woman-years of product use at the end of the vaginal ring use period
- HIV-1 drug resistance mutations among participants who acquire HIV-1 infection

The secondary endpoints will be assessed through:

- Rapid and specialised laboratory testing according to a pre-specified HIV testing algorithm
- Viral genotype (including next generation sequencing [NGS]) and phenotype resistance testing methods which include sensitive methods to detect low frequency drug-resistant variants

The exploratory endpoints are:

- Feasibility of 3-monthly clinical follow-up schedule
- Dapivirine residual amounts in returned used vaginal rings and/or dapivirine concentrations in blood and/or vaginal fluid in correlation with results from the visual inspection of the returned used vaginal rings by research staff
- Proportion of participants opting for HIV rapid tests at the research centre between scheduled 3-monthly research centre follow-up visits
- The proportion of women who report the use of the vaginal ring as acceptable
- Participant self-reported patterns of ring use

The exploratory endpoints will be assessed through:

- Participant report of feasibility regarding a 3-monthly clinical follow-up schedule (Participant Questionnaire)
- Number of women opting not to receive two additional rings at the 3-monthly visits
- Proportion of returned rings (used and unused) during the 3-monthly clinical follow-up schedule
- Dapivirine residual amounts in returned used vaginal rings and/or dapivirine

concentrations in blood and/or vaginal fluid

- Visual inspection of the returned used vaginal rings by research centre staff
- Number of participants undergoing HIV rapid tests at the research centres between scheduled 3-monthly research centre follow-up visits
- Qualitative data regarding reasons for ring acceptability and self-reported patterns of ring use

3. Overall Trial Design

3.1. Trial Design

IPM 032 is a Phase IIIb, multi-centre follow-on open-label trial to evaluate the continued adherence to and safety of the Dapivirine Vaginal Ring-004, inserted at monthly intervals in healthy, HIV-negative women who have participated in the IPM 027 Phase III Dapivirine Vaginal Ring-004 trial. All women who have participated in IPM 027 and are HIV-negative at screening for IPM 032 will be eligible. An estimate of up to 1400 participants will be enrolled.

All participants will receive the dapivirine vaginal ring containing 25 mg dapivirine (Ring-004) at enrolment and will attend a research centre follow-up visit one month after enrolment. Following this visit, at investigator's discretion, a participant can continue on a 3-monthly visit schedule. Monthly visits may however be extended up to the first three months of participation. Once the 3-monthly trial visit schedule commences, three rings will be dispensed. One ring will be self-inserted at the research centre and two additional rings will be dispensed for the participant to take home, or dispensing will take place as arranged with the participant.

3.2. Trial Duration

Each participant will engage in the screening process for up to 45 days prior to enrolment and will use the Dapivirine Vaginal Ring-004 for a period of up to 12 months. IPM will have the option to extend this trial period. Accrual will take place over approximately 6 months and those participants who are enrolled more than 6 months after the onset of the trial site's accrual period may have a shortened follow-up period.

Each participant will have an exit visit approximately 1-2 months after ring discontinuation, to assess safety and identify HIV seroconversions after product discontinuation.

3.3. Trial Population

Up to 1400 HIV-negative women who have participated in the IPM 027 Phase III Dapivirine Vaginal Ring-004 trial, who understand the trial and can provide informed consent are expected to enrol in this open-label trial.

3.3.1. *Inclusion Criteria – Women who Previously Enrolled in IPM 027*

Women must meet all the following criteria to be eligible to enrol in the trial:

1. Previously enrolled in the IPM 027 trial
2. Available for all visits and consent to follow all procedures scheduled for the trial
3. Using an effective method of contraception at the Enrolment Visit, and intending to use an effective contraceptive method for the duration of trial participation, unless postmenopausal with no history of menses for one year prior to screening
4. HIV-negative as determined by the HIV algorithm applied at Screening/Pre-Enrolment
5. Willing to refrain from participation in another research trial using drugs, vaccines, medical devices and microbicides for the duration of the IPM 032 trial
6. Willing to provide adequate locator information for trial retention purposes and be reachable per local standard procedures (*e.g.*, by home visit or telephone; or *via* family or close neighbour contacts); confidentiality to be maintained

3.3.2. *Exclusion Criteria – Women who Previously Enrolled in IPM 027*

Women who meet any of the following criteria are NOT eligible to enrol in the trial:

1. Investigational product use permanently discontinued in response to an AE (where the AE was considered related to investigational product) or safety-related concern while taking part in the IPM 027 trial
2. Currently pregnant, intends to become pregnant or currently breast-feeding
3. Known drug abuse or alcohol dependence in the 12 months prior to screening
4. Participated in another research trial (other than IPM 027) using drugs, medical devices, microbicides or oral pre-exposure prophylaxis agents within 30 days prior to screening
5. Any new illness or condition(s), chronic condition(s) or abnormal laboratory finding(s) that, in the opinion of the investigator, might put the participant at risk, or interfere with the trial objectives or the participant's adherence to trial requirements

4. Trial Visits and Procedures

4.1. Screening Visit

NOTE: *For potential participants who do not meet the eligibility criteria, screening procedures will be discontinued once ineligibility has been determined. Women who fail screening may be re-screened once and may be enrolled if they are found to meet ALL inclusion and NO exclusion criteria at the second screening visit.*

In the event that the IPM 027 trial is stopped prematurely and IPM 032 is activated at the research centre, the IPM 027 LPUV and the IPM 032 Screening and Enrolment Visits may be combined for participants who are eligible to enrol in the IPM 032 trial. In these

situations, a separate Screening visit will not be required, and only the procedures indicated in italics are required.

a. *Explain the screening, enrolment and trial procedures to the potential participant.*
b. *If the potential participant agrees, obtain written informed consent. Illiterate participants may provide a thumbprint or mark witnessed and signed by a person independent from trial staff (refer to Section 5.1). A comprehension assessment checklist will be used to support the consent process (refer to Section 5.2).*
c. *Assign a unique SCR-ID number to the potential participant (refer to section 5.18).*
d. *Conduct a review of inclusion/exclusion criteria with the potential participant.*
e. Collect demographic information from the potential participant.
f. Obtain and record locator information.
g. Record basic menses information, relevant medical history, and concomitant medication taken within the last 30 days (refer to Section 5.7 for more details about relevant medical history).
h. Perform urine pregnancy testing. Refer pregnant women to local prenatal clinic for support services (refer to Section 5.6).
i. Provide HIV/STI risk-reduction counselling (including provision of male and/or female condoms, should participants wish to receive them), contraceptive counselling and *the provision of contraceptives, if necessary* (refer to Sections 5.3.2 and 5.5).
j. Provide HIV pre- and post-test counselling (refer to Section 5.3.1).
k. Perform HIV rapid testing as detailed in Section 5.4.1.
l. *Collect a blood specimen by venepuncture for storage for possible HIV viral genotype* (including NGS) and phenotype *resistance testing* , and HIV-1 RNA PCR testing (Blood volume specified in Appendix C).
m. Perform general physical examination (refer to Section 5.8 for a description of the elements required in the general physical examination).
n. Perform a pelvic examination (refer to Section 5.9). If the pelvic examination indicates abnormal findings, *e.g.*, any symptoms or evidence of genital infections, abrasions, ulcerations, etc., provide or refer for appropriate treatment.

   ***NOTE**: If the participant is menstruating at this visit, the pelvic examination may be conducted as per investigator and participant discretion. If this is not possible, the participant will be asked to return 2 days after completion of menstruation.*
o. Collect cervicovaginal swabs for STI testing and *a specimen for cervical cytology, if no result is evident within the previous year, or abnormal at last cervical cytology* (refer to Sections 5.11.1 and 5.12). Women with Grade 3 cervical cytology findings or Grade 3 intraepithelial neoplasia by biopsy (histology result) at screening should be referred according to National guidelines.
p. Provide treatment and/or referral for STIs and other findings, as necessary (refer to Section 5.11.2).
q. Perform a urine dipstick analysis (microscopy only if clinically indicated). Collect blood samples by venepuncture for syphilis testing (RPR) and confirmatory test (if required), and the following safety laboratory tests *(*Blood volumes specified in Appendix C*):* haematology (FBC with differential and platelet count), and chemistry

(creatinine, ALT, AST) (refer to Section 5.10).

r. Other procedures, as clinically indicated and with prior approval from IPM.

s. Schedule the Enrolment Visit within 45 days.

4.2. Enrolment Visit

Note: *The Enrolment Visit will occur within 45 days after the Screening Visit.*

In the event that the IPM 027 trial is stopped prematurely and the IPM 032 is activated at the research centre, the IPM 027 LPUV and the IPM 032 Screening and Enrolment Visits may be combined for participants who are eligible to enrol in IPM 032. Trial procedures conducted as part of the IPM 027 LPUV will not be repeated for the IPM 032 trial. Only the procedures indicated in italics are required.

Pre-enrolment:

a. Update locator, menses and pre-enrolment medical history information as necessary (refer to Section 5.7).

b. Provide contraceptive counselling *and contraceptives, if necessary* (refer to Section 5.5).

c. Provide HIV/STI risk reduction counselling, including provision of male and/or female condoms if the participant wishes to receive them (refer to Section 5.3.2).

d. *Record possible social harms (refer to Section 10.2).*

e. Obtain and record any concomitant medication information since the last visit.

f. Perform urine pregnancy testing. Refer pregnant women to local prenatal clinic for support services (refer to Section 5.6).

g. Provide HIV pre- and post-test counselling (refer to Section 5.3.1).

h. Perform HIV rapid testing as detailed in Section 5.4.2.

   NOTE: *Additional procedures for participants who test HIV-positive are also described in Section 5.4.2 of the protocol.*

i. Reassess and *confirm eligibility.*

Post-enrolment:

j. *Assign a unique PID number to the participant (refer to Section 5.18)*.

k. Collect a blood specimen by venepuncture for storage for possible HIV viral genotype resistance (including NGS) and phenotype resistance testing, and HIV-1 RNA PCR testing (Blood volume specified in Appendix C).

l. Obtain and record any AE information.

m. *Provide adherence counselling, including adherence to trial visit schedule and requirements and vaginal ring adherence (refer to Section 5.15). Participants will be instructed to keep the ring inserted for a period of one month. Adherence counselling will include information on actions that should be taken in the event of expulsion or removal of the ring. If the ring comes out or is removed during this period, the participant should wash her hands, rinse the ring thoroughly in clean water and re-insert it.*

n. *Provide and explain the use of the diary card to the participant (refer to Section 5.19).*

o. *Dispense one vaginal ring to each participant and provide vaginal ring use and storage instructions (refer to Sections 5.13 and 6.4).*

p. *Instruct the participant to insert the vaginal ring (refer to Section 5.14).*

q. *The following procedures are not required, but may be conducted if clinically indicated*: physical and pelvic examination, cervicovaginal sample collection for STI testing, *provision of treatment and/or referral for STIs and other findings,* laboratory testing for safety assessments, urine dipstick analysis (microscopy only if clinically indicated) and *cervical sample collection for cytology (if no result is evident within the previous year, or abnormal at last cervical cytology).*

r. *Schedule the next visit.*

4.3. Trial Visits (Monthly research centre visits for the first one to three months, and 3-monthly research centre visits thereafter)

Note: *All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit while the participant is on the IP has a window period of ± 7 days.*

a. Update locator and menses information as necessary.

b. Obtain and record any AE and concomitant medication information since the last visit.

c. Record possible social harms (refer to Section 10.2).

d. Perform urine pregnancy test. Refer pregnant women to local prenatal clinic for support services (refer to Section 5.6).

e. Provide HIV pre- and post-test counselling (refer to Section 5.3.1).

f. Perform HIV rapid testing as detailed in Section 5.4.3.

   NOTE: *Additional procedures for participants who test HIV-positive are also described in Section 5.4.3 of the protocol.*

g. Collect a blood specimen by venepuncture for storage for possible HIV viral genotype (including NGS) and phenotype resistance testing, and HIV-1 RNA PCR testing (Blood volume specified in Appendix C). HIV-1 RNA PCR will be performed on samples stored at last product use visit and on the last samples collected for participants who discontinue from the trial without an exit visit. Only samples from participants who consented for analysis will be selected for the additional HIV-1 RNA PCR analysis and additional HIV viral genotype (including NGS) and phenotype resistance testing as needed.

h. Collect blood (Blood volume specified in Appendix C) and vaginal fluid samples (refer to Section 5.18) for possible measurement of dapivirine concentrations.

   NOTE*: For dapivirine concentration measurements, blood and vaginal fluid samples should preferably be collected prior to removal of the vaginal ring.*

i. Instruct the participant to remove the vaginal ring. Collect all used rings from participants. Perform IP accountability and visual inspection of the returned ring(s). Returned rings may be analysed for residual amounts of dapivirine and will be stored until shipment to the analytical laboratory.

Dispense one vaginal ring to participants during monthly visits and three vaginal rings during 3-monthly visits (or dispense as arranged with the participant) and provide vaginal ring use and storage instructions (refer to Sections 5.13 and 6.4).

j. Instruct the participant to insert the vaginal ring during monthly visits. Once the 3-monthly trial visit schedule commences, one ring will be inserted at the research centre and two additional rings will be dispensed for the participant to take home (or dispense as arranged with the participant (refer to Section 5.14).
k. Collect and review the diary card(s) and provide a new diary card(s) if applicable (refer to Section 5.19).
l. Administer the Participant Questionnaire at every trial visit (refer to Section 5.16.1).
m. Provide adherence counselling, including adherence to trial visit schedule and requirements, and vaginal ring adherence (refer to Section 5.15). Participants will be instructed to keep the ring inserted for a period of one month. Adherence counselling will include information on actions that should be taken in the event of expulsion or removal. If the ring comes out or is removed during this period, the participant should wash her hands, rinse the ring thoroughly in clean water and re-insert it.
n. Provide contraceptive counselling and contraceptives, if necessary (refer to Section 5.5).
o. Provide HIV/STI risk reduction counselling; including provision of male and/or female condoms if the participant wishes to receive them (refer to Section 5.3.2).
p. The following procedures are not required, but may be conducted if clinically indicated: physical and pelvic examination, cervicovaginal sample collection for STI testing, provision of treatment and/or referral for STIs and other findings, laboratory testing for safety assessments, urine dipstick analysis (microscopy only if clinically indicated) and cervical sample collection for cytology (if no result is evident within the previous year, or abnormal at last cervical cytology).
q. Schedule the next visit.

4.4. Last Product Use Visit (LPUV) or Early Discontinuation Visit

Note: *LPUVs will be calculated from the enrolment visit as baseline date. This scheduled visit has a window period of ± 7 days.*

a. Update locator and menses information as necessary.
b. Obtain and record any AE and concomitant medication information since the last visit.
c. Perform a pelvic examination (refer to Section 5.9). If the pelvic examination indicates abnormal findings, *e.g.*, any symptoms or evidence of genital infections, abrasions, ulcerations, etc., provide the participant with or refer the participant for appropriate treatment.

   NOTE: *If the participant is menstruating at this visit, the pelvic examination may be conducted as per investigator and participant discretion. If this is not possible, the participant will be asked to return 2 days after completion of menstruation.*
d. Record possible social harms (refer to Section 10.2).
e. Perform a general physical examination (refer to Section 5.8 for a description of

the elements required in the general physical examination).

f. Instruct the participant to remove the vaginal ring. Perform IP accountability and visual inspection of the returned ring(s). Returned rings may be analysed for residual amounts of dapivirine and will be stored until shipment to the analytical laboratory.
g. Collect and review the diary card(s).
h. Administer the Participant Questionnaire (refer to Section 5.16.1).
i. Provide HIV/STI risk reduction counselling; including provision of male and/or female condoms if the participant wishes to receive them (refer to Section 5.3.2).
j. Perform contraceptive counselling and provide contraceptives, if necessary (refer to Section 5.5).
k. Perform urine pregnancy test. Refer pregnant women to local prenatal clinic for support services (refer to Section 5.6).
l. Collect cervicovaginal swabs for STI testing (refer to Sections 5.11.1).
m. Provide STI treatment if needed (refer to Section 5.11.2).
n. Provide HIV pre- and post-test counselling (refer to Section 5.3.1).
o. Perform HIV rapid testing as detailed in Section 5.4.3.
p. Collect a blood specimen by venepuncture for storage for possible HIV viral genotype (including NGS) and phenotype resistance testing , and HIV-1 RNA PCR testing (Blood volume specified in Appendix C). HIV-1 RNA PCR will be performed on samples stored at last product use visit and on the last samples collected for participants who discontinue from the trial without an exit visit. Only samples from participants who consented for analysis will be selected for the additional HIV-1 RNA PCR analysis and additional HIV viral genotype (including NGS) and phenotype resistance testing as needed.
q. Collect blood (Blood volume specified in Appendix C) and vaginal fluid samples (refer to Section 5.17) for possible measurement of dapivirine concentrations.

   NOTE: *For dapivirine concentration measurements, blood and vaginal fluid samples should preferably be collected prior to removal of the vaginal ring.*
r. The following procedures are not required but may be conducted if clinically indicated: laboratory testing for safety assessments, urine dipstick analysis (microscopy only if clinically indicated) and cervical sample collection for cytology (if no result is evident within the previous year, or abnormal at last cervical cytology).
s. Schedule the exit visit.

4.5. Exit Visit

Note: *Exit Visits will occur approximately 1-2 months after ring discontinuation. If the outcome of confirmatory tests is pending, the exit visit may be conducted more than 2 months after the last product use visit, but should be performed as soon as possible after the results are available. Participants will be notified of any abnormal laboratory findings, and return to the research centre prior to the exit visit as needed for treatment*

and/or referral. Additional trial procedures for exit visits scheduled following HIV seroconversion are described in Section 5.4.4.

a. Obtain and record any AE and concomitant medication information since the last visit.
b. Record possible social harms (refer to Section 10.2).
c. Perform contraceptive counselling and provide contraceptives, if necessary (refer to Section 5.5).
d. Provide HIV/STI risk reduction counselling; including provision of male and/or female condoms if the participant wishes to receive them (refer to Section 5.3.2).
e. Provide HIV pre- and post-test counselling (refer to Section 5.3.1).
f. Perform HIV rapid testing as detailed in Section 5.4.4 (additional procedures for participants who test HIV-positive are also described in Section 5.4.4 of the protocol).
g. Collect a blood specimen by venepuncture for storage for possible HIV viral genotype (including NGS) and phenotype resistance, and HIV-1 RNA PCR testing (Blood volume specified in Appendix C). HIV-1 RNA PCR will be performed on samples stored at last product use visit and on the last samples collected for participants who discontinue from the trial without an exit visit. Only samples from participants who consented for analysis will be selected for the additional HIV-1 RNA PCR analysis and additional HIV viral genotype (including NGS) and phenotype resistance testing as needed.
h. Provide final safety and STI laboratory test results to participant.
i. The following procedures are not required, but may be conducted if clinically indicated: physical and pelvic examination, cervicovaginal sample collection for STI testing, provision of treatment and/or referral for STIs and other findings, laboratory testing for safety assessments, urine dipstick analysis (microscopy only if clinically indicated) and cervical sample collection for cytology (if no result is evident within the previous year, or abnormal at last cervical cytology).
j. Exit the participant from the trial.

4.6. Unscheduled Visits

Unscheduled visits may be performed at any time during the trial for HIV, STI or pregnancy testing, collection of rings or if the participant is experiencing any problems, *e.g.*, vaginal complaints, difficulties with re-inserting the ring in cases of accidental expulsion or ring removal, or accidental loss of the ring or product adherence challenges. Participants will also be notified of any abnormal laboratory findings, and return to the research centre prior to the next scheduled visit as needed for treatment and/or referral to an outside medical facility. Additional laboratory testing to evaluate AEs that are suspected to be associated with use of the IP may be performed where indicated, in consultation with the IPM Clinical Physician.

All unscheduled visits will be documented in the source documents and applicable case report forms (CRFs).

4.7. Missed and Late Visits

Trial staff will make every effort to contact participants to return to the research centre for scheduled visits. If a participant does not return to the research centre for a scheduled visit during the trial window, *e.g.*, within ± 7 days of a scheduled visit, continued attempts to contact the participant will be made as per local standard operating procedure (SOP) and documented in the source documents.

If the participant does not return to the research centre for a scheduled visit prior to the start of the trial window of the next visit, the visit will be considered missed. For example, if a participant does not return for Visit 2 by the time the trial window has begun for Visit 3, i.e., within 7 days from Visit 3, Visit 2 will be considered missed. Trial procedures will be performed as scheduled for the current visit (*e.g.* Visit 3 in this instance) or as deemed necessary by the investigator or IPM Clinical Physician (or designee). Missed visits will be documented as protocol deviations. Trial staff should ensure that all used or unused vaginal rings that were to be returned at the missed visit are retrieved as soon as possible.

In the event that a participant will be away and unable to attend one of the Trial Visits where new vaginal rings would be dispensed, the investigator or designee could dispense additional ring(s) on a case-by-case basis. Research centre staff will enquire about adverse events and concomitant medication over the telephone; and other information will be collected as applicable.

If a participant presents for a visit outside the window for a scheduled trial visit but prior to the start of the window for the next visit, it will be treated as a late visit and documented as a protocol deviation. All trial procedures scheduled for the late scheduled visit will still be performed. The participant will then resume her original visit schedule.

If a LPUV is missed, STI testing should be performed at the Exit Visit.

4.8. Protocol Deviations

A protocol deviation is defined as any change, non-compliance or divergence from the approved protocol. The non-compliance may be either on the part of the participant, the investigator, the research centre staff or laboratory staff. It is the responsibility of the research centre to identify and report protocol deviations according to the guidelines of the sponsor and the local IRB/IEC. The research centre must report protocol deviations to IPM using designated forms. The principal investigator and research centre staff are responsible for being familiar with and adhering to their IRB/IEC requirements. In response to noted protocol deviations, research centre personnel are to promptly implement corrective actions.

4.9. Early Discontinuation Visits

Participants may be discontinued early from the trial prior to completion of the last trial visit for any of the following reasons:

- Participant withdraws her consent.
- Participant is lost to follow-up, i.e., research centre is unsuccessful (following

reasonable attempts as defined in the research centre SOP) in contacting participant or bringing the participant back to the research centre.

- Participant tests HIV-positive according to the HIV-testing algorithm in Appendix B.
- If, for safety reasons, the investigator considers it in the best interest of the participant to discontinue her from the trial.
- At the discretion of the investigator, Sponsor, IRB/IEC or the government health authority.

The date and reason for permanent trial discontinuation will be noted in the source documents and applicable CRFs. All participants who are prematurely discontinued from the trial will be encouraged to return to the research centre for a final evaluation, at which time all trial procedures scheduled for the last product use visit will be performed. An optional exit visit approximately 1-2 months after product discontinuation can be completed. For participants who discontinue from the trial without an exit visit, a HIV-1 RNA PCR will be performed on available samples.

Participants who are considered lost to follow-up will be temporarily discontinued from the trial. Reasonable contact attempts will be made according to the locator information provided by the participant and local SOPs, and temporarily early trial termination will be documented in the source documents and applicable CRFs. If a participant already considered lost to follow-up returns to the research centre prior to the centre's trial completion, the participant's file (including CRFs) may be re-opened to perform trial discontinuation procedures. The participant may be considered for continuation on the trial at the discretion of the principal investigator in consultation with the IPM Clinical Project Manager, depending on the reason for the missed visits. A final trial termination will be documented in the source documents and applicable CRFs during the trial closure for all temporarily early trial terminations.

4.10. Premature Discontinuation of the Trial

IPM has the right to terminate this trial at any time for any reason. If the trial is prematurely terminated, the investigator must promptly inform the participants and the IRBs/IECs, and ensure proper medical follow-up of participants in consultation with IPM. If the trial is prematurely terminated, all procedures and requirements pertaining to the archiving of the trial documents will be observed. IPM will provide the research centres with instructions on the proper disposition of any clinical supplies at the centre.

5. Trial Procedure Details

5.1. Informed Consent

The informed consent documents will include all the information about the trial required by GCP and will make provision for the dated signatures of the participant, the principal investigator or designated trial staff conducting the informed consent process, and when required, also for a dated signature by an impartial witness. The informed consent process will be administered at the Screening Visit.

The informed consent process will include adequate time for each potential participant to

have any trial related questions answered by appropriately qualified and trained trial staff as designated by the investigator, and the entire process will be documented in the source documents.

At screening, potential participants who agree to participate in the trial will sign and date the ICF. The ICF will also be signed and dated by the trial staff administering the consent process as delegated by the principal investigator according to the research centre SOP. If a potential participant is functionally illiterate, the informed consent document(s) and any written trial-related materials must be read to her in the language best understood by the potential participant in the presence of an impartial literate witness. After the illiterate participant has orally consented to participate in the trial, and, if capable of doing so, has signed the ICF or provided a thumbprint or mark that was witnessed by the impartial witness, this impartial witness must sign and personally date the ICF. By signing the ICF the impartial witness attests that the information in the participant information sheet and any other written information was explained to, and apparently understood by, the participant or the participant's legally acceptable representative and that informed consent was freely given by the participant or the participant's legally acceptable representative.

The signed and dated ICFs will be retained at the research centre. A copy of the signed and dated ICFs will be offered to the participant. If the participant is not willing to receive the documents, the second copy will be retained at the research centre. Likewise, during the trial, signed and dated ICF updates and any amendments to written trial-related materials to be given to participants will be offered to the participant but retained at the research centre if the participant is unwilling to receive the documents. Documentation of the participant's refusal to accept a copy of the ICF(s) or other trial-related materials will be noted in the source documents.

The consent documents and any trial-related materials given to the participant will be translated and back-translated in the local languages according to local IRB/IEC requirements and regulatory authority guidelines. Information in the informed consent documents and trial-related material will be verbally communicated by trial staff, in the language preferred by the participant, and copies of the documents and trial-related materials will be offered to her in her preferred language. Documentation will be required to verify who performed translation/back-translation of the materials as well as a written statement by the translator indicating that the consent form(s) is an accurate translation of the accompanying English version. This is the principal investigator's responsibility.

All research centre-specific informed consent documents will first be reviewed and approved by IPM and then approved by the responsible IRB and/or local IEC prior to administration to the participants.

If new information becomes available which may be relevant to the participant's willingness to continue trial participation, the information will be provided *via* IRB and/or IEC-approved revised informed consent documents or addenda to the original informed consent documents in a timely manner and will be signed and dated by the participant in the same manner described above.

Written informed consent will be obtained from all participants selected for participation in the in-depth individual interviews (IDIs). Written informed consent will also be obtained for: HIV-1 RNA PCR, viral genotype (including NGS) and phenotype resistance testing on the stored samples of the last product use visit and on the last samples collected for

participants who discontinue from the trial without an exit visit, longer term storage and shipping out of the country, if needed.

5.2. Comprehension Assessment Checklist

Trial staff will assess the potential participant's understanding of informed consent information prior to obtaining a signature on the ICF at the Screening Visit. This assessment will be done using a standardised comprehension assessment checklist. All comprehension problems that are discovered during the assessment will be discussed until staff member(s) are satisfied that the participant can verbalise her understanding of the issue. This process will be documented on the comprehension assessment checklist. This checklist will be recorded in source documentation at the research centre. A participant who cannot demonstrate comprehension of the informed consent information will not be enrolled in the trial.

5.3. HIV Counselling

5.3.1. *HIV Pre- and Post-test Counselling*

At all visits where HIV testing is performed, pre- and post-test counselling will be provided according to the National Guidelines for HIV Counselling and Testing. Adaptations of these guidelines in accordance with locally accepted standards of practice are allowed. Each research centre will document the counselling policies and procedures prior to trial implementation for purposes of staff training, quality assurance, and trial monitoring.

A comprehensive package of post-test counselling and psychosocial support will be provided to women who test HIV reactive at any point during trial participation. Initial counselling services will be provided at the research centre and women will be referred for additional counselling, support services and treatment. These services will be identified by the research centres prior to trial initiation and referral procedures will be documented in writing by the centre.

5.3.2. *HIV/STI Risk Reduction Counselling*

HIV/STI risk reduction counselling will be in accordance with local guidelines. Counselling will be provided at all research centre visits. Efforts will be made to ensure standardisation of risk reduction counselling at the trial research centres.

NOTE: *Risk reduction counselling will include recommendation of male and/or female condom use. Participants will be provided with a supply of male non-spermicidal condoms and/or female condoms during each trial visit, if they are willing to accept them. The use of female condoms is permitted in this trial.*

5.4. HIV Testing and Management

The research centres will inform IPM Medical Safety of any new HIV seroconversions within 48 hours of diagnosis. The applicable regulatory authorities and independent ethics committees who require expedited notification of HIV seroconversion will be notified by either IPM or the research centre in accordance with standard operating procedures and

policies of the regulatory authorities or independent ethics committees. The details of the HIV rapid test kits will be specified in the Laboratory Manual, as part of the SOM. Participants will be tested for HIV using two highly sensitive antibody rapid tests (Test 1 and Test 2).

5.4.1. *Screening Visit*

If both test results are non-reactive, the participant could potentially be enrolled in the trial if she is otherwise eligible.

If both Test 1 and Test 2 are reactive at screening, the potential participant is considered to be HIV seropositive and not eligible for enrolment. Initial counselling services will be provided at the research centre and the participant will be referred for additional counselling, support services and treatment. These referral systems will be implemented by research centres prior to trial start. It is the participant's responsibility to follow up with relevant medical services once referral has been initiated by the research centre.

If Test 1 and Test 2 yield discordant results, a highly specific HIV antibody Test 3 will be performed. If Test 3 is reactive then the potential participant is considered to be HIV-seropositive and is not eligible for enrolment. If Test 3 is non-reactive, the person is considered to be potentially HIV-seronegative and can be given a date for enrolment into the trial. Refer to Appendix B: HIV Testing Algorithms.

A blood sample will be obtained by venepuncture to be sent for sample storage locally or at a central laboratory, for potential HIV-1 RNA PCR, viral genotype (including NGS) and phenotype resistance testing if the participant seroconverts (blood volume specified in Appendix C). Storage samples for participants who do not enrol will be destroyed according to research centre SOPs.

NOTE: For the purposes of HIV rapid testing at screening, blood may be obtained by finger prick or venous sampling. If the national regulatory authority of the country in which the research centre is situated requires that a national testing algorithm be used during the screening process, this will be performed, in addition to the IPM 032 HIV testing algorithm, as part of the screening process and documented as such.

5.4.2. *Enrolment Visit*

On the scheduled day of possible enrolment, the participant will be tested for HIV and will only be enrolled if the results are considered to be HIV-seronegative and the participant is otherwise eligible.

Test 1 and Test 2 will be performed. If both test results are non-reactive and there is no history to suggest recent exposure that could be masked during the window period, the potential participant will be considered HIV-seronegative and eligible for enrolment. A blood sample will be obtained by venipuncture to be sent for sample storage locally or at a central laboratory, for potential HIV-1 RNA PCR, viral genotype (including NGS) and phenotype resistance testing if the participant seroconverts (blood volume specified in Appendix C). Storage samples for participants who do not enroll will be destroyed according to local SOPs.

If both Test 1 and Test 2 are reactive, the participant is considered to be HIV seropositive

and not eligible for enrolment. Initial counselling services will be provided at the research centre and the woman will be referred for additional counselling, support services and treatment.

A rapid Test 3 will be performed for all discordant rapid test results. If Test 3 is reactive then the potential participant is considered to be HIV-seropositive and not eligible for enrolment. She will be counselled and referred to the local health facilities for appropriate follow-up. If Test 3 is non-reactive, the participant is considered to most likely be HIV-seronegative, and a sample will be collected for HIV-1 RNA PCR testing and the Enrolment Visit should be re-scheduled within the screening window period (split visit). If the HIV-1 RNA PCR does not detect HIV RNA copies, the participant can be enrolled. Storage samples should be collected on the second day of the split visit. If the HIV-1 RNA PCR does detect HIV RNA copies then she is not eligible for enrolment. She will be counselled and referred to the local health facilities for appropriate follow-up Refer to Appendix B: HIV Testing Algorithms.

5.4.3. ***Trial Visits and LPUV***

The HIV rapid and confirmatory laboratory tests used in the HIV-testing algorithm will detect both subtypes, HIV-1 and HIV-2. The testing algorithm (refer to Appendix B) will be applied for all Trial Visits and LPUV. HIV testing while the participant is enrolled in the trial will be performed on blood samples obtained by venipuncture (blood volumes specified in Appendix C).

If both the HIV rapid tests (Test 1 and Test 2) are non-reactive, the participant will be considered HIV-seronegative and continue using the IP. If both HIV rapid tests are reactive, IP will be withheld until HIV infection has been confirmed. Trial procedures relevant to the LPUV will be performed. Additional confirmatory testing will be performed by Western Blot and other confirmatory tests, where appropriate. IP may be re-introduced after consultation with IPM, if confirmatory test(s) indicate(s) that the participant is not HIV infected. The participant must have a negative pregnancy test prior to re-introduction of IP. A pelvic examination should be performed according to investigator's discretion prior to re-introduction of IP if clinically indicated. If confirmatory test(s) indicate(s) that the participant is HIV infected, the participant will be permanently discontinued from IP and the trial.

If the Test 1 and Test 2 results are discordant, a HIV rapid Test 3 will be performed on the same blood sample as used for Test 1 and Test 2. If Test 3 is reactive, IP will be withheld until HIV infection has been confirmed. Trial procedures relevant to the LPUV will be performed. Additional confirmatory testing will be performed by Western Blot and other confirmatory tests, where appropriate. IP may be re-introduced after consultation with IPM, if confirmatory test(s) indicate(s) that the participant is not HIV infected. The participant must have a negative pregnancy test result prior to re-introduction of IP. A pelvic examination should be performed according investigator's discretion prior to re-introduction of IP, if clinical indicated. Nucleic acid-amplification testing (NAAT) by a HIV-1 RNA PCR test will be performed on stored samples in reverse sequential order to estimate the time point of HIV infection. The participant will be counselled and referred for appropriate counselling and care.

If Test 3 is non-reactive, the participant is considered to be HIV-seronegative. The participants who have discordant HIV test results at Trial Visits will continue on IP and be

requested to return for repeat HIV rapid testing after two weeks. In such cases the research centre will notify the IPM Clinical Project Manager or designee. Additional confirmatory tests may be indicated at any stage in consultation with the IPM Clinical Project Manager or designee. If a similar result is obtained on testing after two weeks, a sample should be collected for a quantitative HIV-1 PCR test and the research centre will notify the IPM Clinical Project Manager and Laboratory Specialist.

If the HIV-1 RNA PCR result is undetectable:

- The participant is considered to not be HIV-infected.
- The participant should continue in the trial with HIV rapid testing only performed at scheduled visits, even if the same pattern of discordant results continues. It will not be necessary to recall the participant for 2-weekly testing.
- The research centre will notify the IPM Clinical Project Manager or designee of the outcome.

If the HIV-1 RNA PCR result is detectable:

- The participant is considered HIV-infected and IP should be discontinued immediately. The research centre will notify the IPM Clinical Project Manager or designee immediately.

All enrolled participants will in addition, have blood samples collected at each trial visit to be stored locally or at a central laboratory, for possible HIV-1 RNA PCR, genotype (including NGS) and phenotype resistance testing. If a participant subsequently seroconverts (i.e. is confirmed HIV-positive) while on the IP, the stored samples will be tested in reverse sequential order until an undetectable PCR test result is obtained. This will be conducted to approximate the period of HIV infection. If the enrolment HIV-1 RNA PCR test result is positive, the participant is not considered to have been infected while using the IP.

Blood (blood volume as specified in Appendix C) and vaginal fluid samples will also be obtained for dapivirine measurement at the point of HIV seroconversion according to the HIV testing algorithm described above. Stored samples (blood and vaginal fluids) will be analysed retrospectively as described in Section 5.17.

Any participant who is confirmed HIV-infected while on the trial will be permanently discontinued from IP and the trial. An exit visit will be scheduled approximately 1-2 months following IP discontinuation. Initial counselling services will be provided at the research centre and women will be referred for additional counselling, support services and treatment. In addition, these women will be offered the option of enrolling for IPM's seroconverter protocol.

In an instance where a participant is determined to be HIV-seropositive (as determined by HIV rapid tests, Western Blot; and any other confirmatory tests, if applicable), but cannot be confirmed as HIV-infected (HIV-1 RNA PCR) the participant will be discontinued from IP and the protocol-required procedures as per original trial visit schedule will be conducted at the investigator's discretion. Samples for measurement of dapivirine levels will no longer be collected. Additional testing to demonstrate HIV infection may be performed. Participants will be followed up until the exit visit according to the original

enrolment date.

5.4.4. ***Exit Visit***

For participants confirmed as HIV-negative prior to the exit visit
If both HIV rapid tests (Test 1 and Test 2) are non-reactive, the participant will be considered HIV-seronegative. If both Test 1 and Test 2 are reactive, confirmatory testing will be performed by Western Blot and other confirmatory tests, where appropriate. Samples for possible HIV-1 RNA PCR, genotype (including NGS) and phenotype resistance testing will be collected. Once HIV infection has been confirmed, this will be considered an HIV seroconversion after product discontinuation and may be a combination of both women infected during IP use who seroconverted after IP discontinuation, as well as women infected after IP use. Nucleic acid-amplification testing (NAAT) by a HIV-1 RNA PCR test will be performed on stored samples in reverse sequential order to estimate the time point of HIV infection.

Initial counselling services will be provided at the research centre and women will be referred for additional counselling, support services and treatment.

A HIV rapid Test 3 will be performed for discordant rapid Test 1 and Test 2 results. If Test 3 is reactive then the participant will be considered to be HIV-seropositive. Additional confirmatory testing will be performed by Western Blot and other confirmatory tests, where appropriate. Samples for possible HIV-1 RNA PCR, genotype (including NGS) and phenotype resistance testing will be collected. The participant will be counselled and referred to local health facilities for social support or other medical services as clinically indicated. If Test 3 is non-reactive, the participant is considered to be HIV-seronegative and will be counselled appropriately. Refer to Appendix B: HIV Testing Algorithms, and Appendix C: Visit Schedule and Blood Volumes.

For participants confirmed as HIV-infected prior to the exit visit
As stated in Section 5.4.3 above, an exit visit will be scheduled approximately 1-2 months following confirmed HIV-seroconversion and IP discontinuation. Blood samples for HIV-1 RNA PCR, genotype (including NGS) and phenotype resistance testing will be collected from these participants, but no further HIV counselling and testing will be done unless indicated for additional confirmatory testing.

Participants who become infected with HIV during the course of an IPM trial will be referred for appropriate HIV-related care and ARV therapy as above. The threshold for initiation of ARV treatment will be determined with reference to the WHO treatment guidelines if no country specific guidelines are available. Women who become pregnant and HIV positive during the trial will be referred for appropriate Prevention of Mother-to-Child Transmission of HIV (PMTCT) services.

The research centres will inform IPM Medical Safety of any new HIV infections within 48 hours of diagnosis. The applicable regulatory authorities and ethics committees who require expedited notification of HIV seroconversion will be notified by either IPM or the research centre in accordance with standard operating procedures and policies of the regulatory authorities or ethics committees.

5.5. Contraceptive Counselling and Management of Contraception

Contraceptive counselling will be provided at all research centre visits. Counselling will be tailored per research centre, depending on local community and regional guidelines and will be detailed in research centre procedures. Counselling will include information about medication side effects and interactions, the importance of contraceptive adherence for the duration of the trial; what to do in the event of accidental non-adherence and advice on how to remain adherent.

Participants will also be counselled that if they become pregnant during the trial, they will immediately discontinue the IP and be referred to the local prenatal services for support and further management of the pregnancy. Refer to Pregnancy Testing and Management below in Section 5.6.

To meet eligibility criteria, unless postmenopausal with no history of menses for one year prior to screening, participants must be on an effective method of contraception prior to enrolment, have demonstrated adherence to her chosen method of contraception and have no significant resultant problems.

In order to address challenges that participants may experience in consistently obtaining an effective method of contraception, research centres will provide participants with contraceptives from screening for the duration of the trial, if required. The contraceptives provided will be consistent with what is available locally. Alternatively, participants will be referred to the local family planning clinic or continue accessing contraception from local family planning clinics. Under supervision of the investigator or designated qualified personnel, enrolled participants may switch from one contraceptive method to another, if effective contraception is maintained.

5.6. Pregnancy Testing and Management

A urine pregnancy test will be performed at all scheduled trial visits, except for the Exit Visit, and can be performed additionally at unscheduled visits if any reason exists to suspect pregnancy or, in the event of a participant defaulting on her contraception, prior to recommencing contraception.

If a potential participant tests positive for pregnancy during screening, she is not eligible to enrol in the trial, but will receive referrals to prenatal clinics or other appropriate facilities.

A product hold will be implemented if a woman tests positive for pregnancy while on IP. Vaginal ring(s) will be retrieved from the participant, but the participant will not be withdrawn from the trial. Protocol-specified visit schedule and procedures will continue except for IP-related procedures and other examinations if contra-indicated by pregnancy. The participant will be referred to a local prenatal clinic for medical services. The research centres will be asked to report all pregnancies to IPM within 48 hours of a positive pregnancy test or a confirmatory serum pregnancy test, if indicated. A confirmatory serum pregnancy test may be requested at the discretion of the investigator or a designated qualified member of the trial staff if reason exists to suspect a false positive urine pregnancy test. If the serum pregnancy test is negative, the investigator can consider recommencing use of the ring. If the participant indicates a change in pregnancy status or the participant's clinical history indicates a change in her pregnancy status after the

product hold (birth or termination), a urine pregnancy test may be performed. A confirmatory serum pregnancy test may be requested at the discretion of the investigator or a designated qualified member of the trial staff if reason exists to suspect a false positive urine pregnancy test. If the urine pregnancy test is negative, the investigator can consider recommencing IP. The participant must have a negative urine pregnancy test prior to re-introduction of IP, and should not be breast-feeding. A pelvic examination should be performed prior to re-introduction of IP.

Women who become pregnant and HIV-positive during the trial will be referred for appropriate PMTCT services.

Should a participant have a positive pregnancy test in an instance where she was determined to be HIV-seropositive but could not be confirmed as HIV-infected, was discontinued from IP use and consented to continued participation in the trial without IP, she will be allowed to continue in the trial to allow for continued follow-up and evaluation of her HIV status until the Exit Visit according to the original enrolment date or until she is confirmed to be HIV-infected, whichever occurs earlier.

The research centres will be required to provide quarterly updates on the progress and outcome of the pregnancy as well as the first year of life of the child for inclusion in the Sponsor maintained pregnancy registry. This requirement may vary, depending on country-specific regulations.

5.7. Demographics and Medical History

At the Screening Visit basic demographic information will be collected. A confidential master log of participants, with demographic and locator information will be maintained.

At both the Screening and Enrolment Visits (pre-enrolment) relevant medical history will be obtained, including but not limited to history of STIs, gynaecological conditions, hospitalisations, surgery, allergies, any conditions requiring prescription or chronic medication, i.e. > 2 weeks in duration, and acute conditions occurring prior to enrolment.

5.8. Physical Examination

A general physical examination will be conducted at screening and the LPUV, and will include weight, vital signs (body temperature, pulse rate, respiration rate, blood pressure), and examination of skin, respiratory, cardiovascular, central nervous and abdominal systems, as well as an assessment of cervical and axillary lymph nodes. Height will be measured only at the Screening Visit. A symptom-directed physical examination will be conducted at any visit if clinically indicated.

5.9. Pelvic Examination

A pelvic examination will be performed at screening and LPUV, or at any visit if clinically indicated. On-trial examinations will be performed to assess safety, i.e., any local vaginal reactions.

If the participant is menstruating on the day of a visit where pelvic examination is due, all procedures, including the pelvic examination can be conducted as per investigator and participant discretion. If this is not possible, the participant will be asked to return 2 days after completion of menstruation, within the window period of the visit.

Any unexpected or abnormal vaginal bleeding should be investigated to identify the possible source. A follow-up pelvic examination should be performed to ensure resolution of the condition as indicated.

5.10. Laboratory testing for safety assessments and urine dipstick analysis

Safety laboratory assessments and urine dipstick analysis (microscopy only if clinically indicated) will be conducted at the screening visit, or any other trial visit if clinically indicated. Blood specimens for laboratory testing (haematology and chemistry testing) will be obtained by venepuncture. Haematology will include a full blood count, differential, and platelet count. Chemistry tests will include creatinine, AST and ALT. Details of blood volumes are specified in Appendix C. At the discretion of the investigator or designee, each potential participant may be retested once for safety laboratory tests during the screening period.

Additional tests may be performed at the investigator's discretion after discussion with the IPM Clinical Physician (or designee) based on symptomatology and clinical assessment of participants. Additional descriptive information regarding specimen collection and processing for all tests will be detailed in the SOM.

All laboratory results will be reviewed by the investigator or appropriately qualified and trained trial staff as designated by the investigator, and documented on the original laboratory report itself.

5.11. STI Testing and Management

5.11.1. *STI Testing*

Cervicovaginal samples will be collected for STI testing at screening and the LPUV, or any other trial visit if clinical indicated. All participants will be evaluated for *Trichomonas vaginalis* (TV), *Neisseria gonorrhoea*e (NG) and *Chlamydia trachomatis* (CT). At screening, blood will be collected by venepuncture for Syphilis (RPR) testing (Blood volume specified in Appendix C). TPHA/TPPA testing will be performed if the RPR is reactive.

Additional descriptive information regarding specimen collection to test for STIs and processing of all tests will be detailed in the Laboratory Manual, as part of the SOM.

NOTE: *Documentation will be made in applicable CRFs for all cervicovaginal samples obtained in the presence of cervicovaginal blood.*

The investigator or appropriately qualified and trained trial staff as designated by the investigator will review all results, including rapid and laboratory tests, and the review will

be documented by the reviewer on the original laboratory report itself.

5.11.2. ***STI Management***

All participants who present with STIs will be managed appropriately as clinically indicated at the research centre or referred to a local health facility, according to local STI Treatment Guidelines. Cervicovaginal swabs may be collected from these participants, at the investigator's discretion or when required by local standard of care. Etiological management may be applicable following STI testing, according to the etiological diagnosis.

The Clinical Management of Genital Diagnoses will be detailed in the SOM for guidelines to determine whether the vaginal ring requires temporary or permanent removal and to provide guidance regarding follow up recommendations.

5.12. Cervical Cytology

A cervical cytology sample will be collected at the Screening Visit if not done within the previous year, or if the result was abnormal at the last point of testing. Further details will be provided in the Laboratory Manual, as part of the SOM.

Women with abnormal cytology findings will be referred for appropriate medical services based on local standard of care for management of abnormal cervical cytology. Research centres will implement these referral systems prior to trial start.

5.13. Vaginal Ring Dispensing

Vaginal rings will be dispensed at the Enrolment Visit and subsequent Trial Visits. In the event that a participant will be away and unable to attend one of the Trial Visits where new vaginal ring(s) would be dispensed, the investigator or designee could dispense additional ring(s) on a case-by-case basis. All such circumstances must be documented fully by the investigator as described in the IPM 032 SOM. If a participant requires an additional ring at a time other than when they are scheduled to receive one, they will be required to attend the research centre for an interim visit. During the monthly trial visit period, the participants will be instructed to self-insert the newly-dispensed vaginal ring at the research centre and to remove the ring at the next scheduled visit. During the 3-monthly trial visit period, the participants should self-insert one ring during the trial visit and each of the two additional rings at monthly intervals until their next scheduled research centre visit. Vaginal ring bags will be provided to participants during the 3-monthly trial visit period for the storage of the used rings, together with instructions on the storage of the unused and used rings.

During the 3-monthly trial visit period, optional vaginal ring dispensing and return arrangement will be made with participants who prefer not to have additional vaginal rings in their possession. These participants will be provided with the option to return used vaginal rings and to collect new rings at the research centres at time intervals suitable to them, provided that the intervals allow for new vaginal rings to be inserted monthly. Optional HIV rapid tests will be offered to participants during these interim visits and will be conducted according to the Trial Visits HIV algorithm (refer to Appendix B). Participants' preference regarding the intervals for product dispensing and return will be documented

in the source document and applicable CRFs.

5.14. Vaginal Ring Insertion and Ring Removal

At the Enrolment and Trial Visits, participants will insert the vaginal rings under research centre supervision, as applicable. The participant will be instructed to thoroughly wash her hands, relax, and get into a comfortable position either standing with one foot on a chair, lying on her back with her knees up or squatting. After opening the folds of skin around the vagina, she will gently squeeze the ring into an oval shape and push it upwards and backwards towards the back as far as it will go, thereby depositing the ring in the vagina. She will then be instructed to thoroughly wash her hands again. At all research centre visits during which a pelvic examination is performed, the participant will remove the ring prior to the examination.

If the participant requests help with either removal or insertion of the vaginal ring, or after she has made several attempts to remove/insert the ring without success, trained trial staff may give assistance. Re-education of the participant on ring removal/re-insertion will be given. This will be noted in the source documents and applicable CRFs. Additional instructions about ring use will be provided in the SOM.

All rings that are removed will be inspected visually, and an assessment will be made by the principal investigator or designee as to whether the ring appears to have been used or not, together with a reason for the assessment. The rings should then be rinsed in running water, patted dry, placed in a ring return bag, and stored between 15°C and 30°C until shipment to the analytical laboratory for testing of residual dapivirine amounts.

5.15. Vaginal Ring Adherence Counselling

At the Enrolment and Trial Visits, participants will receive vaginal ring adherence counselling, including adherence to trial visit schedule and requirements. At the Enrolment Visit, IPM 032 participants will be provided with feedback on the IPM 027 and MTN-020 trials, which will include information on trial adherence trends, as part of the vaginal ring adherence counselling. Research centre staff will counsel participants to refrain from removing the ring (except as directed during research centre visits) and will provide instructions to all participants in case of accidental ring expulsion (*e.g.*, during sex or exercise), or removal, and guidance will be provided on how the ring should be handled when it is out of the vagina. Research centre staff will also provide instructions to the participants during the 3-monthly trial visit period for insertion of a new ring after a month and the participants will be counselled on how to store the used and unused rings at home, if applicable.

If, for any reason, the participant is non-adherent to the use of the vaginal ring (i.e. she removes the ring for any purpose other than as instructed at a trial visit), this should be documented according to the guidelines specified in the SOM.

5.16. Qualitative Behavioural Assessments

In cases of interest IDIs will be conducted; approximately three participants will be

interviewed per site. These cases of interest may include, but will not be limited to participants who may have experienced social harms, may have had problems using the ring, or who HIV seroconverted.

These assessments will provide data on acceptability and influencers of ring use. The recruitment and sampling strategy will be specified in the study operations manual.

5.16.1. ***Participant Questionnaire***

The Participant Questionnaire will be administered at every trial visit and the LPUV This questionnaire includes acceptability questions about the monthly and 3-monthly research centre follow-up during the trial.

5.17. Sample Storage and Analysis

Blood (blood volume as specified in Appendix C) and vaginal fluid samples will be collected for storage locally or at a central laboratory at all research centre visits. Blood samples for HIV-1 RNA PCR, genotype (including NGS) and phenotype resistance testing will be stored at the Screening Visit, the Enrolment Visit, every Trial Visit, LPUV and Exit Visit and will be tested subsequent to confirmed HIV-1 seroconversion, according to the HIV testing algorithm described in Section 5.4. HIV-1 RNA PCR will be performed on samples stored at last product use visit and on the last samples collected for participants who discontinue from the trial without an exit visit. Only samples from participants who consented for analysis will be selected for the additional HIV-1 RNA PCR analysis and additional HIV viral genotype (including NGS) and phenotype resistance testing as needed. Testing will also be conducted on a random sample of HIV-negative participants. For possible dapivirine concentration measurements, plasma and vaginal fluid samples should preferably be collected prior to removal of the vaginal ring. Further details regarding these procedures will be provided in the Laboratory Manual, as part of the SOM.

All specimens will be collected and analysed according to methods described in the Laboratory Manual and research centre SOPs for proper collection, processing, labelling, and transport of specimens to the laboratories conducting the analysis. Where possible and appropriate, stored specimens will be re-tested to assess validity of unusual or unexpected assay results.

Any residual specimens will be stored at least until the first marketing authorization by a stringent regulatory authority has been granted.

5.18. Screening Identification (SCR-ID) and Participant Identification (PID) Numbers

After informed consent is obtained, a SCR-ID number will be assigned to each participant for identification purposes and the participant will be screened to assess eligibility for the trial. As each new participant enters the trial, a unique PID number will be assigned in consecutive order, starting with the lowest number available at the research

centre at the time.

5.19. Diary cards

Participants will be provided with diary cards at enrolment and at trial visits, as applicable, except the LPUVs and Exit Visits. The diary cards are meant to be completed by the participants, and returned to the research centre at each Trial Visit and the LPUV to serve as a memory aid for participants to review during their scheduled visits and adherence counselling. The diary card will be used to document the removal and insertion date of the additional rings and for documenting AEs experienced and concomitant medications taken between trial visits. Participants will be requested to document the details of all cases of accidental ring expulsion or removal. Additional instructions on diary cards will be provided in the SOM.

5.20. Participant Reimbursement

Participants will be reimbursed for any travel costs incurred in compliance with local regulations. Reimbursements will be made after the completion of each trial visit. Research centre specific reimbursement amounts will be documented in the trial ICF approved by the applicable IRB/IEC. Upfront reimbursement for travel expenses may be made if this has been approved by the relevant ethics committee.
Note: *During the 3-monthly trial visit period, participants who choose to not receive the two additional vaginal rings during trial visits, will be responsible for the travel costs incurred during the optional vaginal ring collection/return visits to the research centre.*

5.21. Participant Compensation

If a participant in an IPM clinical trial becomes ill or injured as a result of participation in the trial, medical treatment for the adverse reaction or injury will be provided appropriately. The research centre staff will refer the participant for ongoing treatment for the injury, if needed. The Sponsor will be responsible for compensation for appropriate medical expenses for treatment of any such illness or injury. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation.

5.22. Participant Responsibility

Referral systems to local medical services will be implemented by research centres prior to trial start. It remains the participant's responsibility to follow up with relevant medical services once referral has been initiated by the research centre.

5.23. Study Operations Manual (SOM)

A SOM will be supplied to all research centres to provide general guidance on the conduct of trial procedures. The Laboratory Manual is contained within the SOM.

6. Investigational Product

6.1. Investigational Product Composition

The dapivirine silicone elastomer vaginal matrix ring is an off-white flexible ring containing 25 mg of dapivirine dispersed in a platinum-catalysed silicone matrix. The dimensions of the ring are 56 mm (outer diameter) and 7.7 mm (cross sectional diameter). The dapivirine silicone elastomer vaginal matrix ring is designed to provide sustained release of dapivirine over a minimum of one month.

The Dapivirine Vaginal Ring-004 is comprised of dapivirine, the polydimethylsiloxane liquid MED-360 and the silicone MED-4870. The safety of dapivirine has been established in a comprehensive nonclinical and clinical development programme described in the IB[14]. Both the silicone elastomers and the liquid silicone dispersant have been evaluated in *in vitro* cytotoxicity, haemolysis tests, cytogenic damage and genotoxicity assays, and in *in vivo* systemic toxicity studies, intracutaneous toxicity studies, pyrogen studies and delayed contact sensitisation studies. The silicone elastomer was also evaluated in muscle implantation studies of up to 12 weeks duration. In addition, a number of preclinical tests were performed on the finished Dapivirine Vaginal Ring-004, including a panel of biocompatibility tests (*in vitro* cytotoxicity and genotoxicity assays, and *in vivo* vaginal irritation and sensitisation studies) using extracts of the ring, and a study in sheep, in which Dapivirine Vaginal Ring-004 containing 25 mg dapivirine was inserted into the vagina (up to 3 consecutive rings; each ring for a period of 30 days). None of these tests identified any significant safety concerns.

6.2. Packaging and Labelling

IPM will bear the responsibility for primary and secondary packaging and labelling. The packaged rings will be labelled according to local regulatory requirements.

6.3. Investigational Product Storage

The recommended storage condition for the dapivirine ring is 15°C to 30°C, excursions permitted. The proposed shelf life is 48 months when stored in the original packaging under the recommended storage conditions. In the event that the IP has been subjected to different storage conditions than specified above, the affected IP will not be used (unless IPM or its designee provides written authorisation for use). IPM should be notified immediately in the event that IP storage conditions have been breached.

The investigator (or pharmacist) will maintain an inventory and acknowledge receipt of all shipments of IP. More information on IP storage will be provided in the SOM.

Participants will be provided with instructions on storage of used and unused rings during the 3-monthly trial visit schedule.

6.4. Investigational Product Administration

The participants will be instructed to self-insert the Dapivirine Vaginal Ring-004 at the

Enrolment Visit, and monthly thereafter. The participants will be reminded of proper vaginal ring insertion and removal procedures.

During the 3-monthly trial visit schedule, participants will be instructed to remove the vaginal rings and self-insert each of the two additional rings at monthly intervals until their next scheduled research centre visit. The self-insertion and removal of the rings should take place at the research centres during the months that the participants attend their scheduled trial visits. Participants should be advised to continue ring use through menses.

6.5. Investigational Product Expulsion or Loss

If a participant accidentally expels the ring, *e.g.*, during sex or exercise, she will be instructed to rinse the vaginal ring thoroughly in clean water and re-insert the ring as soon as possible. If the vaginal ring is expelled and cannot be successfully reinserted, the ring should be appropriately rinsed, patted dry and stored in the bag provided for this purpose, until the earliest possible opportunity the participant can return for help with the reinsertion of a ring at the research centre.

During monthly visits, if the ring is expelled in such a manner that the participant is unwilling to re-insert it, *e.g.*, during urination or a bowel movement, or if the ring is lost, the participant should return to the research centre at the earliest possible opportunity to receive a replacement ring.

During the 3-monthly trial visit schedule, participants will be instructed that if the ring is expelled in such a manner that the participant is unwilling to re-insert it, *e.g.*, during urination or a bowel movement, or if the ring is lost, the participant should use one of the unused, additional rings dispensed. If the expelled ring was the last of the additional vaginal rings dispensed, the participant should return to the research centre at the earliest possible opportunity to receive a replacement ring.

Also, in cases where a ring is removed due to a genital infection, a new ring will be inserted or dispensed. Visits associated with expulsion or loss of rings will be regarded as unscheduled visits unless the visit is within the 7-day window period of the next scheduled visit.

6.6. Retrieval of Investigational Product

All participants who are prematurely discontinued from the trial will be encouraged to return to the research centre for a final evaluation, at which time all vaginal rings in the participant's possession should be retrieved. If the participant does not return her used or unused vaginal ring at this visit, it should be retrieved as soon as possible after this visit, either by the participant returning it to the trial staff, or by trial staff conducting a home visit.

For participants who are considered lost to follow-up and permanently discontinued from the trial, reasonable contact attempts will be made according to the locator information provided by the participant and local SOPs. Any used or unused vaginal rings that could not be retrieved will be documented in the source documents and applicable CRFs.

6.7. Investigational Product (IP) Accountability

The principal investigator or designee will be responsible for adequate and accurate accounting, handling, storage and dispensing of the IP. The IP will be stored safely and properly in a secure location with access available only to the principal investigator and designated trial personnel. IP and clinical supplies are to be dispensed only in accordance with the protocol. Accurate records of IP received from IPM, the amount dispensed to the participants, the amount returned by the participants, the quantity remaining at the conclusion of the trial and any wasted or expired IP will be maintained.

Unused and used rings not analysed for residual amounts of dapivirine will be destroyed according to IPM instruction and local regulatory requirements.

6.8. Concomitant Medications and Products

Prescription and non-prescription medications will be recorded on the source documents and applicable CRFs. Vaginal products and practices including the use of spermicides, intravaginal medication, douches, lubricants, tampons and female condoms may be used during the trial and will be captured. Further details will be provided in the SOM.

7. Adverse Events

7.1. Definition

An AE is any untoward medical occurrence during the course of a trial in a participant who received an IP at any dose, which does not necessarily have a causal relationship with the IP. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of an IP, whether or not considered related to the IP. This definition includes inter-current illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is an adverse event, the nature or severity (intensity) of which is not consistent with the applicable product information (i.e. IB, package insert, or summary of product characteristics). Final determination of whether an event is considered *unexpected* will be made by the Sponsor, however, the investigator should be knowledgeable of the contents of the IB.

Whenever possible, the laboratory abnormalities should be considered in the context of the primary clinical diagnosis and should be reported as such (*e.g.* acute hepatitis with increased bilirubin). Clinically significant laboratory abnormalities will be considered AEs and graded for severity based on the Division of AIDS (DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events) as appropriate.

Any condition occurring prior to enrolment will be reported as a pre-existing condition under Medical or Gynaecological History. All AEs occurring during the trial will be recorded in the source documents and applicable CRFs. All AEs will be reported and graded according to the latest version of the *DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events* and *Female Genital Grading Table for Use in Microbicide Studies (*which will be provided to research centres in the SOM). A vaginal bleeding

abnormality thought to be due to contraception, asymptomatic BV and asymptomatic candidiasis will not be reported as an AE for this trial.

If a unifying diagnosis is possible, the investigator should record a specific disease or syndrome rather than individual associated signs and symptoms. However, if an observed or reported sign, symptom, or clinically significant laboratory abnormality is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE.

All AEs will be monitored until resolution and/or the cause are identified, or until the investigator does not expect any improvement or worsening of condition/symptoms. If a SAE, urogenital AE or related AE remains unresolved at the participant's Exit Visit, the research centre investigator will make a clinical assessment with the IPM Clinical Physician to determine whether continued follow-up of the AE is warranted. All other AEs that are not serious, not urogenital and assessed to be unrelated to IP will be noted as ongoing at trial end if the outcome is not yet determined at the time of the exit visit.

7.2. Assessment of Adverse Event Severity

The investigator is responsible for assessing the severity of AEs occurring on trial. All AEs except genital complaints will be graded according to the latest version of the *DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events*. All genital complaints will be graded according to the latest version of the *Female Genital Grading Table for Use in Microbicide Studies*, which will be provided to research centres in the SOM.

For AEs not listed on either of these tables, the following criteria will be used to estimate the grade of severity:

- **Mild**

  Symptoms causing no or minimal interference with usual social and functional activities
- **Moderate**

  Symptoms causing greater than minimal interference with usual social and functional activities
- **Severe**

  Symptoms causing inability to perform usual social and functional activities
- **Potentially Life-threatening**

  Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent inability, or death

7.3. Relationship to Investigational Product

The investigator is responsible for determining the relationship of all AEs occurring during

the trial and will assess AEs based on the following criteria:

- **Not Related**

  There is not a temporal relationship or a reasonable possibility of a causal relationship (i.e. some level of evidence is lacking) to administration of the investigational product. The AE is clearly explained by another cause (concurrent disease, concomitant medication, environmental or toxic factors, etc.).

- **Related**

  There is a reasonable possibility of a causal relationship between the investigational product and the AE, (i.e. there is some level of evidence as to the causal association). The event may respond to withdrawal of the investigational product (dechallenge), and recurs with rechallenge by administration of the investigational product. In other cases the AE is clearly related and most likely explained by the administration of the investigational product.

7.4. Serious Adverse Event

7.4.1. *Serious Adverse Event Definition*

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- **Results in death.**
- **Is life-threatening.**

  This criterion applies if the participant is at immediate risk of death from the event as it occurred, in the opinion of the investigator; it does not refer to an event which hypothetically might have caused death if it were more severe.

- **Requires in patient hospitalisation or prolongation of existing hospitalisation.**

  This criterion applies if the event requires inpatient hospitalisation and results in an overnight stay in hospital or, if in the opinion of the investigator, prolongs an existing hospitalisation. A hospitalisation (including hospitalisation for an elective procedure or routinely scheduled treatment not associated with an adverse event) for a pre-existing condition which has not worsened does not constitute an SAE.

- **Results in persistent or significant disability/incapacity.**

  This criterion applies if the event causes a substantial disruption of a person's ability to conduct normal life functions.

- **Is a congenital anomaly/birth defect.**

  This criterion applies if a participant gives birth to a child with a congenital anomaly or birth defect or if the anomaly/birth defect is diagnosed by any prenatal tests.

- **Important medical events.**

  In a medically significant event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the participant or may

require intervention in order to prevent one of the outcomes listed above should also be considered serious; e.g., bronchospasm requiring intensive treatment in an emergency room or at home.

NOTE: *A SAE does not have to be severe in nature to meet any of the above criteria.*

All SAEs that occur from the time the participant is enrolled through the duration of the trial, whether considered associated with the IP or not, must be reported to the IPM Medical Safety Physician and/or designee within 24 hours of the centre becoming aware of the event. All SAEs should be recorded in the source documents and the relevant CRFs and reported using the Immediately Reportable Events (IRE) Form provided.

The IRE Report Form should be completed with all the available information at the time of reporting. The investigator is required to write a detailed report and complete SAE follow up in a timely manner until the SAE has resolved, the participant returns to normal health, or until the investigator does not expect any further improvement or worsening of the condition. Medical Records may be requested by IPM to assist in assessing relatedness and severity of the SAE, and for possible submission to the Regulatory or Health Authorities as appropriate. To maintain confidentiality, the participant's name must be blacked out on any medical records submitted and replaced with the PID number and the initials.

More details on SAE reporting requirements and processes are described in the Safety Reporting Plan (provided in the SOM) provided to the research centres.

7.4.2. *Serious Adverse Event Contact Information*

SAEs will be reported to IPM or designee within 24 hours of any research centre staff member becoming aware of the event. If the SAE is related, and life-threatening or fatal, IPM Medical Safety should additionally be notified immediately by email or telephone.

The following email will be used for communication with the IPM Medical Safety team regarding any IREs: safetyreports@ipmglobal.org. Contact details of relevant safety personnel will be provided in the Safety Reporting Plan.

IPM or designee will process all safety events. The IPM Medical Safety Physician or designee will review all SAEs and generate the necessary queries. Further SAE reporting guidelines will be specified in the Safety Reporting Plan.

7.4.3. *Sponsor Notification of SAEs to the Regulatory Authorities*

Any *unexpected* serious adverse events which are deemed related to investigational product, will be considered "associated with the use of investigational product" and, as such, IPM will notify the appropriate regulatory authorities of the event in an expedited manner unless policies of the local regulatory authorities mandate such reporting by the research centre.

Any unexpected SAE deemed to be unrelated to the IP will not be reported to the regulatory authorities in an expedited manner, *unless* policies of the local regulatory authorities mandate such reporting.

7.4.4. *Research Centre Notification of SAEs to Local Independent Ethics Committee or Local Health and Regulatory Authorities*

The investigator will report all SAEs to the local IEC and/or regulatory or health authorities in accordance with standard operating procedures and policies of the IEC and/or regulatory or health authorities.

7.5. Immediately Reportable Events

These are events which, while not necessarily meeting criteria for seriousness, are considered important by IPM and as such warrant immediate reporting to IPM. The following events should be reported to the Sponsor within 48 hours of any research centre staff member becoming aware of the event:

- Pregnancy: Although not considered an AE, pregnancy must be reported if it occurs at any time while on IP during the trial;
- HIV infection any time during the trial;
- Any non-serious AE (including laboratory abnormalities) leading to permanent discontinuation of the investigational product.

All IREs that occur from the time the participant is enrolled should be reported to IPM within the time periods specified above. All IREs should be recorded in the source documents and the relevant CRFs and should be reported to the IPM Medical Safety Physician using the IRE Form provided.

As with SAEs, the IRE form should be completed with all available information at the time of reporting. The investigator is required to follow up the IRE in a timely manner until such time as it is deemed appropriate by IPM that all relevant information has been collected, or until such time as the participant is lost to follow up.

7.6. Safety Monitoring

The IPM 032 trial team will monitor safety and participant recruitment throughout the trial for all participants. Safety data from the trial will be evaluated by an independent Data and Safety Monitoring Board (DSMB). The first scheduled meeting will take place approximately six months after all research centres have been activated and thereafter at approximately annual intervals for the duration of IPM 032. Based on the review of the data, the DSMB is required to provide recommendations about continuation, pausing, termination or other modifications to the trial, including changes to the information provided to participants for obtaining their informed consent. An IPM 032 DSMB charter will describe the roles and responsibilities of the DSMB, its composition, data to be provided to the DSMB, the process for disseminating trial data to the DSMB, and the communication plan between the DSMB and IPM.

7.7. Data Handling at Research Centres

All trial data will first be collected on designated source documents and then recorded on CRFs with the exception of the Participant Questionnaire, for which the CRFs will serve

as the source document, unless otherwise specified by IPM. Research centre staff responsible for completing the CRFs will receive appropriate training prior to the start of the trial, and will follow standardised procedures. Data must be legibly entered onto the CRFs. Data corrections will be made in accordance with standard procedures provided by IPM or its designee. Instructions for CRF completion will be provided on the back of the CRF pages, as well as in the SOM.

The investigator will maintain, and store in a secure manner, complete, accurate and current trial records throughout the trial. Standard GCP practices will be followed to ensure accurate, reliable and consistent data collection.

7.8. Source Data Verification

All trial data must be verifiable to the source documentation (which includes original recordings, laboratory requisitions and reports, medical records, etc.). Source documentation will be made available to the IPM or representative(s) for review to ensure that the collected data is consistent with CRFs and has been completely and accurately reported as required by the trial protocol.

8. Statistical Methods

IPM 032 is a Phase IIIb, multi-centre, open-label follow-on trial to IPM 027 to evaluate the safety of and adherence to Dapivirine Vaginal Ring-004, inserted at monthly intervals in healthy, HIV-negative women who have participated in the IPM 027 trial.

Individuals meeting all inclusion criteria and no exclusion criteria will be eligible to receive the Dapivirine Vaginal Ring-004 with monthly research centre follow-up for one month (which may be extended to three months at the investigator's discretion) followed by 3-monthly research centre follow-up visits.

Up to 1400 participants from the IPM 027 trial are expected to be enrolled in the trial.

Participants will self-insert the vaginal rings. Once participants commence the period of 3-monthly follow up visits, two additional rings will be dispensed at each trial visit, the first of which the participants should self-insert one month later, and the second ring one month after that, before returning to the research centre for their next scheduled visit.

An exit visit will be conducted approximately 1-2 months after removal of the last ring (last product use visit).

8.1. Trial Endpoints

The primary, secondary and exploratory trial endpoints are described in detail in Section 2.2 of the protocol.

8.2. Primary Trial Hypotheses

From previous clinical and safety trials of dapivirine, it is now known that the Dapivirine

Vaginal Ring-004 is well-tolerated and reduces the risk of acquiring HIV-1 infection. These results also showed little to no risk reduction of HIV-1 infection in younger women (aged 18-21 years).

8.3. Sample Size and Power Calculations

This trial will be conducted in healthy, HIV-negative women. who have participated in the IPM 027 trial. No formal sample size or power calculations have been performed. It is expected that up to 70% of the participants enrolled in IPM 027 will participate in this trial. Therefore, a total sample size of up to 1400 HIV-negative women is anticipated.

8.4. Statistical Analyses

The primary analysis will focus on safety as well as adherence assessments.

The primary analysis will be performed under the intent-to-treat (ITT) principle, which will include all participants enrolled in the trial. As it is possible that the inclusion of non-adherent participants or participants who discontinued from the IP may artificially lower the rates of safety outcomes, additional analyses will be conducted on the per-protocol population, which will include only participants who were adherent to the protocol. Details on the definition of the per-protocol population, in addition to models that will be used to examine the exploratory objectives and other technical aspects of these analyses will be provided in a SAP, which will be finalised prior to final database lock.

The analysis of the secondary safety assessments will be mainly descriptive in nature. The incidence density rate of HIV-1 seroconversion and the frequency of HIV-1 drug resistance in women who seroconvert will be summarised descriptively.

The data will be presented using appropriate statistical measures including, but not limited to: mean, standard deviation, median, and interquartile range for continuous data; frequency and relative frequency for categorical data. When appropriate, 95% confidence intervals will be presented.

8.4.1. *Primary Safety Analysis*

A descriptive analysis of all AEs will be presented in tables and listings. AEs will be summarised by MedDRA System Organ Class (SOC) and Preferred term (PT). The proportion of participants experiencing adverse events, including the proportion of participants experiencing product-related adverse events, Grade 3 or 4 AEs, or SAEs, will be determined, and presented with corresponding 95% CIs.

All data will be presented by research centre, and overall across research centres.

8.4.2. *Primary Adherence Analysis*

Residual levels of dapivirine in returned rings and/or plasma and/or vaginal fluid concentrations of dapivirine will be used as measures of adherence to ring use. The data will be listed, summarised and presented graphically. The ring residual levels and/or plasma and/or vaginal fluid concentrations of dapivirine associated with non-adherence

will be informed by the results from IPM 027, and will be described in detail in the SAP, which will be finalised prior to final database lock. The correlation between the amount of residual dapivirine in the used rings and the corresponding plasma and/or vaginal fluid levels of dapivirine will be explored graphically and summarised descriptively.

8.4.3. *Secondary Analyses*

8.4.3.1. *Incidence of HIV-1 seroconversion*

The incidence of HIV-1 seroconversions, the incidence density rate of HIV-1 seroconversion, i.e. HIV-1 seroconversion rate per 100 woman-years of product use at the end of the ring use period, as well as a 95% CI for the HIV-1 seroconversion rate per 100 woman-years based on the normal approximation of the Poisson distribution will be presented for each research centre, and overall. Kaplan-Meier curves will be presented, overall and by research centre.

8.4.3.2. *HIV-1 drug resistance*

The results of the genotype (including NGS) and phenotype resisting analyses will be primarily descriptive in nature, and will depend on the pattern of resistance mutations observed in the HIV-1 seroconverters. The resistance associated mutations observed will be listed by participant, and a frequency tabulation of individual resistance mutations associated with the various classes of antiretrovirals, *e.g.* Protease Inhibitors, Nucleoside Reverse Transcriptase Inhibitors and Non-nucleoside Reverse Transcriptase Inhibitors, will be produced. The proportion of HIV-1 seroconverters with at least one HIV-1 drug resistant mutation will be presented, with the corresponding 95% CI.

8.4.4. *Other results from Qualitative/Quantitative Behavioural assessments*

In cases of interest IDIs will be conducted; approximately three participants will be interviewed per site. These cases of interest may include but will not be limited to participants who may have experienced social harms, may have had problems using the ring, or who HIV seroconverted.

These assessments will provide data on acceptability and influencers of ring use and will be summarised.

8.4.5. *Interim Analysis*

No interim analysis is planned for this trial. However, IPM will review the treatment emergent safety data at regular intervals during the conduct of the trial.

8.5. Data and Safety Monitoring Board

Safety data from the trial will be evaluated by an independent Data and Safety Monitoring Board (DSMB). The first scheduled meeting will take place approximately six months after all research centres have been activated and thereafter at approximately annual intervals for the duration of IPM 032. Based on the review of the data, the DSMB is required to provide recommendations about continuation, pausing, termination or other modifications to the trial, including changes to the information provided to participants for obtaining their

informed consent. An IPM 032 DSMB charter will describe the roles and responsibilities of the DSMB, its composition, data to be provided to the DSMB, the process for disseminating trial data to the DSMB, and the communication plan between the DSMB and IPM.

8.6. Handling of Missing Data and Dropouts

Some degree of missing data, primarily associated with missed visits, is expected. The amount of missing data will be explored and incorporated into the analyses, where appropriate. For the analysis of adherence to monthly ring use, patterns of missing data may be informative. Depending on the proportion of participants who discontinue early, an analysis of time to discontinuation may be conducted. Such an analysis would allow investigation of the covariates associated with early discontinuation and could provide information that would be useful in designing future trials of other microbicide rings. Patterns of missing data may also provide further insight into participants' preference for monthly or 3-monthly follow-up visits to research centres.

9. Investigator Requirements

9.1. Trial Initiation

The trial can be initiated at the research centre once all relevant IRB/IEC and regulatory approvals have been obtained in compliance with country specific requirements, and the relevant essential documents are available on file. Following IPM approval, IPM will notify the research centre in writing *via* letter correspondence to begin trial operations according to the protocol.

9.2. Institutional Review Boards or Independent Ethics Committee Approval

This protocol, the informed consent document, and relevant supporting information will be submitted to the IRBs/IECs for review and must be approved before the trial is initiated.

The principal investigator is responsible for communicating with IRBs/IECs regarding the progress of the trial and changes made to the protocol as deemed appropriate, at least once a year. The principal investigator will also keep the IRBs/IECs informed of any significant AEs and SAEs, in accordance with standard operating procedures and policies of the IRB/IEC.

9.3. Trial Monitoring and Audits

Trial monitors will regularly visit participating research centres to review trial documents including, but not limited to individual participant records, consent forms, source documents, CRFs, supporting data, laboratory specimen records and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts) to ensure protection of trial participants, compliance with the protocol, and accuracy and completeness of records. The trial monitors will also inspect the research centre's

regulatory files to ensure that regulatory requirements are being followed; the research centre's pharmacies to review product storage, management, and drug accountability; and the research centre's laboratory and other clinical supplies to ensure proper storage and continued viability of supplies. All applicable trial documents should be readily available for review during the visits. The trial monitors will also check that clinical trial procedures are observed and will discuss any problems with investigator or designee as applicable.

During or after the clinical trial, the governmental regulatory authorities, local IRB/IEC and/or representatives of the IPM may request access to all trial documents for on-site research centre audit or inspection.

9.4. Case Report Forms (CRFs)

CRFs will be supplied by IPM or its designee and will be handled in accordance with instructions from IPM.

All CRFs will be completed by the designated trial staff in accordance with the instructions provided by IPM. Upon trial completion, the CRF is reviewed, signed, and dated by an investigator listed on the Statement of Investigator, Form FDA 1572.

All CRFs will be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity. When making changes or corrections, the original entry will be crossed out with a single line, and the change initialed and dated. Erasures, overwriting, and correction fluid are NOT allowed on the CRFs.

9.5. Disclosure of Data

Participant medical information is confidential and disclosure to third parties other than those described in Section 9.3 is strictly prohibited. All trial data will be stored securely at the research centre. All participant information including laboratory reports, forms, lists, logbooks, appointment books and administrative forms will be stored in locked file cabinets or rooms in areas with access limited to trial staff.

Participants' trial information will not be released without written permission of the participant, except as necessary for monitoring by IPM, IPM's designated monitors, regulatory authorities, or local IRBs/IECs.

9.6. Record Retention

The principal investigator will retain in a secure manner, complete, accurate and current trial records for a minimum of two years after marketing approval or termination of product development. Trial records include administrative documentation, including research centre registration documents and all reports and correspondence relating to the trial, as well as documentation related to each participant screened and/or enrolled in the trial, including ICFs, CRFs, notations of all contacts with the participant, and all other source documents. All records must be retained on-site throughout the trial's period of performance. IPM will provide the research centre with written instructions for long-term record storage at the completion of the trial.

No records should be destroyed without prior written permission from IPM.

10. Ethical Considerations

10.1. Ethical Review

This protocol, research centre-specific informed consent documents, participant education, outreach, recruitment materials and any other requested documents or subsequent modifications will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the research centre.

Subsequent to initial review and approval, the local IRB and/or IEC will be notified about trial completion within three months following trial termination or completion. This trial will be conducted in accordance with:

- World Medical Association Declaration of Helsinki[17]
- ICH GCP guidelines[18]
- Applicable national ethics and regulatory requirements in countries where the trial is being conducted, e.g. Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa [19].

10.2. Reporting and Management of Social Harms related to trial participation

Social harms, *e.g.*, disruption of family or personal relationships may result due to participation in this trial becoming known to others. In addition, IP use could potentially be unacceptable to the participant's sex partner and result in difficulties with her sex partner. If a participant is or becomes HIV-infected, she may also experience social harms.

During each HIV counselling session, enrolled participants will be asked questions to assess the occurrence of social harms related to trial participation. Participants who experience social harms considered to be related to trial participation will be counselled accordingly and provided with assistance to mitigate the circumstances if possible. This will be recorded in the source documents and applicable CRFs.

10.3. Community Engagement

Community Liaison Officers have been appointed at each research centre to oversee the information provided to local stakeholders, target population and general community. They have been tasked with capturing, monitoring and evaluating feedback from the community. Comments will be captured in various ways at each research centre using methods such as suggestion boxes, door-to-door campaigns, large and small community dialogue sessions, pre/post-tests, distributed feedback forms, etc. Each research centre has a process for consulting with its community. The primary vehicle for this consultation is through formal structures such as the Community Advisory Boards/Groups/Committees. These systems allow investigators and communities to identify and respond rapidly to concerns raised.

11. Publications

Any presentation, abstract, or manuscript shall be reviewed and approved by the Sponsor prior to submission. Publication of the results of this trial will be governed by the IPM's clinical trial agreement with the investigator. Authorship criteria will be based on contributions to the design, work, and analysis of the trial.

12. References

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14. Dapivirine Vaginal Ring Investigator's Brochure, Version 10.0, 09 March 2016.

15. IPM 011; Clinical Study Report; Version 1.0, 15 March 2011.

16. IPM 015; Clinical Study Report; Version 1.0, 06 July 2012.

17. World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects; WMA General Assembly, Fortaleza, Brazil, October 2013. http://www.wma.net/en/30publications/10policies/b3/index.html

18. Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance. http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf

19. Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa. http://www.kznhealth.gov.za/research/guideline2.pdf

APPENDIX A: SCHEDULE OF PROCEDURES

Visits	**Screening**	**Enrolment**	**Trial Visits**	**LPUV**	**Exit Visit**	**As needed**
Trial Months	**Screening must occur within 45 days of enrolment[k]**	**0**	**Months 1-11[h,i]**	**Month 12[i]**	**Months 13-14[i]**	
Informed Consent	***X***					
Comprehension Assessment	***X***					
Assign Screening Identification Number	***X***					
Assign Participant Identification Number		***X***				
Demographics	X					
Medical History	X	X				
Concomitant Medication Evaluation	X	X	X	X	X	X
Inclusion/Exclusion Criteria	***X***	***X***				
Locator Information	X	X	X	X		
Basic Menses Information	X	X	X	X		
Physical Examination	X			X		X
Adverse Event Evaluation		X	X	X	X	X
Social Harms Assessment		***X***	X	X	X	X
Pelvic Exam	X			X		X
Vaginal Ring Dispensing and Insertion		***X***	X			
Vaginal Ring Return/Collection			X	X		
Visual Inspection of Returned Ring(s)			X	X		
Provision of Vaginal Ring Use and Storage Instructions		***X***	X			
Vaginal Ring Adherence Counselling		***X***	X			
Provision of Diary Card(s)		***X***	X[j]			
Collection of Diary Card(s)			X	X		
Participant Questionnaire			X[a]	X		
In-depth individual interviews [l]						X[l]
HIV/STI Risk Reduction Counselling	X	X	X	X	X	
Contraceptive Counselling	X	X	X	X	X	X
Provision of and/or referral for Contraceptives	***X***	***X***	X	X	X	X
Provision of Male and/or Female Condoms (if participant wishes to receive them)	X	X	X	X	X	

Visits	Screening	Enrolment	Trial Visits	LPUV	Exit Visit	As needed
Trial Months	**Screening must occur within 45 days of enrolment[k]**	**0**	**Months 1-11[h,i]**	**Month 12[i]**	**Months 13-14[i]**	
Urine Pregnancy Test (hCG)	X	X	X	X		X
Cervicovaginal Sample Collection for STI Tests *Trichomonas vaginalis* (TV), *Neisseria gonorrhoea*e (NG) and *Chlamydia trachomatis* (CT)	X			X		X
Provision of treatment and/or referral for STIs and Other Findings						X
HIV Pre- & Post-Test Counselling	X	X	X	X	X	
HIV Rapid Tests[b]	X	X	X	X	X	X
HIV-1 RNA PCR Test[c, d]	X	X	X	X	X	
Plasma Viral Genotype (including NGS) and Phenotype Sample[c, d]	X	X	X	X	X	
Plasma Dapivirine Concentrations			X	X		
Vaginal Fluid Dapivirine Concentrations			X	X		
Laboratory Testing for Safety Assessments[e]	X					X
Urine Dipstick Analysis (Urine Microscopy if Clinically Indicated Only)	X					X
RPR[f]	X					
Cervical Sample Collection for Cytology[g]	***X***					X
Final Laboratory results provided					X	

a) Participant Questionnaire will be administered at all Trial Visits.
b) Performed in accordance with HIV testing algorithm.
c) Sample will be stored and will only undergo testing subsequently or after confirmation of seroconversion and at every visit for seroconverters, or if required by HIV testing algorithm.
d) Sample will be obtained at the point of two reactive HIV rapid tests and analysed subsequently or after confirmation of seroconversion.
e) Blood draw by venepuncture for laboratory testing (haematology and chemistry). Haematology will include full blood counts, differential, and platelet count. Chemistry tests will include creatinine, AST and ALT.
f) TPHA/TPPA should be performed if RPR positive.
g) Cervical sample collection for cytology may be conducted at any trial visit if no result is evident within the previous year, or abnormal at last cervical cytology.
h) All women will attend a research centre follow-up visit one month after enrolment. Following this visit, at investigator's discretion, a participant can continue on a 3-monthly visit schedule. Monthly visits may however be extended up to the first three months of participation.
i) IPM will have the option to extend the trial period.
j) Participants will receive a diary card at enrolment and at trial visits, as applicable. Returned diary cards will be reviewed at all scheduled trial visits.

k) Only procedures in bold italics required for participants rolling over directly from LPUV at IPM 027 to IPM 032.
l) In-depth individual interviews will be conducted amongst selected participants.

APPENDIX B: HIV TESTING ALGORITHM

Figure 1: Screening Algorithm

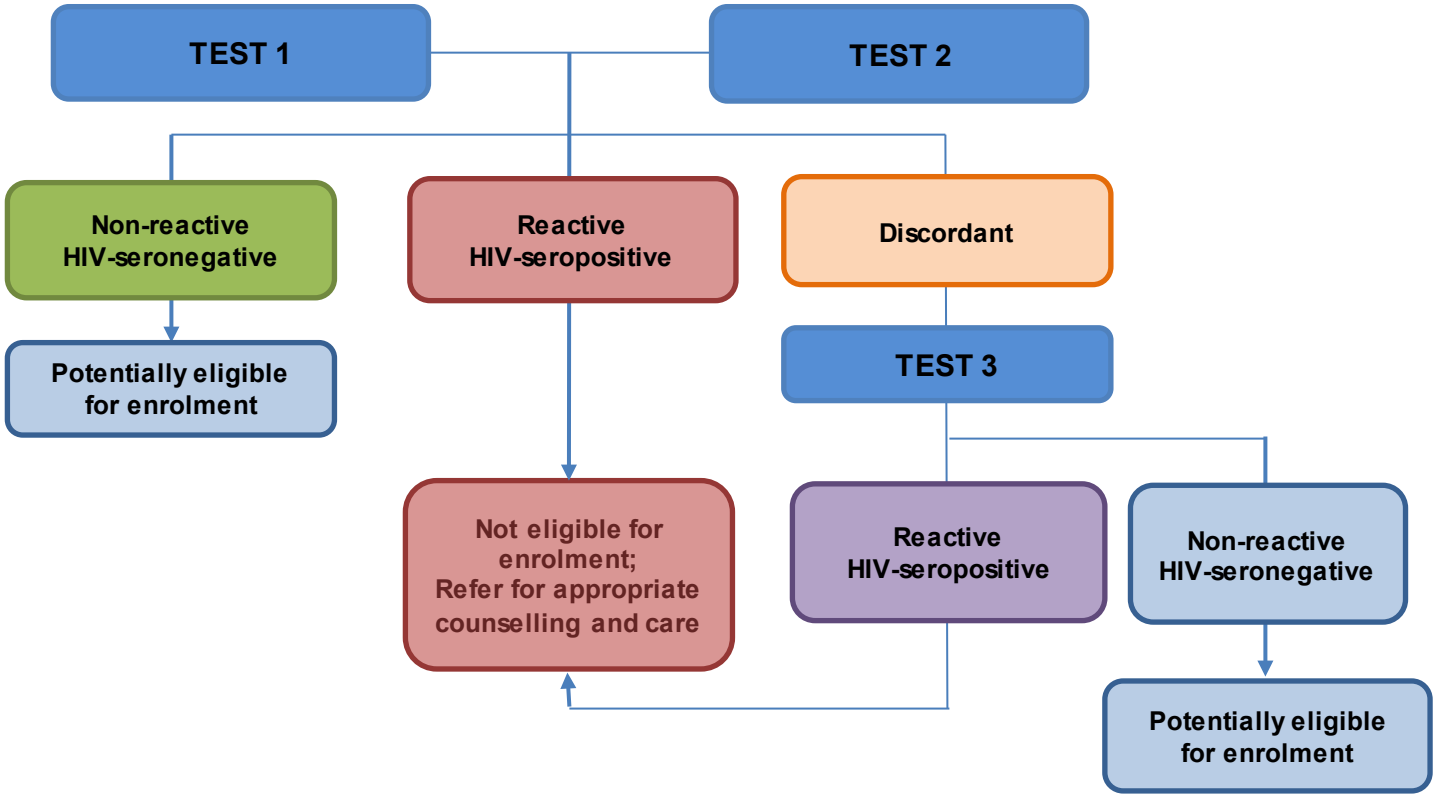


Figure 2: Pre-Enrolment Algorithm

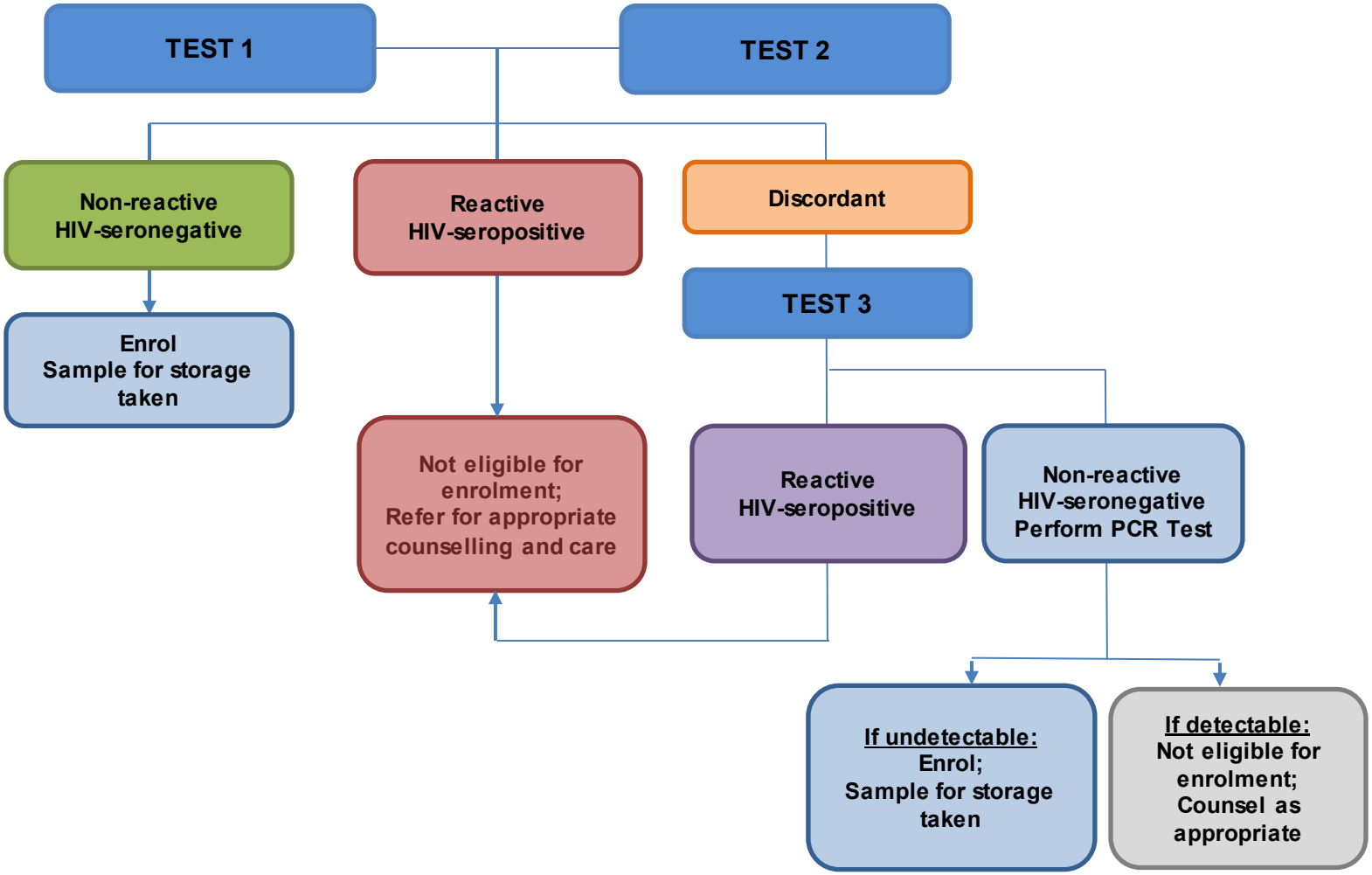


Figure 3: Trial Visits Algorithm

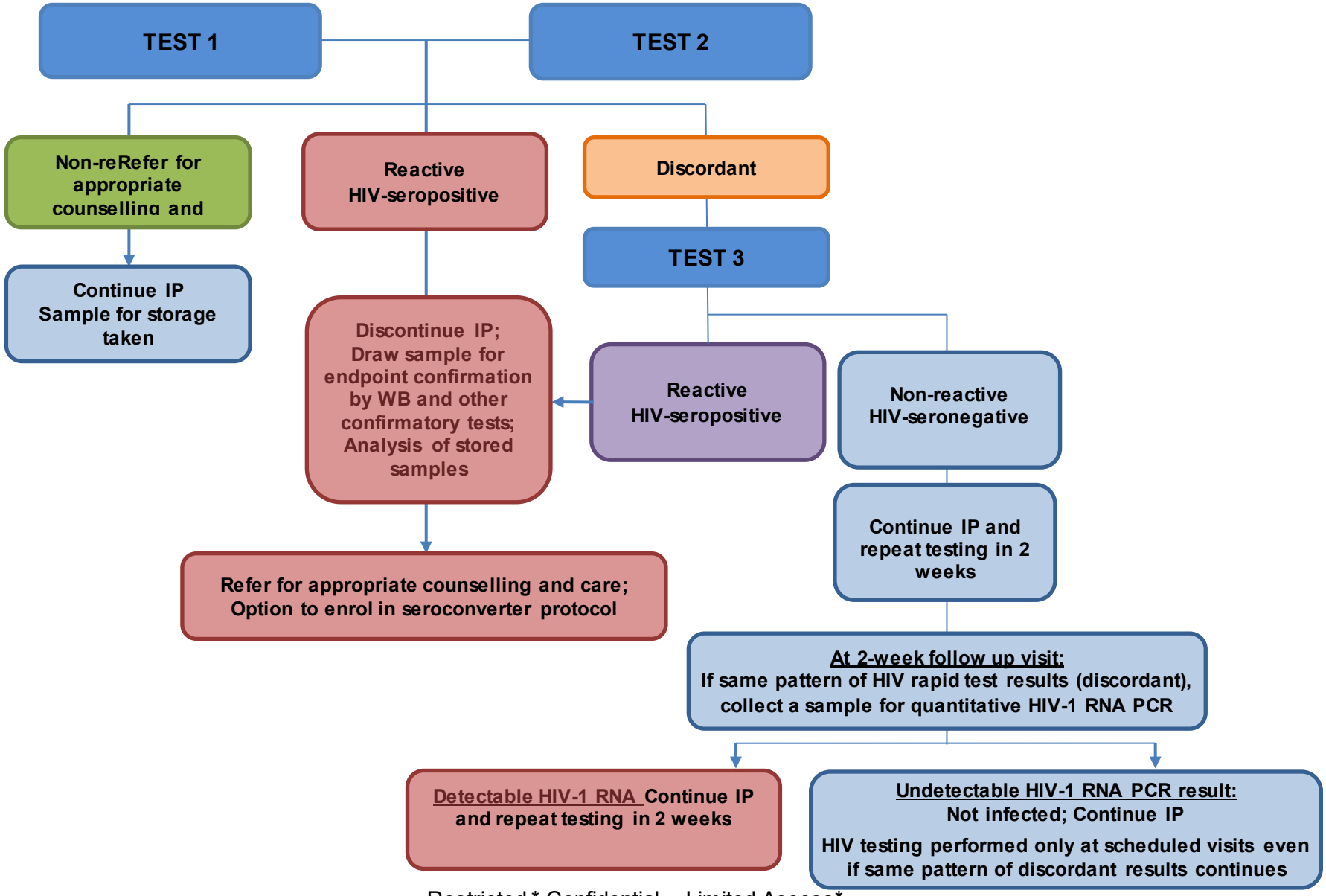
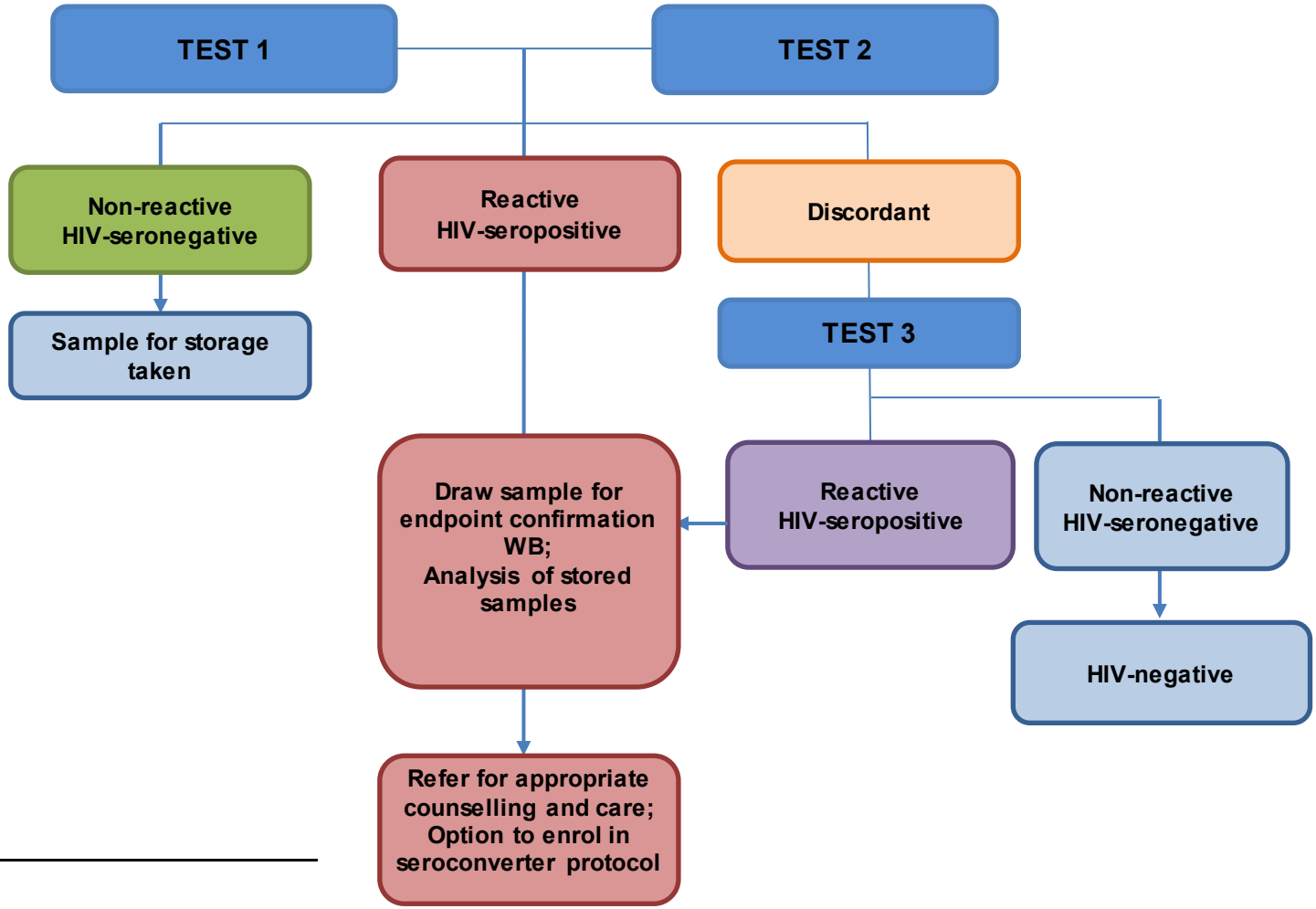
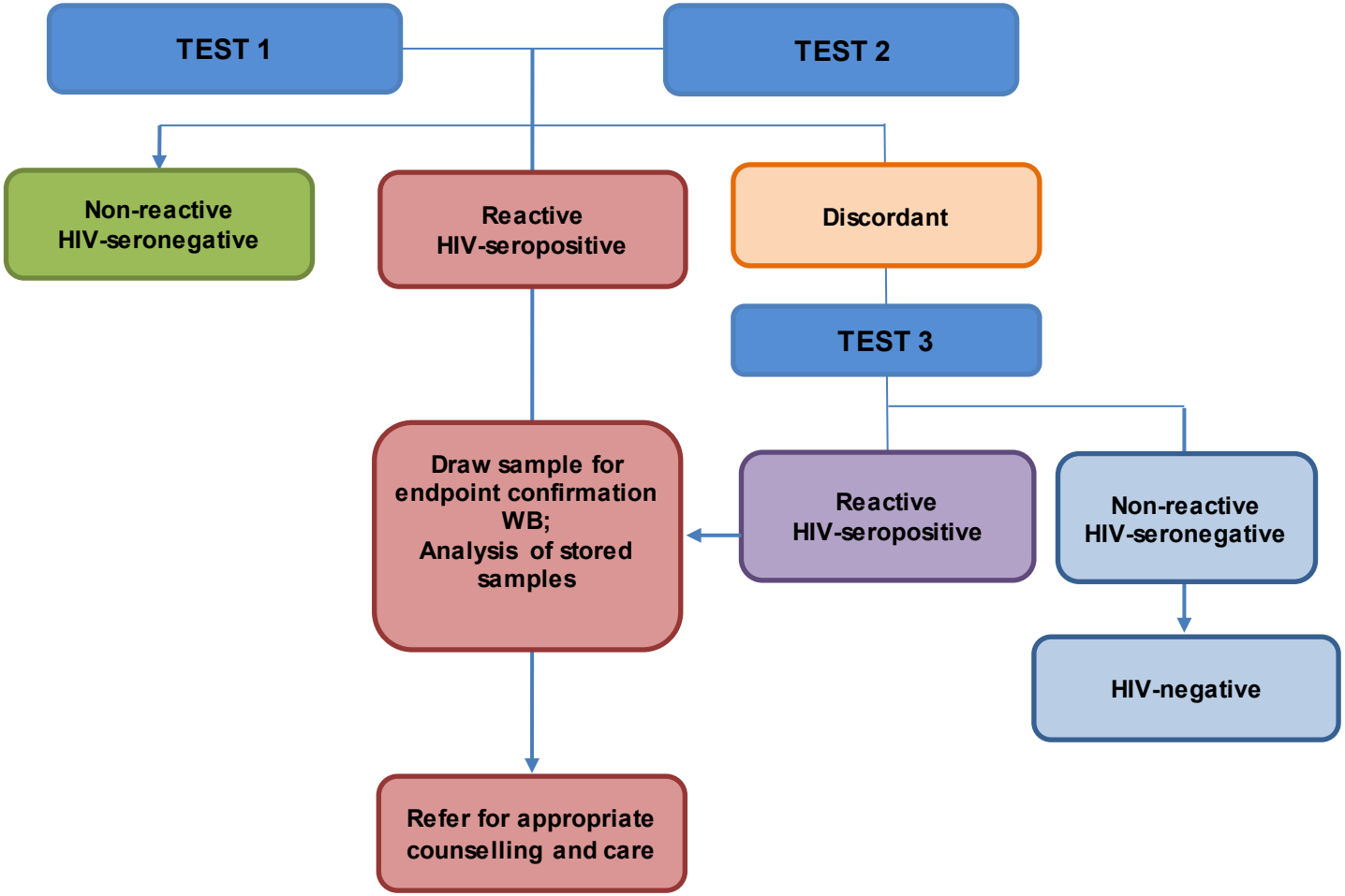


Figure 4: LPUV Algorithm[1]



[1] HIV-1 RNA PCR will be performed on samples stored at last product use visit and on the last samples collected for participants who discontinue from the trial without an exit visit. Only samples from participants who consented for analysis will be selected for the additional HIV-1 RNA PCR analysis and additional HIV viral genotype (including NGS) and phenotype resistance testing as needed.

Figure 5: Exit Visit Algorithm[2]



[2] HIV-1 RNA PCR will be performed on samples stored at last product use visit and on the last samples collected for participants who discontinue from the trial without an exit visit. Only samples from participants who consented for analysis will be selected for the additional HIV-1 RNA PCR analysis.

APPENDIX C: VISIT SCHEDULE AND APPROXIMATE BLOOD VOLUMES

Visit	Test and volume (mL)	Test and volume (mL)	Test and volume (mL)	Test and volume (mL)	Test and volume (mL)	Total Blood Volume
Screening	HIV rapid* 5 mL		Chemistry 5 mL Haematology 5 mL RPR 5 mL	HIV viral genotype resistance# 10 mL	HIV PCR# 5 mL	**35mL**
Enrolment	HIV rapid 5 mL			HIV viral genotype resistance# 10 mL	HIV PCR# 5 mL	**20 mL**
Trial Visits	HIV rapid 5 mL	Dapivirine levels 6 mL		HIV viral genotype resistance# 10 mL	HIV PCR# 5 mL	**26 mL**
LPUV	HIV rapid 5 mL	Dapivirine levels# 6 mL		HIV viral genotype resistance# 10 mL	HIV PCR# 5 mL	**26 mL**
Exit Visit	HIV rapid^ 5 mL			HIV viral genotype resistance## 10 mL	HIV PCR#/## 5 mL	**5 mL or 15 mL##**
Seroconverter tests+	Western blot 5mL	Dapivirine levels++ 6 mL		HIV viral genotype resistance# 10 mL	HIV PCR# 5 mL	**20 mL++ or 26 mL**

- * Depending on the research centre SOP on HIV testing, sampling may be performed by finger prick or venepuncture.
- # Stored plasma samples; tested retrospectively to evaluate different parameters at the time of seroconversion.
- ## Blood samples for HIV-1 RNA PCR, genotype (including NGS) and phenotype resistance testing will be collected at the scheduled exit visit following seroconversion.
- ^ HIV rapid testing will not be conducted at the scheduled exit visit following seroconversion.
- + At the point of seroconversion, these samples will be collected and tested in addition to relevant visit-specific tests, but no samples should be duplicated during the same visit. No additional storage samples will be collected.

  NOTE: *Additional tests may be also performed, as required.*
- ++ Test sample for possible dapivirine measurements will not be required if the seroconversion occurs at the Exit Visit.

APPENDIX D: TRIAL DESIGN