

# Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Nel A, van Niekerk N, Kapiga S, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. *N Engl J Med* 2016;375:2133-43. DOI: [10.1056/NEJMoa1602046](https://doi.org/10.1056/NEJMoa1602046)

**This supplement contains the following items:**

- 1. Original protocol, final protocol, summary of changes**
- 2. Original statistical analysis plan, final statistical analysis plan, summary of changes**

**IPM 027  
Protocol Version 1.0  
13 July 2011**

**A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED  
PHASE II LONG-TERM SAFETY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN  
HEALTHY HIV-NEGATIVE WOMEN**

**SPONSOR:  
International Partnership for Microbicides  
8401 Colesville Road, Suite 200  
Silver Spring, MD 20910 U.S.A.**

## SIGNATURE PAGE

### IPM 027

#### **A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II LONG-TERM SAFETY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-NEGATIVE WOMEN**

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 Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and all applicable regulations and guidelines.

\_\_\_\_\_  
Investigator Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Investigator Name (Printed)

\_\_\_\_\_  
Investigative 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. This trial will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

\_\_\_\_\_  
Chief Medical Officer Signature

\_\_\_\_\_  
Date

Annaléne Nel, MBChB, PhD

Chief Medical Officer Name (Printed)

\_\_\_\_\_  
Protocol Chair

\_\_\_\_\_  
Date

Prof. Saidi Kapiga, MD, MPH, ScD

Protocol Chair Name (Printed)

## TABLE OF CONTENTS

<b>ACRONYMS AND ABBREVIATIONS .....</b>	<b>6</b>
<b>IPM 027 SYNOPSIS.....</b>	<b>8</b>
<b>1. INTRODUCTION .....</b>	<b>19</b>
1.1 BACKGROUND .....	19
1.2 DAPIVIRINE VAGINAL RING .....	20
1.2.1 <i>Dapivirine</i> .....	20
1.2.2 <i>Nonclinical Research</i> .....	21
1.2.3 <i>Clinical Research</i> .....	22
1.2.4 <i>Formulation of a silicone elastomer vaginal matrix ring containing 25mg of dapivirine</i> .....	23
1.3 RATIONALE FOR PROTOCOL IPM 027 .....	23
<b>2. TRIAL OBJECTIVES .....</b>	<b>24</b>
2.1 TRIAL OBJECTIVES .....	24
2.2 TRIAL ENDPOINTS AND ASSESSMENTS.....	25
<b>3. OVERALL TRIAL DESIGN .....</b>	<b>26</b>
3.1 TRIAL DESIGN .....	26
3.2 TRIAL DURATION .....	29
3.3 TRIAL POPULATION.....	29
3.3.1 <i>Inclusion Criteria</i> .....	29
3.3.2 <i>Exclusion criteria</i> .....	30
3.4 PARTICIPANT RECRUITMENT .....	31
3.4.1 <i>Pre-Screening</i> .....	31
3.4.2 <i>Participant Recruitment and Accrual</i> .....	31
<b>4. TRIAL VISITS AND PROCEDURES .....</b>	<b>32</b>
4.1 SCREENING VISITS .....	32
4.1.1 <i>Screening 1</i> .....	32
4.1.2 <i>Screening 2 (Within no more than 4 weeks [28 days] of Screening 1)</i> .....	33
4.2 ENROLMENT VISIT .....	34
4.3 TRIAL VISITS .....	35
4.3.1 <i>4-Weekly Trial Visits (Weeks 4 to 104)</i> .....	35
4.3.2 <i>12-weekly Trial Visits (Weeks 12, 24, 36, 48, 60, 72, 84 and 96)</i> .....	36
4.3.3 <i>24-weekly Trial Visits (Weeks 24, 48, 72 and 96)</i> .....	36
4.3.4 <i>Annual Visits (Weeks 52 and 104)</i> .....	37
4.3.5 <i>Last Product Use Visit (or Early Discontinuation)</i> .....	37
4.4 EXIT VISIT (6 WEEKS AFTER THE LAST PRODUCT USE VISIT) .....	38
4.5 PARTICIPANT RETENTION.....	39
4.6 UNSCHEDULED VISITS .....	39
4.7 MISSED & LATE VISITS.....	39
4.8 EARLY DISCONTINUATION VISIT.....	40
4.9 PREMATURE DISCONTINUATION OF THE TRIAL.....	41
<b>5. TRIAL PROCEDURE DETAILS .....</b>	<b>41</b>
5.1 INFORMED CONSENT .....	41
5.1.1 <i>Informed Consent Process</i> .....	41
5.1.2 <i>Comprehension Checklist</i> .....	42
5.2 HIV COUNSELLING .....	42
5.2.1 <i>HIV Pre- and Post-Test Counselling</i> .....	42

5.2.2	<i>HIV/STI Risk Reduction Counselling</i> .....	43
5.3	HIV TESTING AND MANAGEMENT .....	43
5.3.1	<i>Screening 1</i> .....	43
5.3.2	<i>Screening 2 and Enrolment</i> .....	43
5.3.3	<i>Trial Visits</i> .....	44
5.3.4	<i>Exit Visit</i> .....	45
5.4	MANAGEMENT OF CONTRACEPTION .....	46
5.5	PREGNANCY TESTING AND MANAGEMENT .....	47
5.6	DEMOGRAPHICS AND MEDICAL HISTORY .....	47
5.7	VITAL SIGNS AND PHYSICAL EXAMINATION .....	48
5.8	PELVIC EXAMINATION .....	48
5.9	SAFETY LABORATORY ASSESSMENTS .....	48
5.10	STI TESTING AND MANAGEMENT .....	49
5.10.1	<i>STI Testing</i> .....	49
5.10.2	<i>STI Management</i> .....	49
5.11	CERVICAL CYTOLOGY .....	49
5.12	VAGINAL RING INSERTION AND PLACEMENT CHECK AND RING REMOVAL .....	50
5.13	VAGINAL RING ADHERENCE COUNSELLING .....	50
5.14	QUESTIONNAIRES .....	51
5.14.1	<i>Baseline Behavioural Questionnaire</i> .....	51
5.14.2	<i>Adherence Questionnaire</i> .....	51
5.14.3	<i>Acceptability Questionnaire</i> .....	51
5.14.4	<i>Qualitative interviews</i> .....	51
5.15	SAMPLE STORAGE AND ANALYSIS .....	51
5.16	METHOD OF TREATMENT ASSIGNMENT .....	52
5.17	REIMBURSEMENT .....	52
5.18	PARTICIPANT COMPENSATION .....	52
5.19	PARTICIPANT RESPONSIBILITY .....	53
5.20	STUDY OPERATIONS MANUAL .....	53
<b>6.</b>	<b>INVESTIGATIONAL PRODUCT</b> .....	<b>53</b>
6.1	INVESTIGATIONAL PRODUCT COMPOSITION .....	53
6.2	PACKAGING AND LABELLING .....	54
6.3	RANDOMISATION .....	54
6.4	BLINDING AND UNBLINDING .....	54
6.5	INVESTIGATIONAL PRODUCT STORAGE .....	54
6.6	INVESTIGATIONAL PRODUCT ADMINISTRATION .....	55
6.7	INVESTIGATIONAL PRODUCT EXPULSION OR LOSS .....	55
6.8	INVESTIGATIONAL PRODUCT ACCOUNTABILITY .....	55
6.9	CONCOMITANT MEDICATIONS & PRODUCTS .....	55
<b>7.</b>	<b>ADVERSE EVENTS</b> .....	<b>56</b>
7.1	DEFINITION .....	56
7.2	ASSESSMENT OF ADVERSE EVENT SEVERITY .....	57
7.3	RELATIONSHIP TO INVESTIGATIONAL PRODUCT .....	57
7.4	SERIOUS ADVERSE EVENTS .....	58
7.4.1	<i>Serious Adverse Event Definition</i> .....	58
7.4.2	<i>Serious Adverse Event Contact Information</i> .....	59
7.4.3	<i>Sponsor Notification of SAEs to Regulatory Agencies</i> .....	59
7.4.4	<i>Research centre Notification of SAEs to Local Ethics Committee or Local Health or Regulatory Authorities</i> .....	59
7.5	IMMEDIATELY REPORTABLE EVENTS .....	59
7.6	SAFETY MONITORING .....	60

<b>8. DATA MANAGEMENT.....</b>	<b>60</b>
8.1 DATA HANDLING AT RESEARCH CENTRES .....	60
8.2 SOURCE DATA VERIFICATION .....	60
<b>9. STATISTICAL METHODS .....</b>	<b>61</b>
9.1 GENERAL DESIGN.....	61
9.2 TRIAL ENDPOINTS.....	61
9.3 PRIMARY TRIAL HYPOTHESES .....	61
9.4 SAMPLE SIZE AND POWER CALCULATIONS .....	62
9.5 STATISTICAL ANALYSES .....	63
9.5.1 <i>Primary Safety Analysis</i> .....	64
9.5.2 <i>Secondary Analyses</i> .....	64
9.5.3 <i>Subgroup Analysis of participants of women over 40 years of age</i> .....	67
9.6 DATA SAFETY MONITORING BOARD (DSMB).....	68
9.7 HANDLING OF MISSING DATA AND DROPOUTS .....	68
<b>10. INVESTIGATOR REQUIREMENTS .....</b>	<b>68</b>
10.1 TRIAL INITIATION.....	68
10.2 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE APPROVAL .....	68
10.3 TRIAL MONITORING AND AUDITS .....	69
10.4 CASE REPORT FORMS .....	69
10.5 DISCLOSURE OF DATA .....	69
10.6 RECORD RETENTION .....	70
<b>11. ETHICAL CONSIDERATIONS.....</b>	<b>70</b>
11.1 ETHICAL REVIEW .....	70
11.2 REPORTING AND MANAGEMENT OF SOCIAL HARMS.....	70
11.3 COMMUNITY ENGAGEMENT .....	71
<b>12. PUBLICATIONS.....</b>	<b>71</b>
<b>13. REFERENCES .....</b>	<b>72</b>
<b>APPENDIX A: SCHEDULE OF CLINICAL PROCEDURES .....</b>	<b>73</b>
<b>APPENDIX B: SCHEDULE OF LABORATORY PROCEDURES .....</b>	<b>75</b>
<b>APPENDIX C: HIV TESTING ALGORITHMS .....</b>	<b>77</b>
<b>APPENDIX D: VISIT SCHEDULE AND BLOOD VOLUMES.....</b>	<b>82</b>

## ACRONYMS AND ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARV	Antiretroviral
ASCUS	Atypical Squamous Cells of Undetermined Significance
AST	Aspartate aminotransferase
AUC	Area Under plasma concentration-time Curve
CDC	U.S. Centers for Disease Control and Prevention
CI	Confidence Interval
CRF	Case Report Form
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAPY	Di-aminopyrimidine
DSMB	Data and Safety Monitoring Board
FACTS	Follow on Africa Consortium for Tenofovir Studies
FBC	Full Blood Count
FDA	Food & Drug Administration (U.S.)
GCP	Good Clinical Practice
GEE	General Estimating Equation
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
HPTN	HIV Prevention Trials Network
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
IRE	Immediately Reportable Event
IUD	Intrauterine Device
MTD	Maximum Tolerated Dose
MTN	Microbicide Trials Network
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PCR	Polymerase Chain Reaction
PID	Participant Identification number
PMTCT	Prevention of Mother-to-Child Transmission of HIV
PrEP	Pre-Exposure Prophylaxis
RNA	Ribonucleic Acid
RPR	Rapid Plasma Reagin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STI	Sexually Transmitted Infection



TEAE	Treatment Emergent Adverse Event
TPHA	Treponema Pallidum Haemagglutination Test
TPPA	Treponema Pallidum Particle Agglutination Assay
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
USP	United States Pharmacopeia
VOICE	Vaginal and Oral Interventions to Control the Epidemic
WHO	World Health Organization

## IPM 027 SYNOPSIS

### A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II LONG-TERM SAFETY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-NEGATIVE WOMEN

**BACKGROUND:** HIV/AIDS is the leading cause of death globally in women ages 15 – 44, and exerts an especially high toll in sub-Saharan Africa, where 60% of people living with HIV are women and girls. Developing new HIV prevention options that women can use remains a public health priority. The current generation of vaginal microbicide candidates, containing highly-specific antiretroviral (ARV) drugs, are currently undergoing extensive safety and efficacy trials. ARV-based microbicides specifically target HIV and can be designed in various forms (e.g. vaginal gels, rings, films, tablets) for more flexible dosing, including products for use around the time of sex, or daily or monthly products that could be used independent of sexual activity. Other recently completed and ongoing clinical trials are exploring whether oral daily ARVs taken as pre-exposure prophylaxis (PrEP) are safe and effective for HIV prevention.

Recent research confirms the potential of ARV-based HIV prevention. In July 2010, in an important milestone for HIV prevention, the CAPRISA 004 Phase IIB microbicide trial found a 39% lower HIV infection rate in women using 1% *tenofovir gel* as compared to the women using a placebo gel. 1% *Tenofovir gel* is the first ARV-based microbicide to be tested in an efficacy trial. It is now being tested as a once-daily product in the MTN-003 (VOICE) Phase IIB trial, with another confirmatory Phase III trial, FACTS 001, planned to start in 2011 (using the CAPRISA 004 BAT24 dosing regimen).

Successes with *oral ARVs* for prevention have also been observed. In November 2010, the iPrEx Phase III trial showed that oral Truvada® was 42% effective in reducing the risk of HIV infection among men who have sex with men. And in May 2011, results of the HPTN 052 “treatment for prevention” trial showed that immediate use of ARV therapy by HIV-positive individuals can reduce the risk of transmitting the virus to their uninfected partner by 96%. However, another recent Phase III trial, FEM-PrEP, which tested the effectiveness of daily oral Truvada® in 1,951 high-risk women in Africa, was stopped after an Independent Data Monitoring Committee determined that it was highly unlikely that the trial would be able to show that this strategy was effective.

With a successful proof of concept for ARV-based gels and pills, it is evident that ARV approaches to prevention have the potential to transform the response to the HIV/AIDS pandemic. For women, in addition to confirmatory trials on tenofovir gel, 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 and improve upon the level of effectiveness seen in CAPRISA 004.

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. In addition, a product used independently of sex could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse. As seen in the CAPRISA 004 and iPrEx trials, higher adherence to the test product was associated with increased effectiveness of the product. It is likely that products that can be applied less frequently will be more acceptable and will achieve better adherence. Vaginal rings that need only be replaced monthly may therefore have benefits over dosage forms that need to be used more frequently. The dapivirine (25 mg) silicone elastomer vaginal matrix ring is IPM's lead candidate for advancement to Phase II long-term safety and Phase III safety and efficacy testing.

Multiple Phase I and I/II clinical trials have evaluated the safety of dapivirine in vaginal rings and gels and in an oral formulation. These clinical trials support the favourable safety profile and tolerability of dapivirine in general, and specifically in vaginal delivery formulations. IPM 027 is a Phase II clinical trial that has been designed to assess the long-term safety of dapivirine administered in a silicone elastomer vaginal matrix ring containing 25mg of dapivirine (Ring-004), inserted once every 4 weeks; in healthy, HIV-negative, sexually active women – as compared with a placebo vaginal ring.

**OBJECTIVES:**

**The Primary Objective is:**

1. To assess and compare the safety of dapivirine administered in a silicone elastomer vaginal matrix ring to the placebo vaginal ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks).

**The Secondary Objectives are:**

1. To assess and compare the incidence of HIV-1 and HIV-2 (for safety) in the dapivirine and placebo vaginal ring groups.
2. To assess and compare the incidence of curable sexually-transmitted infections (STIs), and changes in vaginal flora in the dapivirine and placebo vaginal ring groups.
3. To determine the incidence of pregnancy in both trial arms.
4. To assess reported adherence to the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.

5. To assess reported acceptability of the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.
6. To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection while using the investigational product.

**The Exploratory Objectives are:**

1. To evaluate the association between HSV-2 and HIV-1 infection in both trial arms.
2. To explore the potential relationship between method of contraception, pregnancy incidence and HIV seroconversion in both trial arms.
3. To explore the relationship between drug concentrations and trial outcomes (HIV-1 seroconversion and viral resistance).
4. To explore the correlation of drug concentrations and self-reported adherence measures.

**ENDPOINTS AND ASSESSMENTS:**

**The primary endpoints are:**

- Grade 2 adverse events (AEs) judged to be related to the investigational product;
- Grade 3 and 4 AEs.

**The primary endpoints will be assessed through:**

- Self-reports, physical examination, gynaecological assessments, including pelvic/speculum examination, laboratory tests and other indicated investigations. All AEs will be reported regardless of grade or relatedness.

**The secondary endpoints are:**

- Seroconversion rates of HIV-1 and HIV-2 per woman years of product use at the end of the investigational product (IP) use period;
- The incidence of curable STIs (i.e. *N.gonorrhoea*, *C.trachomatis* and *T.vaginalis*), and changes in vaginal flora in each trial arm over the IP use period;
- The incidence of pregnancy in each trial arm over the IP use period;

- The proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period;
- The proportion of women who report the use of the vaginal ring as acceptable;
- HIV-1 drug resistance mutations among participants who acquire HIV-1.

**The secondary endpoints will be assessed through:**

- Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C;
- STI testing, vaginal flora and vaginal pH testing;
- Pregnancy testing;
- Questionnaires and qualitative data regarding sexual behaviour and adherence to the use of a vaginal ring inserted once every 4 weeks over the trial period;
- Questionnaires and qualitative data regarding the acceptability of the use of a vaginal ring inserted once every 4 weeks over the trial period;
- Viral genotyping methods.

**The exploratory endpoints are:**

- The proportion of HSV-2 among analysed samples;
- Incidence of pregnancy in correlation with HIV seroconversion rates and method(s) of contraception used by participants;
- Steady-state drug concentrations in blood and vaginal fluid;
- Steady-state drug concentrations in correlation with self-reported adherence as outlined above for the secondary objective.

**The exploratory endpoints will be assessed through:**

- HSV-2 testing;
- Pregnancy testing and HIV testing as outlined above for the secondary objective, and documentation of participant contraceptive method/s;
- Drug concentrations in blood and vaginal fluid;
- Vaginal fluid, plasma and/or ring residual drug concentrations and self-reported behavioural measures as outlined above for the secondary objective.

**TRIAL DESIGN:**

IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled Phase II trial to evaluate the long-term safety of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks; in healthy, sexually active HIV-negative women, when compared to a placebo vaginal ring. Approximately 1,650 participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.

**TRIAL DURATION:** Each participant will engage in the screening process for up to 4 weeks (28 days) prior to enrolment and will use the IP for a period of approximately 24 months (104 weeks).

Each participant will have an additional 6 weeks of follow-up after ring discontinuation, to assess safety and identify HIV seroconversions after product discontinuation.

**POPULATION:** Approximately 1,650 sexually active HIV-negative women, 18 – 60 years of age, who understand the trial and can provide informed consent, will be enrolled and randomised in a 2:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a placebo vaginal ring.

Approximately 300 participants over 40 years of age will be enrolled in the trial.

**INCLUSION CRITERIA:**

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

1. Women  $\geq 18$  and  $\leq 60$  years of age, at screening, who can provide informed consent;
2. Available for all visits and consent to follow all procedures scheduled for the trial;
3. Self-reported sexually active (defined as an average of at least one penetrative penile vaginal coital act per month for the last 3 months prior to screening);
4. HIV-negative as determined by the HIV algorithm applied at screening and enrolment;
5. On a stable form of contraception as defined within section 5.4 and willing to continue on stable contraception for the duration of the clinical trial; unless post-menopausal or surgically sterilised;
6. Asymptomatic for genital infections at the time of enrolment (if a woman is diagnosed with any clinically significant curable STI, she must have initiated treatment at least 1 week prior to enrolment and have completed the full course of treatment);
7. Willing to answer questions about adherence, sexual behaviour, and ring acceptability;
8. 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;

9. Willing to refrain from participation in another research trial using drugs, vaccines, medical devices, microbicides or oral pre-exposure prophylaxis investigational drugs for the duration of the IPM 027 trial;
10. Willing to refrain from use of vaginal products or objects including spermicides, lubricants, intravaginal medication, other vaginal rings, female condoms, cotton wool, rags, diaphragms, cervical caps (or any other vaginal barrier method), douches, drying agents and herbs within 14 days from enrolment and for the duration of the trial. Tampons are not included in this list and may be used for the duration of the trial.

#### **EXCLUSION CRITERIA:**

Women who have any of the exclusion criteria below are not eligible:

1. Currently pregnant or last pregnancy within 3 months prior to screening;
2. Currently breast-feeding;
3. Women who have had a hysterectomy;
4. Participated in another research trial using drugs, medical devices, microbicides or oral pre-exposure prophylaxis agents within 60 days prior to screening;
5. Previously participated or currently participating in any HIV vaccine trial;
6. Untreated, clinically significant urogenital infections , e.g., urinary tract, or other sexually transmitted infections, or other gynaecological symptoms within 1 week prior to enrolment;
7. Has a Grade 2 or higher pelvic examination finding, according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; Addendum 1 Female Genital Grading Table for Use in Microbicide Studies;
8. History of significant urogenital or uterine prolapse, undiagnosed vaginal bleeding, diagnosed chronic and/or recurrent vulvovaginal candidiasis, urethral obstruction, incontinence or urge incontinence;
9. Any gynaecological surgery within 90 days prior to screening;
10. Any Grade 2, 3 or 4 baseline haematology, chemistry or urinalysis laboratory value according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events;

11. Any history of anaphylaxis or severe allergy resulting in angioedema; or a history of sensitivity/allergy to latex or a silicone elastomer;
12. Any history of diabetes mellitus and chronic use of oral corticosteroid therapy; and any uncontrolled serious chronic or progressive disease;
13. Cervical cytology at screening that requires cryotherapy, biopsy or treatment (other than for infection). Women with Grade 1 cervical cytology findings can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology);
14. Any condition(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 and enrolment: Potential participants who consent will be invited to screen for the trial. At screening 1, these potential participants will provide information on inclusion and exclusion criteria, including locator and menses information, demographic information, 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 condoms), contraceptive counselling and HIV pre- and post-test counselling, and tested for pregnancy, HIV, STIs and cervical cytology, as well as safety laboratory assessments. At screening 2, further information will be collected on medical history, concomitant medication, locator and menses information. Those women who meet specified inclusion criteria and no exclusion criteria, have a normal pelvic examination, negative pregnancy and HIV rapid tests, and consent to participate in the trial, will be invited to enrol in the trial. Eligible women will be randomly assigned in a 2:1 ratio to one of the two trial arms. At enrolment, each participant will receive a baseline behavioural questionnaire and a diary card to record sexual activity and ring experiences over the upcoming 4-week period. Blood samples will be collected for storage, and will be tested retrospectively for HIV-RNA PCR, HIV viral genotyping and HSV-2 serology subsequent to HIV-1 seroconversion. In addition, vaginal specimens will be taken prior to ring insertion to determine vaginal pH and assess vaginal flora.

At enrolment, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled visit.

Trial visits: Dapivirine or placebo vaginal rings will be inserted at 4-weekly intervals for the duration of the IP use trial period. Similar to the enrolment visit, at each regularly scheduled trial visit while on the IP, each participant will be instructed to self-insert a newly-



dispensed vaginal ring, which will be removed at the next scheduled visit. All participants will receive pre- and post-test HIV counselling; HIV/STI risk reduction counselling, condom and vaginal ring adherence counselling, HIV and pregnancy testing; and collection of locator, menses, and concomitant medication information. Male condoms will be provided at all visits as part of HIV/STI risk reduction counselling. Contraceptive counselling will be provided at all visits.

Blood and vaginal fluid samples will be collected for storage at all visits; including the last product use visit. These stored blood samples will be tested for HIV-RNA PCR and viral genotyping only in HIV-1 seroconverters, while HSV-2 serology, blood and vaginal fluid dapivirine concentrations measurement will be conducted in confirmed HIV-1 seroconverters and a randomly selected control group of HIV-negative participants.

The rapid and confirmatory laboratory tests used in the HIV testing algorithm will be able to detect both subtypes, HIV-1 and HIV-2. At the point of HIV seroconversion, the IP will be discontinued, and additional samples will be collected and tested for viral genotyping (blood and vaginal fluid), dapivirine concentrations (blood and vaginal fluid) and HSV-2 serology (blood). In addition, blood and vaginal fluid samples for viral genotyping will also be collected at the scheduled exit visit, approximately 6 weeks following seroconversion. No further storage samples will be collected in these participants.

Adherence assessments will be conducted through an interviewer-administered questionnaire at all 4-weekly trial visits, except the exit visit. Participants will be provided with diary cards at all 4-weekly visits except the last product use and exit visits. The participant may consult the diary card during the adherence assessments and the adherence counselling sessions at each 4-weekly visit. The cards will be collected at each visit. Acceptability questionnaires will be administered at the second trial visit (week 4), and at 24-weekly intervals thereafter, until the last product use visit.

Twenty-four (24) to 36 weeks after trial initiation, each research centre will conduct 6 – 10 qualitative individual interviews with participants, and 6 – 10 qualitative individual interviews with male partners. These interviews will provide data on acceptability, sexual behaviour and adherence issues. The recruitment and sampling strategy will be specified in the Statistical Analysis Plan (SAP).

AEs will be assessed at all visits post-randomisation. In addition, safety laboratory assessments, pelvic examination, vaginal pH and vaginal flora as well as STI tests will be performed at 12-weekly intervals. Cervical cytology will be repeated at the end of the first and second year of IP use. Residual dapivirine levels in returned rings will be measured for a selected group of participants at predetermined time-points.

Last product use visit: At the last product use visit, participants will return the last used rings; report any medical problems and/or concomitant medications since the last visit; provide locator and menses information; receive pre- and post-test HIV counselling, contraceptive counselling and HIV/STI risk-reduction counselling (including provision of male condoms); complete vaginal ring use, adherence and acceptability questionnaires; undergo a physical examination as well as a pelvic examination for evaluation of STIs and changes in vaginal flora; and provide blood and vaginal fluid specimens for storage, and specimens for pregnancy and HIV testing, and safety laboratory assessments.

Each research centre will conduct 2 – 3 focus groups with participants who have been recruited for these groups at the last product use visit. Additionally, 6 – 10 qualitative individual interviews with male partners will be conducted at each research centre. These interviews will provide data on acceptability and adherence issues. The recruitment and sampling strategy will be specified in the SAP.

Exit visit - 6 weeks after ring discontinuation: Participants may be notified of any abnormal findings and asked to return to the research centre prior to the exit visit; as needed for treatment and/or referral. On the day of the scheduled exit visit, participants will return to the research centre to receive results from their pelvic examination/STI testing and safety laboratory assessments done at the last product use visit, and treatment or referral as needed. AEs and concomitant medications will also be recorded at this visit.

Participants will receive pre- and post-test counselling for HIV and undergo final HIV testing. HIV/STI risk reduction counselling (including provision of male condoms) and contraceptive counselling will also be provided at the exit visit. If a clinically significant gynaecological or other related AE remains unresolved at the time of trial completion, a clinical assessment will be made by the research centre's investigator or designated qualified physician and the IPM Clinical Physician or designee to determine whether continued follow-up of the AE is warranted.

Participants will then be considered to have completed trial participation, and informed that they may be re-contacted at a future date to be provided information about trial results including individual unblinding.

## **STATISTICAL CONSIDERATIONS:**

General: IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled Phase II trial to assess the long-term safety of dapivirine in a silicone elastomer vaginal matrix ring; to be conducted at approximately 7 clinical research centres. Individuals meeting all inclusion criteria and no exclusion criteria will be randomised in a 2:1 (dapivirine: placebo) ratio to either the investigational product or placebo. Randomisation will be stratified

by research centre and age at the time of enrolment ( $\leq 40$  years of age,  $> 40$  years of age;  $N = 1,350$  and  $N = 300$  respectively) using a pre-specified block size and will be determined via the use of an automated randomisation system to ensure balance of the treatment assignments.

Sample Size and Power Calculations: IPM 027 will be conducted in a sample of approximately 1,650 HIV-negative women in a 2:1 ratio such that 1,100 participants will be assigned to the investigational product and 550 participants will be assigned to the placebo ring. The sample size is determined based on the probability of detecting rare AEs in the active arm and the ability of the trial to detect differences in the proportion of primary endpoints between the two trial arms assuming an AE rate of 1% in the placebo arm. In a trial with 1,000 participants assigned to the investigational product, there is a 95% probability of detecting an AE occurring at a rate of 0.3% or higher.

Using a Fisher's Exact Test under 0.05 type I error, a trial with 1,000 participants assigned to the active arm and 500 participants assigned to the placebo arm would provide approximately 91% power to detect a difference of 4% or larger if the AE rate in the placebo arm were 1%. To adjust for loss-to-follow-up the sample size of  $N=1,500$  is inflated by 10% for a final sample size of 1,650.

Statistical Analyses: The analysis of the primary safety assessments will be descriptive in nature; all estimated treatment effects will be provided with 95% confidence intervals (CIs) and will be evaluated under a significance level of 0.05. Descriptive analyses of participant characteristics will be provided. The safety population will include all participants who were randomised to the investigational product and received at least one dose of the investigational product. A per-protocol analysis will also be performed and will exclude participants who did not adhere to the trial protocol.

The safety parameters will be compared between participants assigned to the dapivirine-containing vaginal ring and participants assigned to the placebo vaginal ring, using Chi-square and a Fisher's Exact Test, when appropriate. Poisson and/or logistic regression models may be used to estimate the crude and adjusted effect of the dapivirine ring on the safety of the trial participants. Time to event outcomes will be assessed using Kaplan-Meier survival curves, and may utilise the log-rank test statistic and Cox proportional hazards model.

The analysis of the social and behavioural secondary endpoints will focus on the assessment of acceptability of the vaginal ring, adherence to the use of the vaginal ring, as well as investigation of possible factors influencing adherence of women participating in the trial. Data for vaginal ring acceptability, sexual behaviour, condom use and vaginal ring use will be collected by self-report through interviewer-administered questionnaires, focus groups and individual interviews. Comparison between the two treatment arms

will be conducted and will take into account the repeated measures by using a general estimating equation (GEE) framework.

Appropriate statistical analyses of the exploratory endpoints will be performed.

**Subgroup Analyses:** To assess the long-term safety of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks in healthy, HIV-negative women over 40 years of age, when compared to a placebo vaginal ring, an analysis of the primary, secondary and exploratory endpoints will be performed on a subgroup of women over 40 years of age.

A subgroup with approximately 200 participants over 40 years of age in the active arm, or approximately 300 participants in both arms, would be sufficient to detect at least one AE with a rate of 2% and at least three events if the AE rate was 5%. The subgroup analysis will not be powered to detect small differences in the safety profile between the active and placebo arms. However, with 300 participants in the subgroup, the trial has 94% power to detect a difference when the AE rate in the active arm is 20% and the AE rate in the placebo arm is 5%. The qualitative individual interviews will include a sample of women over 40 years of age, to provide further descriptive information on acceptability, sexual behaviour and adherence issues for this population.

The Data and Safety Monitoring Board (DSMB) will perform thorough reviews of the data at pre-specified time points during the trial duration. They may recommend the early termination of the trial or modification due to evidence of safety concerns among participants.

## 1. INTRODUCTION

### 1.1 Background

According to UNAIDS, the estimated number of people living with HIV worldwide in 2010 (30 years after the HIV/AIDS epidemic first started) was 34 million<sup>1</sup>. In 2009, 2.6 million people became newly infected with HIV and 1.8 million lost their lives to AIDS<sup>2</sup>. Over 95 percent of new infections are occurring in developing countries, specifically sub-Saharan Africa, where new infections threaten the sustainability of expanded access to HIV/AIDS treatment. According to UNAIDS, for every 3 people placed on antiretroviral treatment in 2010, 5 others become newly infected worldwide<sup>1</sup>. The ongoing development of safe and effective HIV prevention technologies that can be made easily accessible to developing countries remains a public health priority.

“AIDS at 30: Nations at the Crossroads”, the report published by UNAIDS in 2011, shows that women and girls continue to be affected disproportionately by HIV in sub-Saharan Africa, where they account for 60% of people living with HIV<sup>1</sup>. Unprotected heterosexual intercourse is currently the leading mode of HIV transmission among women. Correct and consistent use of latex condoms is one proven method of preventing HIV transmission; however, condoms are widely regarded as inadequate prevention options for women, because many women are unable to negotiate condom use with their partners. Most current HIV prevention methods require the consent (as well as some action or behaviour change) of the male partner<sup>3</sup>.

Developing HIV prevention options that women can use remains a global concern, given the high rates of HIV infection among women. Vaginal microbicides, which are self-initiated, would offer women a critically needed new tool to prevent HIV. Microbicide candidates, based on antiretroviral (ARV) drugs that specifically target HIV, are planned to undergo extensive safety and efficacy trials. 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 July 2010, an important milestone for HIV prevention came from the CAPRISA 004 Phase IIB microbicide trial, which found a 39% lower HIV infection rate in women using 1% *tenofovir gel* within 12 hours before and after sex (i.e. two applications per sex act), as compared to the women using a placebo gel. In women who reported using the gel with more than 80% of sex acts, the protection level was even higher, at 54%<sup>4</sup>. *Tenofovir gel* is the first ARV-based microbicide to be tested in an efficacy trial. It is also being tested as a once-daily product in the MTN-003 (VOICE) Phase IIB trial in Africa, and an additional confirmatory Phase III trial, FACTS 001, is planned to start in 2011 using the same BAT24 dose regimen as in the CAPRISA 004 trial.

Successes with *oral ARVs* for prevention have also been observed. In November 2010, the iPrEx Phase III trial showed that oral Truvada® was 42% effective in reducing the risk of HIV infection among men who have sex with men<sup>5</sup>. And in May 2011, results of the HPTN 052 “treatment for prevention” trial showed that immediate use of ARV therapy by HIV-positive individuals can reduce the risk of transmitting the virus to their uninfected partner by 96%<sup>6</sup>.

However, another recent Phase III trial, FEM-PrEP, which tested the effectiveness of daily oral Truvada® in preventing HIV transmission in 1,951 high-risk women in Africa, was stopped after an Independent Data Monitoring Committee (IDMC) determined that it was highly unlikely that the trial would be able to show that this strategy was effective. In this trial, 56 new HIV infections were equally distributed among women who received Truvada® and those who received placebo<sup>7</sup>. The reasons for this failure are still being investigated.

With a successful 'proof of concept' that an ARV-based microbicide can reduce the risk of HIV acquisition in women (coupled with similar research findings from the iPrEx oral PrEP trial for men who have sex with men, and from the HPTN 052 treatment for prevention trial in serodiscordant partners), it is evident that ARV approaches to prevention have the potential to transform the response to the HIV/AIDS epidemic. For women, in addition to confirmatory work on tenofovir gel, further research is needed on microbicides that contain different ARV compounds in different formulations and using different dosing strategies, to provide options and improve upon the level of effectiveness seen in CAPRISA 004.

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. In addition, a product used independently of sex could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse. As seen in the CAPRISA 004 trial, higher adherence to product may translate into higher effectiveness of the product. It is likely that products that can be applied less frequently will be more acceptable and will achieve better adherence. Vaginal rings that need only be replaced monthly may therefore have benefits over dosage forms that need to be used more frequently. The dapivirine (25 mg) silicone elastomer vaginal ring is IPM's lead candidate for advancement to Phase II long-term safety and Phase III safety and efficacy testing.

Multiple Phase I and I/II clinical trials have evaluated the safety of dapivirine in vaginal rings, gels and in an oral formulation. These clinical trials support the favourable safety profile and tolerability of dapivirine in general and specifically in vaginal delivery formulations.

## 1.2 Dapivirine Vaginal Ring

### 1.2.1 Dapivirine

Dapivirine is a substituted di-aminopyrimidine (DAPY) derivative and one of a new generation of non-nucleoside reverse transcriptase inhibitors (NNRTIs). NNRTIs bind to the HIV reverse transcriptase (RT) enzyme preventing viral replication and therefore production of infectious virus. Dapivirine was originally developed by 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 also 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.

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

- Clinical trials have demonstrated sustained delivery of high levels of dapivirine throughout the cervicovaginal vault for up to 1 month;
- Since the ring is able to deliver drug for at least 1 month, the burden of user adherence is lower than for once daily products;
- Product acceptability studies and the experience gained from marketed vaginal ring products have established a high level of acceptance and adherence from women using vaginal rings with similar physical characteristics;
- The overall cost for the ring is relatively low;
- Minimal storage space is required for the ring when compared with once daily products;
- Vaginal rings can be used more discreetly than daily or pre-coital products.

The safety and tolerability of dapivirine have been evaluated by IPM and Tibotec Pharmaceuticals in both animal and human studies via the oral and vaginal routes. Below is a summary of the data collected through these studies. Detailed information on dapivirine is available in the Dapivirine Vaginal Ring Investigator's Brochure<sup>8</sup> (IB).

### 1.2.2 Nonclinical Research

The potential of dapivirine as a microbicide for prevention of sexual transmission of HIV has been assessed and confirmed in different *in vitro*, *ex vivo* and *in vivo* models:

- 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<sub>50</sub> values ranging from 0.9 nM (0.3 ng/mL) against laboratory isolates to less than 100 nM (32.9 ng/mL) for HIV-1 isolates encoding one or more known NNRTI resistance mutations. Dapivirine is equally active against both CCR5 tropic and CXCR4 tropic strains of HIV-1.
- *In vitro* studies in monocyte-derived dendritic cells and autologous CD4+ T-cells, which are important cells in mucosal transmission, indicated that dapivirine is able to prevent viral replication at 10 nM (3.3 ng/mL). Long-term treatment with dapivirine aborted HIV-1 replication in cells infected with cell-free virus at 10 nM (3.3 ng/mL), or those infected by cell-to-cell transmission at 100 nM (32.9 ng/mL).
- In a cervical explant model using tissue from hysterectomised women, dapivirine potently inhibited HIV infection of tissue (IC<sub>50</sub> = 1.5 nM [0.49 ng/mL]), with > 99% inhibition at 10 nM (3.3 ng/mL). Furthermore, dapivirine inhibited the transfer of HIV from migratory dendritic cells to permissive T-cells with an IC<sub>50</sub> of 0.1 nM (0.03 ng/mL), and at 100 nM (32.9 ng/mL) transfer was completely inhibited.

- In an *in vivo* hu-SCID mouse model in which mice were treated with dapivirine gels (2.25 to 225  $\mu\text{M}$  [0.7 to 74.1  $\mu\text{g}/\text{mL}$ ]) vaginally, and then challenged vaginally with human peripheral blood lymphocytes infected with either R5 or X4 virus, the gels demonstrated 70 – 100% protection.

The toxicity of dapivirine has been evaluated in a comprehensive program of preclinical studies. These are described in the IB and included chronic vaginal toxicity studies in rabbits using gel formulations of dapivirine. No local or systemic toxicity was observed following repeat administration at up to 20 mg/mL for 14 days, up to 5 mg/mL (0.5%) for 13 weeks or up to 2 mg/mL (0.2%) for 39 weeks. Furthermore, vaginal reproductive toxicity studies in rats and rabbits using dapivirine gel at up to 2.0 mg/mL (0.2%) did not identify any adverse effects on the maternal animals or the developing embryo/foetus.

A study was conducted in sheep to evaluate Ring-004 containing 25 mg dapivirine for potential local and systemic toxicity and compare the findings with those in animals receiving dapivirine gel. There were no treatment related findings in sheep that received up to 3 rings (each ring for a period of 30 days, after which the ring was removed and replaced with a fresh ring) or daily 2 mg/mL (0.2%) gel (dose volume= 2.5 mL) for a total exposure of 90 days.

The no adverse effect level (NOAEL) in rats and dogs following oral administration was 20 mg/kg/day. The  $C_{\text{max}}$  at the NOAEL was 0.39  $\mu\text{g}/\text{mL}$  in rats and 1.21  $\mu\text{g}/\text{mL}$  in dogs; which is, respectively, more than 990 and 3000 times the maximum mean plasma concentration (0.392 ng/mL) in women using Ring-004. AUC at the NOAEL was 4.80  $\mu\text{g}\cdot\text{h}/\text{mL}$  in rats and 12.98  $\mu\text{g}\cdot\text{h}/\text{mL}$  in dogs, which is over 570 and 1500 times, respectively, the mean AUC (8.379 ng.h/mL) in women using Ring-004.

### 1.2.3 Clinical Research

To date, 25 Phase I and Phase I/II clinical trials of dapivirine have been conducted: six trials of dapivirine vaginal rings in 393 participants (222 using dapivirine rings and 183 using placebo rings); eight 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. The data analysis of three of these trials, one vaginal ring trial (IPM 015) and two vaginal gel trials (IPM 014A and IPM 020) is ongoing, and no results are available as yet.

In a safety and pharmacokinetic trial in healthy HIV-negative women to assess delivery of dapivirine from both the matrix and reservoir vaginal rings containing 25 mg of dapivirine (IPM 018), the mean maximum dapivirine concentration in cervicovaginal fluids was 2.866 mg/g, and in one subject a concentration of 11 mg/g was detected. These levels were associated with the matrix configuration (much lower levels were observed for the reservoir ring) and occurred at about 24 hours post ring insertion, after which they decreased rapidly. Since the highest gel concentration of dapivirine previously evaluated in vaginal toxicity studies was approximately 2 mg/mL, an additional 14-day vaginal study in rabbits was performed at concentrations up to 20 mg/mL. Again, no evidence of local or systemic toxicity was observed.

The maximum tolerated dose (MTD) was established in oral trials as 350 mg for a single dose and 300 mg when administered twice daily for 14 days. The highest daily dose of dapivirine delivered from a vaginal gel to date (Gel 4759 and Gel 4789, approximately 1250  $\mu\text{g}/\text{day}$  for 84 days) is 280 times lower than the MTD for a single dose of oral



dapivirine (350 mg) and 480 times lower than the MTD for multiple doses of oral dapivirine (300 mg b.i.d. for 14 days). The drug load for the dapivirine vaginal ring is 25 mg, which is also much lower than the oral MTD. Studies measuring the amount of residual dapivirine in the vaginal ring post-use indicate that < 10 mg of the total drug load is released over a 28-day period of ring use.

No drug-related serious adverse events (SAEs) have been reported to-date and no trials were stopped for safety reasons. Adverse events (AEs) documented in 5 or more participants (>2%) after oral exposure to dapivirine were headache, dizziness, nausea, diarrhoea, fatigue, tremor, somnolence, flatulence, and vomiting. Most of these treatment emergent adverse events (TEAEs) were Grade 1 or Grade 2 and most (≥80%) were considered to be drug-related. Grade 3 TEAEs included headache, dizziness, injury, nausea, tremor, paraesthesia, disturbance in attention, abrasion, AST increased, ALT increased, polyuria, fever, diarrhoea, and vomiting. Elevated liver function was documented in laboratory tests. These increases in AST and ALT were transient and did not result in any liver impairment related to use of the investigational product. AEs which have been documented in at least 5% of participants in all dapivirine ring and dapivirine gel trials include headache, vaginal haemorrhage (“vaginal bleeding”)<sup>1</sup>, lower abdominal pain, metrorrhagia, and vulvovaginal/genital pruritus. Events that were considered related to the dapivirine vaginal ring include headache, fatigue, vulvovaginal or genital pruritus, vulvovaginal discomfort, abdominal pain, urinary incontinence, nausea, and vaginal or genital discharge.

A complete summary of the safety data from preclinical studies and previous clinical trials of dapivirine via the oral and vaginal routes and the different dosage forms are contained in the Dapivirine Vaginal Ring IB.

#### **1.2.4 Formulation of a silicone elastomer vaginal matrix ring containing 25mg of dapivirine**

The dapivirine silicone elastomer vaginal matrix ring (Ring-004) is an off-white flexible ring containing 25 mg of drug substance dispersed in a platinum-cured silicone matrix. The dimensions of the ring are 56 mm and 7.7 mm – the outer diameter and cross-sectional diameter, respectively. Details regarding the formulation and dimensions are provided in the IB. The dapivirine silicone elastomer vaginal matrix ring is designed to provide sustained release over a minimum of 28 days.

### **1.3 Rationale for Protocol IPM 027**

Based on *in vitro*, *in vivo*, and *ex vivo* studies described in the Dapivirine Vaginal Ring IB, dapivirine shows great promise as a topical microbicide to prevent HIV-1 infection.

In order for a microbicide to be most effective, it is essential that it is used correctly and consistently. It is likely that products that can be applied less frequently, and have a minimal effect on the vaginal environment during sex will be more acceptable to women and their male partners and will achieve better user-adherence. Vaginal rings that need

---

<sup>1</sup> Based on the MedDRA version that was used, the following Lower Level Terms would have coded to a Preferred Term of “vaginal haemorrhage”: vaginal bleeding, bloody vaginal discharge, vaginal haemorrhage, vaginal ecchymosis, and vaginal petechiae.

only be replaced every month may have benefits over dosage forms that need to be used more frequently.

Silicone elastomer vaginal rings have already been developed and approved as delivery methods for medications. For example, Pfizer (formerly Pharmacia and Upjohn Company) has marketed Estring<sup>®</sup> (estradiol vaginal ring), a vaginal ring that is also made from silicone elastomer and contains estradiol used to treat local symptoms of urogenital atrophy, since 1993. Prior to the launch of Estring<sup>®</sup>, the biological safety of the silicone elastomer was studied in various *in vitro* and *in vivo* test models. The results show that the silicone elastomer is non-toxic, non-pyrogenic, non-irritating, and non-sensitising<sup>9</sup>.

Femring<sup>®</sup> (estradiol acetate vaginal ring), a hormone replacement product approved in June 2003 by the United States (U.S.) Food and Drug Administration (FDA), is another silicone ring that treats menopause-induced vasomotor symptoms (e.g., hot flashes) and symptoms of vulvar and vaginal atrophy (e.g., dryness)<sup>10</sup>. Although these rings are not exactly the same as the IPM ring, the extensive clinical trial and post-marketing experience gained from these products provides further assurance of the safety of silicone elastomer rings as vaginal drug delivery devices. An acceptability trial of the silicone elastomer ring used in Femring<sup>®</sup> (but containing no drug) among postmenopausal women in the U.S. demonstrated very high acceptability and ease of use<sup>11</sup>. IPM recently evaluated the acceptability and safety of a similar placebo vaginal ring in the IPM 011 study (n=170). This study confirmed that the placebo ring was safe and acceptable to users and their male partners<sup>12</sup>.

IPM 027 has been designed to compare the safety of dapivirine (25 mg) in a silicone elastomer vaginal matrix ring (Ring-004), inserted once every 4 weeks in healthy, HIV-negative sexually active women, with a placebo vaginal ring.

## 2. TRIAL OBJECTIVES

### 2.1 Trial Objectives

#### Primary Objective

1. To assess and compare the safety of dapivirine administered in a silicone elastomer vaginal matrix ring to the placebo vaginal ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks).

#### Secondary Objectives

1. To assess and compare the incidence of HIV-1 and HIV-2 (for safety) in the dapivirine and placebo vaginal ring groups.
2. To assess and compare the incidence of curable sexually-transmitted infections (STIs), and changes in vaginal flora in the dapivirine and placebo vaginal ring groups.
3. To determine the incidence of pregnancy in both trial arms.

4. To assess reported adherence to the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.
5. To assess reported acceptability of the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.
6. To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection while using the investigational product.

### Exploratory Objectives

1. To evaluate the association between HSV-2 and HIV-1 infection in both trial arms.
2. To explore the potential relationship between method of contraception, pregnancy incidence and HIV seroconversion in both trial arms.
3. To explore the relationship between drug concentrations and trial outcomes (HIV-1 seroconversion and viral resistance).
4. To explore the correlation of drug concentrations and self-reported adherence measures.

## **2.2 Trial Endpoints and Assessments**

### **The primary endpoints are:**

- Grade 2 adverse events (AEs) judged to be related to the investigational product;
- Grade 3 and 4 AEs.

The primary endpoints will be assessed through:

- Self-reports, physical examination, gynaecological assessments, including pelvic/speculum examination, laboratory tests and other indicated investigations. All AEs will be reported regardless of grade or relatedness.

### **The secondary endpoints are:**

- Seroconversion rates of HIV-1 and HIV-2 per woman years of product use at the end of the IP use period;
- The incidence of curable STIs (i.e. *N.gonorrhoea*, *C.trachomatis* and *T.vaginalis*), and changes in vaginal flora in each trial arm over the IP use period;
- The incidence of pregnancy in each trial arm over the IP use period;
- The proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period;

- The proportion of women who report the use of the vaginal ring as acceptable;
- HIV-1 drug resistance mutations among participants who acquire HIV-1.

The secondary endpoints will be assessed through:

- Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C;
- STI testing, vaginal flora and vaginal pH testing;
- Pregnancy testing;
- Questionnaires and qualitative data regarding sexual behaviour and adherence to the use of a vaginal ring inserted once every 4 weeks over the trial period;
- Questionnaires and qualitative data regarding the acceptability of use of a vaginal ring inserted once every 4 weeks over the trial period;
- Viral genotyping methods.

**The exploratory endpoints are:**

- The proportion of HSV-2 among analysed samples;
- Incidence of pregnancy in correlation with HIV seroconversion rates and method(s) of contraception used by participants;
- Steady-state drug concentrations in blood and vaginal fluid;
- Steady-state drug concentrations in correlation with self-reported adherence as outlined above for the secondary objective.

The exploratory endpoints will be assessed through:

- HSV-2 testing;
- Pregnancy testing and HIV testing as outlined above for the secondary objective, and documentation of participant contraceptive method/s;
- Drug concentrations in blood and vaginal fluid;
- Vaginal fluid, plasma and/or ring residual drug concentrations and self-reported behavioural measures as outlined above for the secondary objective.

### **3. OVERALL TRIAL DESIGN**

#### **3.1 Trial Design**

IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled Phase II trial to evaluate the long-term safety of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks in healthy, sexually active HIV-negative women, when

compared to a placebo vaginal ring. The trial will be conducted at approximately 7 clinical research centres in sub-Saharan Africa. Approximately 1,650 participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.

Each participant will engage in the screening period of up to 4 weeks (28 days) prior to enrolment, and will use the IP for an estimated period of 24 months. Each participant will have an additional 6 weeks of follow-up after ring discontinuation to assess for safety and identify HIV seroconversions after product discontinuation.

### **Screening and enrolment**

Potential participants who consent will be invited to screen for the trial. At screening 1, these potential participants will provide information on inclusion and exclusion criteria, including locator, demographic and menses information, 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 condoms), contraceptive counselling and HIV pre- and post-test counselling, and tested for pregnancy, HIV, STIs and cervical cytology, as well as safety laboratory assessments. At screening 2, further information will be collected on medical history, concomitant medication, locator and menses information. Those women who meet specified inclusion criteria and no exclusion criteria, have a normal pelvic examination, negative pregnancy and HIV rapid tests, and consent to participate in the trial, will be invited to enrol in the trial. Eligible women will be randomly assigned in a 2:1 ratio to one of the two trial arms. At enrolment, each participant will receive a baseline behavioural questionnaire and a diary card to record sexual activity and ring experiences over the upcoming 4-week period. Blood samples will be collected for storage. These stored samples will be tested retrospectively for HIV-RNA PCR, HIV viral genotyping and HSV-2 serology subsequent to confirmed HIV-1 seroconversion; HIV-RNA PCR and HIV viral genotyping will be tested only in HIV-1 seroconverters, while HSV-2 serology will be tested in HIV-1 seroconverters and also in a randomly selected control group of HIV-negative participants. In addition, vaginal specimens will be taken prior to ring insertion to determine vaginal pH and assess vaginal flora.

At enrolment, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled visit. After initial ring insertion at enrolment, women will remain in the research centre under observation for 30 minutes to be assessed for immediate reactions.

### **Trial visits (during investigational product use)**

Dapivirine or placebo vaginal rings, according to the allocated randomisation group, will be inserted at 4-weekly intervals for the duration of the IP use period. Similar to enrolment, at each regularly scheduled trial visit while on the IP, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled trial visit. All participants will receive pre- and post-test HIV counselling; HIV/STI risk reduction counselling, condom and vaginal ring adherence counselling, HIV and pregnancy testing; and collection of locator, menses, and concomitant medication information. Male condoms will be provided at all visits as part of HIV/STI risk reduction counselling. Contraceptive counselling will be provided at all visits. Blood samples and vaginal fluid samples will be collected for storage at all visits. These stored blood samples will be tested for HIV-RNA PCR and viral genotyping only in HIV-1 seroconverters, while HSV-2 serology, blood and vaginal fluid dapivirine concentrations measurement will be conducted in these seroconverters and a randomly selected control group of HIV-negative participants.

The rapid and confirmatory laboratory tests used in the HIV testing algorithm will detect both subtypes, HIV-1 and HIV-2. At the point of HIV seroconversion, the IP will be discontinued, and additional samples will be collected and tested for viral genotyping (blood and vaginal fluid), dapivirine concentrations (blood and vaginal fluid) and HSV-2 serology (blood). In addition, blood and vaginal fluid samples for viral genotyping will also be collected at the scheduled exit visit approximately 6 weeks following seroconversion. No further storage samples will be taken in these participants.

Adherence assessments will be conducted through an interviewer-administered questionnaire at all 4-weekly trial visits, except the exit visit. Participants will be provided with a diary card at each 4-weekly visit except the last product use and exit visits. The diary card will be self-administered, and record the participant's sexual activity and ring use during the 4-week period. The diary card is meant to be completed daily by the participant, and returned to the research centre at each 4-weekly visit, to serve as a memory aid for participants to review during adherence counselling, and the adherence questionnaires. Acceptability questionnaires will be administered at the second trial visit (week 4), and 24-weekly intervals from week 24 thereafter, until the last product use visit.

Twenty-four (24) to 36 weeks after trial initiation, each research centre will conduct 6 – 10 qualitative individual interviews with participants, and 6 – 10 qualitative individual interviews with male partners. These interviews will provide data on acceptability, sexual behaviour and adherence issues. The recruitment and sampling strategy will be specified in the Statistical Analysis Plan (SAP).

AEs will be assessed at all visits post-randomisation. In addition, safety laboratory assessments, pelvic examination, vaginal pH and vaginal flora as well as STI tests will be performed at 12-weekly intervals. Cervical cytology will be repeated at the end of the first and second year of IP use. Residual dapivirine levels in returned rings will be measured for a selected group of participants at pre-determined time-points.

#### **Last product use visit**

At the last product use visit, participants will return the last used rings; report any medical problems and/or concomitant medications since the last visit; provide locator and menses information; receive pre- and post-test HIV counselling, contraceptive counselling and HIV/STI risk-reduction counselling (including provision of male condoms); complete vaginal ring use, adherence and acceptability questionnaires; undergo a physical examination as well as a pelvic examination for evaluation of STIs and changes in vaginal flora; and provide blood and vaginal fluid specimens for storage, and specimens for pregnancy and HIV testing and safety laboratory assessments.

Each research centre will conduct 2 – 3 focus groups with participants who have been recruited for these groups at the last product use visit. Additionally, 6 – 10 qualitative individual interviews with male partners will be conducted at each research centre. These interviews will provide data on acceptability and adherence issues. The recruitment and sampling strategy will be specified in the SAP.

#### **Exit visit (6 weeks after ring discontinuation)**

Participants may be notified of any abnormal findings and asked to return to the research centre prior to the exit visit; as needed for treatment and/or referral. On the day of the scheduled exit visit, participants will return to the research centre to receive results from their pelvic examination/STI testing and safety laboratory assessments done at the last product use visit, and treatment or referral as needed. AEs and concomitant medications will also be recorded at this visit.

Participants will receive pre- and post-test counselling for HIV and undergo final HIV testing. HIV/STI risk reduction counselling (including provision of male condoms) and contraceptive counselling will also be provided at the exit visit. If a clinically significant gynaecological or other related AE remains unresolved at the time of trial completion, a clinical assessment will be made by the research centre's investigator or designated qualified physician and the IPM Clinical Physician or designee to determine whether continued follow-up of the AE is warranted.

Participants will then be considered to have completed trial participation, and informed that they may be re-contacted at a future date to be provided information about trial results including individual unblinding.

### **3.2 Trial Duration**

Each participant will be followed on the IP over a period of approximately 24 months (104 weeks).

Each participant will have an additional 6 weeks of follow-up after ring discontinuation. In total, each participant will complete approximately 25.5 months on the trial after enrolment.

### **3.3 Trial Population**

Approximately 1,650 sexually active HIV-negative women, 18 – 60 years of age, who understand the trial and can provide informed consent, will be enrolled and randomised in a 2:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a placebo vaginal ring.

Approximately 300 participants over 40 years of age will be enrolled in the trial.

#### **3.3.1 Inclusion Criteria**

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

1. Women  $\geq 18$  and  $\leq 60$  years of age, at screening, who can provide informed consent;
2. Available for all visits and consent to follow all procedures scheduled for the trial;
3. Self-reported sexually active (defined as an average of at least one penetrative penile vaginal coital act per month for the last 3 months prior to screening);
4. HIV-negative as determined by the HIV algorithm applied at screening and enrolment;
5. On a stable form of contraception as defined within section 5.4 and willing to continue on stable contraception for the duration of the clinical trial; unless post-menopausal or surgically sterilised;

6. Asymptomatic for genital infections at the time of enrolment (if a woman is diagnosed with any clinically significant treatable STI, she must have initiated treatment at least 1 week prior to enrolment and have completed the full course of treatment);
7. Willing to answer questions about adherence, sexual behaviour, and ring acceptability;
8. 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;
9. Willing to refrain from participation in another research trial using drugs, vaccines, medical devices, microbicides or oral pre-exposure prophylaxis investigational drugs for the duration of the IPM 027 trial;
10. Willing to refrain from use of vaginal products or objects including spermicides, lubricants, intravaginal medication, other vaginal rings, female condoms, cotton wool, rags, diaphragms, cervical caps (or any other vaginal barrier method), douches, drying agents and herbs within 14 days from enrolment and for the duration of the trial. Tampons are excluded from this list and may be used for the duration of the trial.

### 3.3.2 Exclusion criteria

Women who have any of the exclusion criteria below are not eligible:

1. Currently pregnant or last pregnancy within 3 months prior to screening;
2. Currently breast-feeding;
3. Women who have had a hysterectomy;
4. Participated in another research trial using drugs, medical devices, microbicides or oral pre-exposure prophylaxis agents within 60 days prior to screening;
5. Previously participated or currently participating in any HIV vaccine trial;
6. Untreated, clinically significant urogenital infections, e.g., urinary tract, or other sexually transmitted infections, or other gynaecological symptoms within 1 week prior to enrolment;
7. Has a Grade 2 or higher pelvic examination finding, according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; Addendum 1 Female Genital Grading Table for Use in Microbicide Studies;
8. History of significant urogenital or uterine prolapse, undiagnosed vaginal bleeding, diagnosed chronic and/or recurrent vulvo-vaginal candidiasis urethral obstruction, incontinence or urge incontinence;
9. Any gynaecological surgery within 90 days prior to screening;



10. Any Grade 2, 3 or 4 baseline haematology, chemistry or urinalysis laboratory value according to the according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events;
11. Any history of anaphylaxis or severe allergy resulting in angioedema; or a history of sensitivity/allergy to latex or a silicone elastomer;
12. Any history of diabetes mellitus and chronic use of oral corticosteroid therapy; and any uncontrolled serious chronic or progressive disease;
13. Cervical cytology at screening that requires cryotherapy, biopsy or treatment (other than for infection). Women with Grade 1 cervical cytology findings can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology);
14. Any condition(s) that, in the opinion of the investigator, might put the participant at risk, or interfere with the trial objectives, or adherence to trial requirements.

### **3.4 Participant Recruitment**

#### **3.4.1 Pre-Screening**

Research Centres may use formal or informal pre-screening tools in the community and in the research centre in order to pre-identify basic eligibility requirements of potential participants before actually screening for the trial. Formal IRB/IEC-approved pre-screens may include actual clinical procedures such as HIV, STI and pregnancy tests. Informal pre-screens may include recruiter/outreach worker potential participant checklists that identify basic eligibility criteria such as age, contraception, participant location within the area for the given time of the trial, ownership of a legal identification card, etc. The pre-screening methods may vary between centres according to target populations.

#### **3.4.2 Participant Recruitment and Accrual**

It is anticipated that eligible participants will be enrolled over a 6-month period (excluding the trial initiation and screening period) at each research centre. At regular intervals, the Principal Investigators, in consultation with the Sponsor will assess progress in recruitment and retention at each of the research centres and may reallocate enrolment numbers and targets across the research centres, as deemed necessary to achieve the enrolment targets. The enrolment period may be extended at the discretion of the sponsor in order to ensure sufficient participant numbers are reached to complete the trial accrual targets.

## 4. TRIAL VISITS AND PROCEDURES

### 4.1 Screening Visits

#### 4.1.1 Screening 1

**NOTE:** For potential participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility has been determined.

- a. Explain screening and trial procedures to the potential participant.
- b. If the potential participant agrees to be screened, obtain written informed consent (screening consent). Illiterate participants may provide a thumbprint or mark witnessed and signed by a person independent from trial staff. A comprehension assessment will be performed as part of the screening consent process.
- c. Assign a unique Participant Identification number to the potential participant. A confidential master log of screening participants, with demographic and locator information will be maintained.
- d. Conduct a preliminary 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 menses information, relevant medical history, and concomitant medication taken within the last 30 days (Refer to Section 5.6 for more details about relevant medical history).
- h. Perform urine pregnancy and urinalysis dipstick testing (microscopy only if indicated). Refer pregnant women to local prenatal clinic for support services (Refer to Sections 5.5 and 5.9).
- i. Provide HIV/STI risk-reduction counselling (including provision of male condoms) and contraceptive counselling. (Refer to Sections 5.2.2 and 5.4)
- j. Provide HIV pre- and post-test counselling. (Refer to Section 5.2.1)
- k. Perform HIV rapid testing as detailed in Section 5.3.
- l. Perform general physical examination (Refer to Section 5.7 for a description of the elements required in the general physical examination).
- m. Perform pelvic examination (Refer to Section 5.8). If 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.*

- n. Collect cervicovaginal swabs for STI testing and a specimen for cervical cytology (Refer to Sections 5.10 and 5.11).
- o. Collect blood samples by venipuncture for syphilis testing (RPR), and the following safety laboratory tests (Blood volumes specified in Appendix D):
  - haematology (FBC with differential and platelet count),
  - chemistry (sodium, potassium, phosphate, chloride, calcium, urea, creatinine, total bilirubin, ALT, AST and ALP). (Refer to Section 5.9)
- p. Invite potential participant to return to the research centre within no more than 4 weeks for the screening 2 and enrolment visit.

#### **4.1.2 Screening 2 (Within no more than 4 weeks [28 days] of Screening 1)**

- a. Obtain locator and menses information.
- b. Obtain and record any medical problems and concomitant medication since the screening visit. *NOTE: Record any conditions as part of the relevant Medical History (Refer to Section 5.6).*
- c. Perform urine pregnancy testing. If a woman is pregnant, she is not eligible for the trial. Refer pregnant women to the local prenatal clinic for support services (Refer to Section 5.5).
- d. Provide HIV/STI risk-reduction counselling; including provision of male condoms (Refer to Section 5.2.2).
- e. Provide HIV pre- and post-test counselling. (Refer to Section 5.2.1)
- f. Perform HIV rapid testing as detailed in Section 5.3. **NOTE:** *Research centres using venipuncture for HIV testing at screening 2 may opt to collect the enrolment storage samples (as described below) at the same time the screening 2 HIV test sample is drawn. If this option is taken, storage samples for participants who do not enrol will be destroyed according to local SOPs.*
- g. If the HIV and pregnancy tests are negative, perform a pelvic examination (Refer to Section 5.8). **NOTE:** *The potential participant must be asymptomatic for genital infections (and have initiated treatment for any STI diagnosed during screening at least 1 week prior to enrolment and have completed the full course of treatment) and have a normal pelvic examination at the time of enrolment.*
- h. If all inclusion criteria and none of the exclusion criteria are met, invite the woman to enrol immediately. **NOTE:** *At the discretion of the investigator or*

*designee, each potential participant may be retested once for safety laboratory tests before enrolment, within the 4-week screening period.*

## 4.2 Enrolment Visit

**NOTE:** *If the potential participant is menstruating at this visit, the entire visit should be rescheduled for two days after completion of menses, but must be completed within 4 weeks of screening 1. The enrolment visit may occur on the same day as screening 2 or subsequently; provided it is still within 4 weeks of screening 1.*

- a. If a potential participant agrees to enrol in the trial, obtain written informed consent (enrolment consent). Illiterate participants may provide a thumbprint or mark witnessed and signed by a person independent from trial staff. A comprehension assessment checklist will be used to support the enrolment consent process.
- b. Administer the baseline behavioural questionnaire.
- c. Provide and explain the use of the diary card to the participant.
- d. Dispense one vaginal ring to the participant according to the unique participant identification number assigned at screening 1.
- e. Collect specimen for assessment of vaginal flora and vaginal pH.
- f. Instruct the participant to insert the vaginal ring (Refer to Section 5.12). Perform brief digital examination to verify the vaginal ring has been properly placed.
- g. After ring insertion, the participant will remain in the research centre under observation for 30 minutes to be observed for immediate reactions (immediate reactions will be recorded as AEs).
- h. Provide adherence counselling, including contraceptive adherence, adherence to trial visit schedule and requirements and vaginal ring adherence. (Refer to Sections 5.4 and 5.13). Participants will be instructed to keep the ring inserted for a period of 28 consecutive days (4 weeks). 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. Adherence counselling will include information on actions that should be taken in the event of expulsion or removal.
- i. Collect a blood specimen by venipuncture for HSV-2 serology, HIV viral genotyping and HIV-RNA PCR sample storage (Blood volume specified in Appendix D). **NOTE:** *Research centres using venipuncture for HIV testing at screening 2 may have opted to collect these storage samples at the same time as the screening 2 HIV test sample.*
- j. Schedule the next visit.

### 4.3 Trial Visits

#### 4.3.1 4-Weekly Trial Visits (Weeks 4 to 104)

**(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  $\pm 7$  days. Although the visit window is  $\pm 7$  days, consecutive visits should be no less than 21 days and no more than 35 days apart).**

**NOTE:** Additional procedures for participants who test HIV-positive are described in Section 5.3 of the protocol.

- a. Update locator and menses information as necessary.
- b. Obtain and record any AEs and concomitant medications since the last visit.
- c. Collect and review the diary card and provide a new diary card. Administer the adherence questionnaire.
- d. Provide adherence counselling, including contraceptive adherence, adherence to trial visit schedule and requirements and vaginal ring adherence. (Refer to Sections 5.4 and 5.13). Participants will be instructed to keep the ring inserted for a period of 28 consecutive days (4 weeks). 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. Adherence counselling will include further details on actions that should be taken in the event of expulsion or removal.
- e. Administer the acceptability questionnaire (**NOTE: ONLY at the second trial visit (week 4) after enrolment, and at 24-weekly intervals thereafter, starting at week 24 until the last product use visit**).
- f. Provide HIV/STI risk reduction counselling; including provision of male condoms (Refer to Section 5.2.2).
- g. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).
- h. Perform HIV rapid testing as detailed in Section 5.3. (Additional procedures for participants who test HIV-positive are also described in Section 5.3 of the protocol).
- i. Perform urine pregnancy testing.
- j. Collect blood specimens by venipuncture for storage (Blood volume specified in Appendix D).
- k. Instruct the participant to remove the vaginal ring. Perform IP accountability.
- l. Collect vaginal fluid samples through the use of Tear Test Strips for storage (Refer to Section 5.15). **NOTE: For dapivirine concentration measurements, blood and vaginal fluid samples must be collected prior to removal of the vaginal ring. Blood and vaginal fluid samples will also be taken for analysis**

*following HIV seroconversion according to the HIV testing algorithm described in Section 5.3 (Blood volume specified in Appendix D).*

- m. Dispense a new vaginal ring and instruct participant to self-insert the new ring.
- n. Perform brief digital examination to ensure the ring is properly placed (Refer to Section 5.12).
- o. Schedule the next visit.

#### **4.3.2 12-weekly Trial Visits (Weeks 12, 24, 36, 48, 60, 72, 84 and 96)**

**(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of  $\pm 7$  days. Although the visit window is  $\pm 7$  days, consecutive visits should be no less than 21 days and no more than 35 days apart.)**

***NOTE:*** Participants will 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.

- a. Complete all 4-weekly trial visit procedures as detailed above. ***NOTE:*** A new vaginal ring will only be dispensed to the participant after vaginal fluid sampling for dapivirine concentration measurements and the pelvic examination have been conducted. Pelvic examination is described below.
- b. Perform pelvic examination (Refer to Section 5.8) and collect specimen for assessment of vaginal flora and vaginal pH, and cervicovaginal swabs for STI testing (Refer to Section 5.10). If 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 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.
- c. Obtain urine and blood specimens for safety laboratory assessments as listed in Section 4.1.1 (Blood volume specified in Appendix D).

#### **4.3.3 24-weekly Trial Visits (Weeks 24, 48, 72 and 96)**

**(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of  $\pm 7$  days. Although the visit window is  $\pm 7$  days, consecutive visits should be no less than 21 days and no more than 35 days apart).**

***NOTE:*** Participants will 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.

- a. Complete all 4-weekly and 12-weekly trial visit procedures as detailed above.

- b. Administer the acceptability questionnaire.
- c. Invite 6 – 10 participants to participate in an individual interview to be held at each research centre during weeks 24 – 36.
- d. Request permission from these participants to recruit their male partner for an individual interview, and recruit from this pool of partners until 6 – 10 of these interviews have been conducted at each research centre.

#### **4.3.4 Annual Visits (Weeks 52 and 104)**

**(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of  $\pm 7$  days. Although the visit window is  $\pm 7$  days, consecutive visits should be no less than 21 days and no more than 35 days apart).**

- a. Complete all 4-weekly trial visit procedures as detailed above.
- b. Collect a specimen for cervical cytology.

#### **4.3.5 Last Product Use Visit (or Early Discontinuation)**

**(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of  $\pm 7$  days. Although the visit window is  $\pm 7$  days, consecutive visits should be no less than 21 days and no more than 35 days apart).**

***NOTE:*** These trial procedures will also apply at the point of HIV seroconversion, and the visit will be considered the last product use visit for the participant.

- a. Update locator and menses information as necessary.
- b. Obtain and record any AEs and concomitant medications since the last visit.
- c. Collect the diary card.
- d. Administer the adherence questionnaire.
- e. Administer the acceptability questionnaire.
- f. Provide HIV/STI risk-reduction counselling (including dispensing of condoms) and contraceptive counselling (Refer to Sections 5.2.2 and 5.4).
- g. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).
- h. Perform HIV rapid testing as detailed in section 5.3. (Additional procedures for participants who test HIV-positive are also described in Section 5.3 of the protocol)
- i. Perform pregnancy testing and urinalysis dipstick testing (microscopy only if indicated).

- j. Collect blood specimen by venipuncture for syphilis testing (RPR) and safety laboratory tests (haematology and chemistry). Blood volume is specified in Appendix D.
- k. Collect blood specimen by venipuncture for sample storage (Blood volume specified in Appendix D).
- l. Perform physical examination.
- m. Collect vaginal fluid sample for storage. **NOTE:** *For dapivirine concentration measurements, blood and vaginal fluid samples must be collected prior to removal of the vaginal ring.*
- n. Instruct the participant to remove the last vaginal ring. Perform IP accountability.
- o. Perform pelvic examination (Refer to Section 5.8) and collect specimen for assessment of vaginal flora and vaginal pH, and cervicovaginal swabs for STI testing (Refer to Section 5.10). If pelvic examination indicates abnormal findings, e.g., any symptoms or evidence of genital infections, abrasions, ulcerations, etc., provide or refer for appropriate treatment.
- p. Schedule the exit visit.
- q. Each research centre will conduct 2 – 3 focus groups with participants who have been recruited for these groups at the last product use visit. Additionally, 6 – 10 individual interviews with male partners will be conducted at each research centre.

#### 4.4 Exit Visit (6 weeks after the Last Product Use Visit)

**(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of  $\pm 7$  days. Although the visit window is  $\pm 7$  days, consecutive visits should be no less than 21 days and no more than 35 days apart).**

**NOTE:** *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 5.3 (No further HIV counselling and testing will be done unless indicated for additional confirmatory testing).*

- a. Update locator information as necessary.
- b. Obtain and record any AEs and concomitant medications since the last visit.
- c. Provide final safety and STI laboratory results to participant.
- d. Provide HIV/STI risk-reduction counselling; including provision of male condoms (Refer to Section 5.2.2).
- e. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).



- f. Perform HIV rapid testing as detailed in Section 5.3.
- g. Exit the participant from the trial.

#### **4.5 Participant Retention**

The target retention rate during the trial is > 90% per annum. Retention rates will be monitored and tracked and any required action will be taken to address below-target retention rates. Once a participant is enrolled in the trial, trial staff will make every reasonable effort to retain her in the trial. This may include obtaining and checking locator information, home visits, issuing telephonic and in-person reminders of scheduled visits, and maintaining a schedule of enrolled participants as part of a strategy to achieve the target.

#### **4.6 Unscheduled Visits**

Unscheduled visits may be performed at any time during the trial for HIV or pregnancy testing, or if the participant is experiencing any problems, e.g., vaginal complaints, difficulties with re-inserting the ring in cases of accidental expulsion or removal, or accidental loss of the ring. 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. Laboratory testing may be performed during unscheduled visits, 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 & 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 clinic for a scheduled visit during the trial window, e.g., within  $\pm 7$  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 and applicable CRFs.

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 3 by the time the trial window has begun for Visit 4, i.e., within 7 days from Visit 4, Visit 3 will be considered missed. Trial procedures will be performed as scheduled for the current visit (e.g. Visit 4 in this instance) or as deemed necessary by the investigator or IPM Clinical Physician or designee. Missed visits will be documented as protocol deviations.

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 be put back on her original visit schedule.

#### 4.8 Early Discontinuation Visit

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 fails to follow protocol requirements which are deemed to be serious enough by the investigator to warrant a discontinuation, e.g., in the absence of an AE or discomfort, participant refuses to keep vaginal ring inserted for duration of the trial.
- Participant is lost to follow-up, i.e., research centre is unsuccessful (following reasonable attempts as defined in the local SOP) in contacting participant or bringing the participant back to the research centre and she misses 3 consecutive visits.
- Participant is confirmed to be pregnant.
- Participant tests HIV-positive according to the HIV-testing algorithm in Appendix C.
- If for safety reasons the investigator considers it in the best interest of the participant to discontinue her from the trial. Genital AEs that may warrant permanent IP discontinuation are described in the Clinical Management of Genital Diagnoses section of the Study Operations Manual. For laboratory investigations, any of the following abnormal parameters may apply:
  - Haemoglobin < 9.0 g/dL **or** < 1.40 mmol/L
  - Absolute Neutrophil Count (ANC): < 1000/mm<sup>3</sup> **or** < 1.0 x 10<sup>9</sup>/L
  - Absolute Lymphocyte Count (ALC): ≤ 500/mm<sup>3</sup> **or** ≤ 0.5 x 10<sup>9</sup>/L
  - Platelets: ≤ 90,000 ≥ 550,000/mm<sup>3</sup> **or** ≤ 90 x 10<sup>9</sup> ≥ 550 x 10<sup>9</sup>/L
  - Creatinine: > 1.4 x ULN
  - AST: > 3.0 x ULN
  - ALT: > 3.0 x ULN
- At the discretion of the investigator, Sponsor, IRB/IEC or the government health agency.

**NOTE:** The DSMB may provide recommendations to the Sponsor or to the investigators regarding participants who should be discontinued, or allowed to continue in the trial.

The date, time, and reason for permanent trial discontinuation will be noted in the source documents and applicable CRFs. All participants who prematurely discontinue 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 6 weeks after product discontinuation can be completed.

Participants who miss three (3) consecutive trial visits and cannot be contacted during this time will be considered lost to follow-up and will be permanently discontinued from the trial. Reasonable contact attempts will be made according to the locator information provided by the participant and local SOPs, and final 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 clinic chart (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 communication with the IPM Clinical

Project Manager, depending on the reason for the missed visits. Participants who discontinue early from the trial will not be replaced.

#### **4.9 Premature Discontinuation of the Trial**

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

### **5. TRIAL PROCEDURE DETAILS**

#### **5.1 Informed Consent**

##### **5.1.1 Informed Consent Process**

The informed consent documents will describe the purpose of the trial, the procedures to be followed, and the risks and benefits of participation. Two consent forms will be administered at screening 1 and at enrolment: a screening consent form and an enrolment consent form.

The informed consent process will include adequate time for each potential participant to have any trial 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 screening consent form. The form will be signed and dated by the person administering the consent process as delegated by the Principal Investigator according to Research Centre SOP. If a potential participant is functionally illiterate, the 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 observer. After the potential participant has verbally consented and provided a thumbprint or mark which is witnessed by the impartial observer, this independent observer will sign and date the consent form as a witness.

Prior to enrolment, eligible participants who agree to participate in the trial will sign and date the enrolment consent form. It will be signed and countersigned in the same manner as the screening consent form.

The signed and dated consent forms will be retained at the research centre. A copy of the signed and dated consent forms will be offered to the participant. If the participant is not willing to receive the forms, the second copy will be retained at the research centre. Likewise, during the trial, signed and dated consent document 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 forms.

Documentation of the participant's refusal to accept a copy of the informed consent 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 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 consent documents or addenda to the original consent documents in a timely manner and will be signed and dated by the participant in the same manner described above.

### **5.1.2 Comprehension Checklist**

Trial staff will assess the candidate participant's understanding of informed consent information prior to obtaining a signature on the informed consent form at Screening 1 and Enrollment. At enrolment, this assessment will be done using a standardised comprehension checklist. All comprehension problems that are discovered during the assessment will be discussed until staff are satisfied that the participant can verbalise her understanding of the issue. This process will be documented on the comprehension checklist. The comprehension 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.

## **5.2 HIV Counselling**

### **5.2.1 HIV Pre- and Post-Test Counselling**

At screening and all trial visits where HIV testing is performed, pre- and post-test counselling will be provided according to the CDC Revised 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.

### 5.2.2 HIV/STI Risk Reduction Counselling

HIV/STI risk reduction guidelines will be developed in conjunction with local voluntary counselling and testing (VCT) guidelines. Counselling will be provided at both screening visits, and all trial visits including the exit visit. Efforts will be made to ensure standardisation of risk reduction counselling at the trial clinics.

**NOTE:** *Risk reduction counselling will include recommendation of male condom use. Participants will be provided with a supply of male non-spermicidal condoms during each trial visit. The use of female condoms is not permitted in this trial, in order to protect the integrity of the lower genital tract and reduce the possibility of AEs due to agents other than the investigational product.*

## 5.3 HIV Testing and Management

### 5.3.1 Screening 1

The details of the HIV rapid testing kits will be specified in the Laboratory Manual. At screening 1, potential participants will be tested for HIV using a highly sensitive antibody Rapid test (Test 1). If the test result is non-reactive, the participant could potentially be enrolled in the trial if she is otherwise eligible. If Test 1 is reactive, the potential participant will be retested using a highly specific HIV antibody Rapid test (Test 2). If Test 2 is reactive, the woman is considered to be HIV-infected and not eligible for enrolment. Initial counselling services will be provided at the research centre and women 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 2 is non-reactive, (yielding discordant results from Test 1), a highly specific HIV antibody Test 3 will be performed for all discordant results. If Test 3 is reactive then the potential participant is considered to be HIV-infected and is not eligible for enrolment. If Test 3 is non-reactive, the person is considered to be potentially HIV-negative and can be given a date for enrolment into the trial. Refer to Appendix C: HIV Testing Algorithms.

**NOTE:** *For the purposes of HIV rapid testing at screening, blood may be obtained by finger prick or venous sampling. However, if Test 2 is required, this must be done on a venous sample. 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 027 HIV testing algorithm, as part of the screening process and documented as such.*

### 5.3.2 Screening 2 and Enrolment

On the scheduled day of possible enrolment, as part of the screening 2 procedure, the participant will be tested for HIV and will only be enrolled if the result is considered to be HIV-negative and the participant is otherwise eligible. Test 1 will be performed. If the test is 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-negative and eligible for enrolment. After enrolment, a blood sample will be obtained by venipuncture to be sent for sample storage at a central laboratory, for potential HIV-RNA PCR testing if the participant seroconverts (blood volume specified in Appendix D). Research centres using venipuncture for HIV testing at screening 2 may opt to collect the storage samples at the same time the screening 2 HIV test sample is drawn. If this option is taken, storage samples for participants who do not enrol will be destroyed according to local SOPs.

If HIV Test 1 is reactive, the potential participant will be retested using Test 2, which must be done with a venous sample. If Test 2 is reactive, the woman will be considered HIV-infected 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. If Test 2 is non-reactive the result is discordant. Rapid Test 3 will be performed for all discordant rapid tests. If Test 3 is reactive then the potential participant is considered to be HIV-infected and not eligible for enrolment. If Test 3 is non-reactive, the person is considered to be probably HIV-negative BUT the participant is NOT eligible for enrolment. She will be counselled and referred to the local health facilities for appropriate follow-up. The participant can return to the research centre for rescreening after 8 weeks for one more cycle of HIV testing. Refer to Appendix C: HIV Testing Algorithms.

### 5.3.3 Trial Visits

Both the 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 C) will be applied for all 4-weekly trial visits, including the last product use visit. HIV-testing while the participant is enrolled in the trial will be performed on blood samples obtained by venipuncture (blood volumes specified in Appendix D).

If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative and continue using the IP. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2 (done on the same blood sample). If Test 2 is reactive, the participant is considered to have been infected while on the trial, and will be permanently discontinued from the IP. Additional confirmatory testing will be performed by Western Blot or another confirmatory test where appropriate. Additional testing will be performed on stored samples of seroconverters as described in Section 5.15. Nucleic acid-amplification testing (NAAT) by an HIV-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.

If Test 2 is non-reactive, the result is discordant and 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 then the participant is considered to be HIV-infected. The IP is stopped immediately and a sample drawn for endpoint confirmation (by Western Blot). Nucleic acid-amplification testing (NAAT) by an HIV-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 probably HIV-negative. The participant will continue on the IP and be requested to return for repeat testing after two weeks. In such cases the research centre will notify the IPM Clinical Physician or

designee. If a similar result is obtained on testing after two weeks, the process of repeat testing after 2 weeks may continue for a third cycle.

All enrolled participants will, in addition, have blood taken at each trial visit to be stored at a central laboratory, for possible HIV-RNA PCR 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 the PCR test result is negative. This will be done to approximate the period of HIV infection. If the enrolment HIV-RNA PCR test result is positive, the participant is not considered to have been infected while using the IP.

Additional blood (blood volume as specified in Appendix D) and vaginal fluid samples will also be obtained for analysis at the point of HIV seroconversion according to the HIV testing algorithm described above. Stored samples (blood and vaginal fluids) will also be analysed retrospectively as described in section 5.15.

Any participant who is confirmed HIV-positive while on the trial and will be discontinued from the IP. Trial procedures relevant to the last product use visit as detailed in Section 4.3.5 will be performed, and an exit visit will be scheduled approximately 6 weeks 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 (IPM 007A).

#### 5.3.4 Exit Visit

At the exit visit, the participants will be tested using the same testing algorithm. If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2. If Test 2 is reactive, this will be considered an HIV seroconversion after product discontinuation. This 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 an HIV-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.

If Test 2 is non-reactive, the result is discordant. HIV Rapid Test 3 will be performed for discordant rapid test results. If Test 3 is reactive then the participant will be considered to be HIV-infected. 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-negative and will be counselled appropriately. Refer to Appendix C: HIV Testing Algorithms.

As stated in Section 5.3.3 above, an exit visit will be scheduled approximately 6 weeks following HIV-seroconversion and IP discontinuation. Blood and vaginal fluid samples for viral genotyping will be collected from these participants. Additional trial procedures for exit visits scheduled following HIV seroconversion are described in Section 4.4 (No further HIV counselling and testing will be done unless indicated for additional confirmatory testing).

**NOTE:** Up to 15% of all HIV rapid test samples will be retested at a central laboratory, for quality control purposes. Details of this testing will be provided in the Laboratory Manual.

*The Laboratory Manual will also provide details of the IPM specified Test 1; Test 2 and Test 3.*

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 (PMTCT) services.

The research centres will inform IPM Medical Safety of any new HIV infections within 24 hours of diagnosis. The applicable regulatory authorities and ethics committees who require expedited notification of HIV seroconversions 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.

#### **5.4 Management of Contraception**

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

Stable contraception is defined, for the purposes of the trial, as surgical sterilisation at least 3 months prior to enrolment OR one of the following:

Participants who have used contraceptives for at least the preceding year should be on the same:

- Oral contraceptive regimen for at least 2 months prior to enrolment, OR
- Transdermal contraceptive patch for at least 2 months prior to enrolment, OR,
- Long-acting injectable progestins for at least 2 consecutive injections, OR,
- Subcutaneous implant inserted at least 3 months prior to enrolment, OR
- An IUCD inserted at least 3 months prior to enrolment.

Participants who have newly commenced contraceptive use or have recommenced contraceptive use after a period of greater than 6 months should be on the same:

- Oral contraceptive regimen for at least 3 months prior to enrolment, OR
- Transdermal contraceptive patch for at least 3 months prior to enrolment, OR,
- Long-acting injectable progestins for at least 6 months, OR,
- Subcutaneous implant inserted at least 3 months prior to enrolment, OR
- An IUCD inserted at least 3 months prior to enrolment.

As referred in the inclusion criteria in Section 3.3.1, the use of contraceptive rings will not be allowed.

In order to address challenges that participants may experience in consistently obtaining reliable contraception, research centres will provide participants with contraceptives from enrolment for the duration of the trial. The contraceptives provided will be consistent with what is available locally and what the participant had been using prior to enrolment. Alternatively, participants will be referred to the local family planning clinic if a referral



system has been implemented. Under supervision of the investigator or designated qualified personnel, the participant may switch from one contraceptive method to another, provided that stable contraception is maintained.

Contraceptive counselling will be provided at screening and all trial visits; including the last product use and exit 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 5.5.

## **5.5 Pregnancy Testing and Management**

A urine pregnancy test will be performed at all scheduled trial visits while the participant is using the IP 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.

If a participant tests positive for pregnancy while on the IP, ring use will be discontinued immediately, and she will be referred to a local prenatal clinic for medical services. The research centres will be asked to report all pregnancies to IPM within 24 hours of confirming a positive pregnancy test. A confirmatory serum pregnancy test may be requested at the discretion of the investigator or a designated qualified 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 after discussion with the IPM Clinical Physician or designee.

Women who become pregnant and HIV positive during the trial will be referred for appropriate Prevention of Mother-to-Child Transmission (PMTCT) services.

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.

## **5.6 Demographics and Medical History**

At screening 1, basic demographic information will be obtained. At both screening 1 and 2, relevant medical history will also be collected, 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.

## **5.7 Vital Signs and Physical Examination**

A general physical examination will also be conducted at screening 1 and the last product use visit; which includes weight, vital signs, 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 screening 1. A symptom-directed physical examination will be conducted at screening 2 and as needed throughout the trial.

## **5.8 Pelvic Examination**

A pelvic examination will be performed at screening 1 and 2 and at 12-weekly trial visits, including the last product use visit, 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 will be investigated and the source identified. A follow-up pelvic examination will be performed to ensure resolution of the condition.

## **5.9 Safety Laboratory Assessments**

Safety laboratory assessments will be conducted at screening 1 and at all 12-weekly trial visits thereafter; until the last product use visit. These safety tests will include urine obtained for urinalysis dipstick testing (urine microscopy as indicated only) and blood drawn by venipuncture for laboratory testing (haematology, chemistry, including renal and liver functions). Haematology will include full blood counts, differential, and platelet count. Chemistry tests will include electrolytes (sodium, potassium, chloride, phosphate and calcium), renal functions (urea and creatinine), liver functions (total bilirubin, AST, ALT, and ALP). Details of blood volumes are specified in Appendix D. At the discretion of the investigator or designee, each potential participant may be retested once for safety laboratory tests.

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

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

## 5.10 STI Testing and Management

### 5.10.1 STI Testing

Cervicovaginal samples will be collected for STI testing at screening 1 and at 12-weekly visits. All participants will be evaluated for *Trichomonas vaginalis* (TV), *Neisseria gonorrhoea* (NG) and *Chlamydia trachomatis* (CT). Pelvic samples will also be collected for assessment of vaginal flora and vaginal fluid pH at enrolment and 12-weekly visits.

At screening 1 and at the last product use visit, blood will be collected by venipuncture for Syphilis (RPR) testing (Blood volume specified in Appendix D). TPHA/TPPA will be performed if RPR reactive.

Blood samples will be stored at enrolment and at every scheduled trial visit for HSV-2 serology. Testing will be conducted in HIV-1 seroconverters and a randomly selected control group of HIV-negative participants. In addition, a blood sample for HSV-2 serology will be collected at the point of confirmed seroconversion.

Additional descriptive information regarding specimen collection to test for STIs and vaginal flora, and processing for all tests will be detailed in the Laboratory Manual.

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

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

### 5.10.2 STI Management

Participants will be treated at the research centre or referred to a local health facility; according to local STI Treatment Guidelines. During routine trial visits, all participants who present with STIs will be managed syndromically; however, cervicovaginal swabs will also be collected from these participants in order to document the aetiological diagnosis. Aetiological management may be applicable following 12-weekly STI testing, according to the aetiological diagnosis.

The *Clinical Management of Genital Diagnoses* will be detailed in the Study Operations Manual for guidelines to determine whether the vaginal ring requires temporary or permanent removal, as well as follow-up recommendations. To ensure that participants are not treated with topical urogenital treatments, they will be instructed to seek treatment at the research centre and not from local physicians, should they experience any symptoms between scheduled visits. All cases of symptomatic vulvovaginal candidiasis will be treated with oral fluconazole.

## 5.11 Cervical Cytology

A cervical cytology sample will be collected at screening 1, week 52 and week 104. Women with Grade 1 abnormal cervical cytology findings at screening can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology). Cervical cytology will be repeated according to the local standard of care, or after 6 months; whichever is more conservative.

Women with Grade 1 cervical cytology findings at week 52 will continue using the IP, and cervical cytology will be repeated according to the local standard of care, or after 6 months; whichever is more conservative.

Women with Grade 2 or 3 cervical cytology findings at week 52 will discontinue IP use and will be referred for appropriate medical services. These referral systems 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.

### **5.12 Vaginal Ring Insertion and Placement Check and Ring Removal**

At the enrolment and 4-weekly trial visits, participants will insert their vaginal rings under clinic supervision. The participant will be instructed to wash her hands thoroughly, 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 wash her hands thoroughly again. A brief digital examination will be performed immediately after by an appropriately qualified and trained trial staff member as designated by the investigator, to verify proper placement of the ring. If upon digital examination the ring is not inserted correctly, the investigator or nurse will allow the participant a maximum of 2 additional attempts to re-insert the ring properly or provide assistance as required to put the ring in place. At all trial visits when a pelvic examination is performed, the participant will remove the ring prior to the examination. If the participant requests help with either removal or re-insertion of the vaginal ring, or after she has made a maximum of 3 attempts to remove/re-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 Study Operations Manual.

### **5.13 Vaginal Ring Adherence Counselling**

At all 4-weekly trial visits except the last product use and exit visits, participants will receive vaginal ring adherence counselling at the time of ring insertion. Research centre staff will counsel participants to refrain from removing the ring (except as directed during clinic visits) and from using concomitant vaginal products or other objects. However, tampon use is permitted. Research centre staff will also provide instructions for re-insertion 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.

If, for any reason, the participant is non-adherent in her 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 in the source documents and applicable CRFs. The behavioural questionnaires will document the reason for non-adherence and additional adherence counselling will be provided.

## **5.14 Questionnaires**

### **5.14.1 Baseline Behavioural Questionnaire**

The baseline behavioural questionnaire will be administered at the enrolment visit. This questionnaire includes behavioural, acceptability and adherence questions about sexual behaviour, vaginal practices and anticipated adherence and acceptability issues.

### **5.14.2 Adherence Questionnaire**

Trained staff will administer adherence questionnaires at 4-weekly visits, from week 4, until the last product use visit. Adherence questionnaires include questions about ring use. The diary cards will serve as a memory aid for the participant during the adherence questionnaire session, and will be collected at each 4-weekly visit.

### **5.14.3 Acceptability Questionnaire**

Trained staff will administer an acceptability questionnaire at week 4 and at 24-weekly intervals, starting from week 24 until last product use visit. Acceptability questionnaires will include questions about use of the vaginal ring, vaginal practices, sexual behaviour, worries and concerns about ring use, male partner issues, and willingness to use a proven effective vaginal ring.

### **5.14.4 Qualitative interviews**

Qualitative interviews (focus groups and individual interviews) will be conducted at two points in the trial 24 – 36 weeks after trial initiation, and following last product use visits. Focus groups and individual interviews will be conducted with a sample of trial participants, and individual interviews will be conducted with a sample of participant's male partners. These interviews will provide further information on acceptability and adherence for the exploratory objectives.

## **5.15 Sample Storage and Analysis**

Blood and vaginal fluid samples will be collected for storage at a central laboratory at all trial visits, to be tested subsequent to confirmed HIV-1 seroconversion. Blood samples for HSV-2 serology, HIV viral genotyping and HIV-RNA PCR will be stored from enrolment (or screening 2 for research centres that use this option). Testing will be conducted on stored samples from confirmed HIV-1 seroconverters and specifically for dapivirine concentration measurements and HSV-2 serology from both HIV-1 seroconverters and a random sample of HIV-negative participants. Blood samples will be collected by venipuncture and vaginal fluids will be collected through the use of Tear Test Strips. For dapivirine concentration measurements, blood and vaginal fluid samples must be collected prior to removal of the vaginal ring. Further details regarding these procedures will be provided in the Laboratory Manual (which forms part of the Study Operations Manual).

As described in Section 5.3.3 above, additional blood (blood volume as specified in Appendix D) and vaginal fluid samples will also be obtained for analysis at the point of HIV seroconversion according to the HIV testing algorithm described in Section 5.3.

The blood samples will be tested retrospectively for HIV-RNA PCR and HSV-2 serology, while both blood and vaginal fluid will be tested for dapivirine concentrations and viral genotyping. Plasma and vaginal fluid drug concentrations will be used to evaluate the relationship between drug concentrations and HIV seroconversion. HSV-2 serology and dapivirine concentration analyses will be conducted in HIV-1 seroconverters and a randomly selected control group of HIV-negative participants.

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

Any residual specimens will be destroyed at the end of the trial after all protocol-required and quality assurance testing has been completed.

### **5.16 Method of Treatment Assignment**

Participants who meet all of the trial inclusion criteria and no exclusion criterion at baseline will be randomly assigned in a 2:1 ratio to one of two groups receiving either the vaginal ring containing dapivirine or the placebo vaginal ring respectively. Randomisation will be stratified by research centre and age at the time of enrolment ( $\leq 40$  years of age,  $> 40$  years of age) using a pre-specified block size and will be determined via the use of an automated randomisation system to ensure balance of the treatment assignments. Both groups will use a 4-weekly administered ring continuously for the duration of trial participation and have a follow-up visit 6 weeks after ring removal.

A master randomisation list for the trial will be generated which links each participant identification number to a trial treatment assignment (dapivirine ring or placebo ring). At each research centre, as each new participant enters the trial, a unique participant identification number will be assigned to that participant using an automated response system.

### **5.17 Reimbursement**

Participants will be reimbursed for any travel costs incurred as per local regulations. Reimbursements will be made after the completion of each trial visit. Research centre specific reimbursement amounts will be documented in the trial informed consent approved by the applicable IRB/IEC.

### **5.18 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.

## 5.19 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.

## 5.20 Study Operations Manual

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

# 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 drug substance dispersed in a platinum-cured silicone matrix. The dimensions of the ring are 56 mm and 7.7 mm – the outer diameter and cross sectional diameter, respectively. The dapivirine silicone elastomer vaginal matrix ring is designed to provide sustained release over a minimum of 28 days.

The placebo ring composition is the same as the dapivirine ring with the exception of the absence of dapivirine, and inclusion of titanium dioxide USP colourant. Pharmacopoeial grade titanium dioxide is included as a colourant to maintain blinded conditions during clinical evaluation. Details regarding the composition of the dapivirine and placebo rings are included in the IB.

Silicone elastomer vaginal rings have already been developed and approved as delivery methods for medications. For example, Pfizer (formerly Pharmacia and Upjohn Company) has marketed Estring<sup>®</sup> (estradiol vaginal ring), a vaginal ring that is also made from silicone elastomer and contains estradiol used to treat local symptoms of urogenital atrophy, since 1993. Prior to the launch of Estring<sup>®</sup>, the biological safety of the silicone elastomer was studied in various *in vitro* and *in vivo* test models. The results show that the silicone elastomer is non-toxic, non-pyrogenic, non-irritating, and non-sensitising<sup>9</sup>. Femring<sup>®</sup> (estradiol acetate vaginal ring), a hormone replacement product approved in June 2003 by the United States (U.S.) Food and Drug Administration (FDA) treats menopause-induced vasomotor symptoms (e.g., hot flashes) and symptoms of vulvar and vaginal atrophy (e.g., dryness)<sup>9</sup>. Although these rings are not exactly the same as the IPM ring, the extensive clinical trial and post-marketing experience gained from these products provides further assurance of the safety of silicone elastomer rings as vaginal drug delivery devices.

The Dapivirine 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. 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 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 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 Randomisation**

A randomisation schedule will be generated and validated according to specifications required for IPM's process of packaging and dispensing. The schedule will contain participant identification numbers and treatment assignment. At each research centre, each enrolled participant will be assigned a participant identification number using an automated response system.

## **6.4 Blinding and Unblinding**

The Principal Investigator or his/her designee will be able to unblind each enrolled participant, through the automated system, if necessary. If during the course of the trial a medical emergency requires knowledge of the test agent used by a particular participant, the trial blind or code may be broken for that specific participant, after discussion with the IPM's Clinical Physician or designee whenever possible. Any unblinding of participant treatment assignments will be justified and explained in the source documents and applicable CRF and reporting forms. If the blinding code is broken by the Principal Investigator or his/her designee, the participant will be withdrawn from the trial and followed up if appropriate. The blinding and unblinding process will be performed by the automated response system.

## **6.5 Investigational Product Storage**

The recommended storage condition for the dapivirine and placebo rings is 15°C to 30°C. 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.

The investigator (or pharmacist) will maintain an inventory and acknowledge receipt of all shipments of IP. The automated response system will also be used to confirm receipt of and activate dispensed kits.



## 6.6 Investigational Product Administration

Participants will self-insert a new vaginal ring at enrolment and each 4-weekly visit through the period of trial participation. A brief digital examination will be performed by an appropriately delegated trial staff member at each 4-weekly trial visit to ensure the ring is properly placed. Participants should continue ring use through menses.

## 6.7 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 it. If the vaginal ring is expelled and cannot be successfully reinserted, the ring should be appropriately rinsed and stored in a clean place, until the earliest possible opportunity the participant can return for reinsertion of a new ring at the clinic. After second expulsion the IPM Clinical Physician should be consulted with regards to appropriate follow up action.

The participant 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 return to the clinic. Also in cases where a ring is removed due to a genital AE, a new ring will be dispensed and inserted. Visits associated with expulsion or loss of rings will be regarded as unscheduled visits and management thereof will be on a case by case basis following discussion by the investigator with the IPM Clinical Physician or designee, unless the visit is within the  $\pm 7$  days window period of the next scheduled visit.

## 6.8 Investigational Product 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 will be destroyed at the end of the trial according to IPM instruction and local regulatory requirements.

## 6.9 Concomitant Medications & Products

All prescription and non-prescription medications, including any treatment for STIs and other reproductive tract infections, will be collected and recorded on the source documents and applicable CRFs.

All cases of symptomatic candidiasis will be treated with oral fluconazole. Concomitant use of vaginal products or other objects including spermicides, lubricants, intravaginal medication, other vaginal rings, female condoms, cotton wool, rags, diaphragms, cervical caps (or any other vaginal barrier method), douches, drying agents and herbs are prohibited for the duration of the trial. **NOTE:** *If any of these products are used, this will be considered a protocol deviation and will be documented on the source document and*

*applicable CRFs. Tampons are not included in this list and may be used for the duration of the trial.*

## 7. ADVERSE EVENTS

### 7.1 Definition

An adverse event (AE) is any untoward medical occurrence during the course of a trial in a participant who received an investigational product at any dose, which does not necessarily have a causal relationship with the investigational product. 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 investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational medicinal product). Final determination of whether an event is considered unexpected will be made by IPM, but 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 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 (treatment assignment) at Visit 1 will be reported as a pre-existing condition under Medical History. All AEs occurring during the trial will be recorded in the source documents and applicable CRFs.

If possible, a specific disease or syndrome rather than individual associated signs and symptoms should be recorded by the investigator. 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 is identified, or until the investigator does not expect any improvement or worsening of condition/symptoms. If a related AE remains unresolved at the participant's last trial 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 Study Operations Manual.

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 or causal relationship to the investigational product administration. The AE is clearly explained by another cause (concurrent disease, concomitant medication, environmental or toxic factors, etc.).
- **Related**  
There is a reasonable causal relationship between the investigational product and the AE. 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 Events

### 7.4.1 Serious Adverse Event Definition

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that at any dose meets any of the following criteria:

- 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 inpatient hospitalisation or prolongation of existing hospitalisation.  
This criterion applies if the event requires inpatient hospitalisation and results in an overnight stay in hospital or, in the opinion of the investigator, prolongs an existing hospitalisation. A hospitalisation (including hospitalisation for an elective procedure or routinely scheduled treatment) 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.
- Is an important and significant medical event that may not be immediately life threatening or result in death or hospitalisation but, based upon appropriate medical judgment, may jeopardise the participant or require intervention to prevent one of the other outcomes listed above. e.g., bronchospasm requiring intensive treatment in an emergency room or at home.

**NOTE:** An SAE need not be severe in nature to meet any of the above criteria.

All SAEs that occur from the time the participant is enrolled (receives treatment assignment) through the duration of the trial, whether considered to be associated with investigational product or not, must be reported to the IPM Medical Safety Physician or designee within 24 hours of the research centre becoming aware of the event. All SAEs should be reported using the designated Immediately Reportable Event (IRE) Report Form.

The IRE Report Form will be completed with all available information at the time of reporting. The investigator is required to write a detailed written report and complete SAE follow-up in a timely manner until the SAE returns to baseline, the participant returns to normal health or until the investigator does not expect further improvement or worsening

of the event. Medical records may be requested by IPM to assist in assessing relatedness and severity of the SAE, and for possible submission to Regulatory or Health authorities. To maintain confidentiality, the participant's name will be blacked out and replaced with the Participant Identification Number and initials on any medical records submitted.

More details on SAE reporting requirements are described in a separate Safety Reporting Plan.

#### **7.4.2 Serious Adverse Event Contact Information**

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

The following email will be used for communication with the Medical Safety team regarding any IREs: [safetyreports@ipmglobal.org](mailto:safetyreports@ipmglobal.org).

IPM will process all safety reports. The Medical Safety team will review all SAEs and generate the necessary queries.

#### **7.4.3 Sponsor Notification of SAEs to Regulatory Agencies**

All SAEs will be reported according to the guidelines of the local ethics and regulatory agencies in the countries in which IPM clinical trials are being conducted. Any unexpected SAE which is deemed to be Related to the investigational product will be considered "associated with the use of the investigational product" and thus IPM will notify appropriate regulatory authorities of the event in an expedited manner unless policies of local regulatory authorities mandate such reporting by the trial research centres.

Any unexpected SAE deemed to be Not Related will not be reported to regulatory authorities in an expedited manner unless otherwise requested by the local authorities.

#### **7.4.4 Research centre Notification of SAEs to Local Ethics Committee or Local Health or Regulatory Authorities**

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

### **7.5 Immediately Reportable Events**

In addition to the SAEs the following events will be considered Immediately Reportable events (IRE) and will be reported to IPM within 24 hours:

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

## **7.6 Safety Monitoring**

The IPM 027 trial team will monitor safety and participant recruitment throughout the trial for all participants. Safety data from the trial will be evaluated at predetermined regular intervals by an independent Data and Safety Monitoring Board (DSMB). The DSMB has the option to recommend stopping the trial at any point, if warranted, based on AEs observed during the trial or other concerns regarding participant safety or trial conduct.

Close monitoring by the DSMB will be necessary to evaluate trial progress and respond to occurrences of toxicity in a timely manner. Rates of accrual, data queries, trial product adherence, follow-up, and AE incidence will be monitored by the DSMB on a regular basis. The DSMB will meet via conference call at predetermined intervals during the trial; ad hoc calls may be convened if requested by the DSMB or IPM. A separate DSMB charter will describe the DSMB composition and its charges related to the trial.

## **8. DATA MANAGEMENT**

### **8.1 Data Handling at Research centres**

All trial data will first be collected on designated source documents and then recorded on Case Report Forms (CRFs) with the exception of the Behavioural, Acceptability and Adherence questionnaires, 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 Study Operations Manual. Qualitative data (focus groups and individual interviews) will be audio-recorded, password protected, and transcribed, following standardised procedures to be specified by IPM.

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.

### **8.2 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 available for review to the Sponsor or representative(s), IRB, IEC and other regulatory inspectors to ensure that the collected data is consistent with the CRFs and has been completely and accurately reported as required by the trial protocol.

## **9. STATISTICAL METHODS**

### **9.1 General Design**

IPM 027 is a Phase II clinical trial that has been designed to assess the long-term safety of dapivirine administered in a silicone elastomer vaginal ring (Ring-004) containing 25mg of dapivirine and inserted once every 4 weeks; among approximately 1,650 healthy, HIV-negative, sexually active women aged 18 – 60 years – as compared with a placebo vaginal ring.

Individuals meeting all inclusion criteria and no exclusion criteria will be randomised in a 2:1 ratio to either the investigational product or a placebo vaginal ring. To maintain the treatment ratio within each research centre and to ensure that a similar balance is preserved within the subgroup of participants over 40 years of age, randomisation, via an automated randomisation system, will be stratified by research centre and age group ( $\leq 40$  years of age,  $> 40$  years of age;  $N = 1,350$  and  $N = 300$  respectively), using a pre-specified block size.

All enrolled participants will self-insert a vaginal ring (either placebo or containing dapivirine) at enrolment to be worn continuously for the duration of the trial participation period, with ring replacements at 4-weekly intervals until the last product use visit. Participants will be asked to return to the research centre at 4-weekly intervals post-enrolment to monitor safety outcomes (AEs and SAEs). A follow-up visit will be conducted 6 weeks after removal of the last ring (last product use visit). In addition, all participants will be tested at 12-weekly visits for curable STIs and changes in vaginal flora and tested for pregnancy at all trial visits. Safety laboratory assessments will be performed at 12-weekly intervals. Blood and vaginal fluid samples will be collected for storage at all visits. These stored samples will be tested for HIV-RNA PCR (blood) and viral genotyping (blood and vaginal fluid) only in HIV-1 seroconverters, while HSV-2 serology (blood), blood and vaginal fluid dapivirine concentrations measurement will be conducted in HIV-1 seroconverters and a randomly selected control group of HIV-negative participants. Adherence, sexual behaviour, vaginal practices and condom use pre-randomisation and during follow-up will also be assessed at all 4-weekly trial visits. Ring acceptability will be assessed at week 4 after enrolment and at 24-weekly intervals thereafter.

### **9.2 Trial Endpoints**

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

### **9.3 Primary Trial Hypotheses**

From previous safety trials of dapivirine, there is reason to believe that the investigational product is safe and well tolerated. Thus, it is hypothesised that the dapivirine vaginal ring will be safe and well tolerated in healthy HIV-negative women, aged 18 – 60 years, over a 24-month period of exposure.

## 9.4 Sample Size and Power Calculations

IPM 027 will be conducted in a sample of approximately 1,650 HIV-negative women in a 2:1 ratio, such that 1,100 participants will be assigned to the investigational product and 550 participants will be assigned to the placebo ring. The sample size is determined based on the probability of detecting rare AEs in the active arm and the ability for the trial to detect differences in the proportion of primary endpoints between the two trial arms assuming an AE rate of 1% in the placebo arm.

In a trial with 1,000 participants assigned to the investigational product, there is a 95% probability of detecting an AE occurring at a rate of 0.3% or higher. The table below presents the probability of detecting at least one and at least two AEs in a sample of 1,000 participants assigned to the investigational product for varying AE rates. A sample of this size has a high probability of detecting at least one AE that occurs at a rate of 0.3%; the probability of detecting at least two AEs is high for events with rates greater than 0.5%. A trial of this size is sufficient to observe at least three or higher events during the trial duration if the event occurs at a rate less than 0.6%.

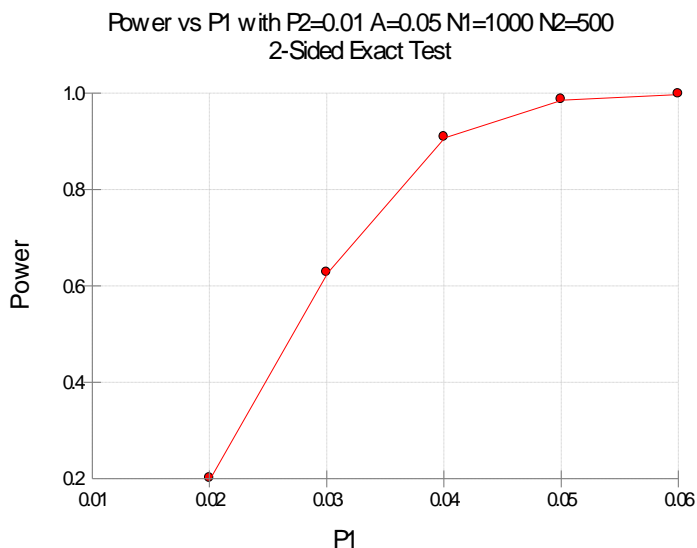
AE rate	Probability* of detecting		
	at least 1 event	at least 2 events	at least 3 events
0.003	95%	80%	58%
0.004	98%	91%	76%
0.005	99%	96%	88%
0.006	100%	98%	94%

\*based on binomial distribution, n=1000, p=AE rate

The Fisher's Exact Test is used to estimate the appropriate sample size which would provide sufficient to detect differences in the proportion of participants with Grade 3 and 4 AEs, and related Grade 2 AEs between the two arms.

Using a Fisher's Exact Test under 0.05 type I error, a trial with 1,000 participants assigned to the active arm and 500 participants assigned to the placebo arm would provide approximately 91% power to detect a difference of 4% or larger if the AE rate in the placebo arm were 1%. The figure below is a power curve that demonstrates the change in power for detecting the difference in the AE rates between the placebo arm (assumed 1% rate) and the active arm (varying rates). The vertical axis displays power, and the horizontal axis displays the AE rate in the active arm. In the figure, P1 and N1 denote the AE rate and sample size in the active arm, respectively; P2 and N2 denote the AE rate and sample size in the control arm, respectively. All calculations are based on 2-sided Fisher's Exact Test, alpha = 0.05, and were computed using PASS 2008.





To adjust for loss to follow-up and product discontinuation the sample size of  $N = 1,500$  is inflated by 10% for a final sample size of 1,650.

## 9.5 Statistical Analyses

The primary analysis will focus on safety assessments. The primary analysis will be conducted using the safety population, which will include all participants who received at least one dose of the IP. 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.

The active and placebo arms will be compared to assess the safety of the dapivirine ring. As this is a randomised trial, it is anticipated that the two groups will be comparable at baseline with respect to pre-existing conditions, and furthermore, that women with pre-existing conditions will be treated and evaluated before being enrolled into the trial. For this reason, no baseline adjustments are planned prospectively, but the data will be thoroughly reviewed to assess any potentially relevant baseline imbalances. Chi-square tests of association will be used to evaluate differences in categorical variables between the two groups under a 0.05 alpha level. For categorical variables with small sample size (<30), Fisher's Exact test may be used. Continuous data may be compared between the two treatment arms using student t-tests or Wilcoxon signed rank tests.

The safety profile is not expected to differ across research centres and it is unlikely that the difference in the safety profile between the active and control arms is affected by the research centre. However, for each analysis subsequently discussed, research centres will be evaluated via inclusion as a main effect and with a treatment-centre interaction term in appropriate regression models.

For the secondary analyses, the incidence density rates of seroconversions (HIV-1 and HIV-2) and pregnancies will be compared between treatment groups. Additional analyses will be performed to evaluate adherence and acceptability to 4-weekly use of the vaginal

ring over the IP use period as well as additional predictors of adherence (including sexual behaviour and condom use of women using a vaginal ring). The frequency of HIV-1 drug resistance in women who seroconvert while using the IP will also be assessed.

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.

### **9.5.1 Primary Safety Analysis**

The primary safety analysis will include the risk ratio, which is the ratio of the proportion of participants with Grade 3 and 4 AEs, and related Grade 2 AEs in the active arm versus in the placebo arm. The corresponding 95% CIs will also be presented. Fisher's Exact test will be provided to compare the proportion of participants, in the active and placebo arms, with Grade 3 and 4 AEs, and related Grade 2 AEs; at a 0.05 significance level. Similar analyses will be performed using the per-protocol population.

Although balance of baseline characteristics is expected across trial arms, a Poisson regression model may be used to provide risk ratios adjusted for unbalance in any baseline characteristics.

In addition to the analyses described above, all AEs reported during the trial will be presented in tables, overall, by treatment arm, and by research centre.

### **9.5.2 Secondary Analyses**

- **Incidence of HIV-1 and HIV-2 seroconversion**

Hazard ratios will be estimated with corresponding 95% CIs to quantify the effect of the dapivirine ring on HIV-1 and HIV-2 seroconversion. Time to HIV-1 seroconversion will be calculated as the number of days between the date of HIV-1 seroconversion and the randomisation date. Participants who do not seroconvert before the last product visit will be censored on the day of their last negative HIV test, and time to censoring will be calculated as the number of days between the date of censoring and the randomisation date. Kaplan-Meier survival curves will be provided to graphically describe the probability of remaining HIV-1 negative over the trial duration for each treatment arm, and will be used to assess the assumption of proportional hazards. The log-rank test (two-sided,  $\alpha=0.05$ ) will be used to evaluate the effect of the dapivirine ring on HIV-1 incidence, and will be stratified by research centre. Cox proportional hazards will be used to estimate the median time to HIV-1 seroconversion in the treatment groups adjusting for any imbalance in baseline covariates.

HIV-1 seroconversions detected at the exit visit are not included in the analysis described previously but, because they may be a result of infections acquired while the participant was off-product between the last product use visit and the exit visit, they are considered a safety concern. To ensure that IP use is not associated with higher risk of HIV-1 seroconversion following extended use of the IP, an additional analysis will be performed which will include all HIV-1 seroconversions detected during the trial following randomisation and will include the period between the last product use visit and the exit visit. For this analysis, time to HIV-1 seroconversion will be calculated as the number of days between the date of HIV-1 seroconversion and the randomisation date. Participants who do not seroconvert before the exit visit will be censored on the day of their last

negative HIV test. Time to censoring will be calculated as the number of days between the date of censoring and the randomisation date.

Similar analyses will be conducted for HIV-2 seroconversion.

- **Curable STIs**

The incidence density rates of first occurrence of curable STIs (i.e. *N.gonorrhoea*, *C.trachomatis* and *T.vaginalis*) will be compared between treatment groups. For each treatment group, the numerator will include the number of participants that were diagnosed with at least one curable STI and the denominator will include the total number of STI-free days that each participant contributed to the trial (i.e., from enrolment to their first STI or trial completion, whichever occurs first). The application of General Estimating Equations (GEE) will be used to evaluate the trends in curable STIs during the trial period. In addition, the Kaplan-Meier survival curves describing the time until the first occurrence of a curable STI in each treatment arm will be provided. Cox proportional hazards will be used to estimate the median time to the first occurrence of a curable STIs between the treatment groups.

- **Changes in vaginal flora**

The incidence density rates of first occurrence of vaginal flora changes will be compared between treatment groups. For each treatment group, the numerator will include the number of participants that were diagnosed with vaginal flora changes and the denominator will include the total number days with no vaginal flora changes that each participant contributed to the trial (i.e., from enrolment to their first incident of vaginal flora changes or trial completion, whichever occurs first). The application of GEE will be used to evaluate the trends in vaginal flora changes during the trial period. In addition, the Kaplan-Meier survival curves describing the time until the first occurrence of vaginal flora changes in each treatment arm will be provided. Cox proportional hazards will be used to estimate the median time to the first occurrence of changes in vaginal flora between the treatment groups.

- **Incidence of Pregnancy**

The incidence density rates of pregnancies will be compared between treatment groups. For each treatment group, the numerator will include the number of participants that had a positive urine pregnancy test during the trial period and the denominator will include the total number of days that each participant contributed to the trial (i.e., from enrolment to pregnancy or trial completion, whichever occurs first). In addition, Cox proportional hazards will be used to estimate the median time to pregnancy between the two treatment groups.

- **Adherence to the ring regimen**

Definitions for adherence to the ring regimen may be categorised by the percent of days that the participant reportedly wore the ring out of the total number of days that the participant was expected to wear the ring. Such categorisations will be further defined in the SAP. In addition, a dichotomous variable will be created to define “adherent participants” based on a predefined cut-off percent of adherence deemed acceptable. This percent will be described more fully in the SAP. The proportion of participants that are not adherent to the ring regimen will be compared in each treatment group. For each

treatment group, the numerator will include the number of participants who were not adherent during the trial period and the denominator will include the total number of days that each participant contributed to the trial (i.e., from enrolment to becoming non-adherent or to trial completion, whichever occurs first). The application of GEE will be used to evaluate the trends in missed days of the ring regimen during the trial period. In addition, Cox proportional hazards will be used to compare the time to the first missed day of the ring regimen between the two treatment groups. Additional exploratory and explanatory analysis will utilise the qualitative data from focus groups and individual interviews.

Multiple methods of data collection will be utilised to examine adherence; comparisons across the different methods will be explored and will be provided in greater detail in the SAP.

- **Acceptability of the ring regimen**

Two types of acceptability assessments will be performed; these are referred to as (1) simple approximation of acceptability and (2) comprehensive assessment of acceptability. These assessments will be fully described in the SAP.

For both types of assessments, cross-tabulations and simple descriptive statistics will be calculated for socio-demographic variables and psychosocial variables collected in the acceptability and adherence questionnaires. If between group differences arise and/or there are differential rates of drop-out on potentially confounding characteristics, we will include the variable(s) as covariates in the analyses. If numerous confounders are identified, a propensity scoring approach will be used to adjust for confounding.

Simple approximation of acceptability will be assessed by analysis of stated willingness to use the vaginal ring if proven effective against HIV infection, and reported consistent use of the vaginal ring during the trial. A participant will be classified as having found the vaginal ring acceptable if she responds positively to questions about willingness to use and consistent use. Logistic regression analysis will be performed to examine the relationship between this acceptability and other variables of interest.

Comprehensive assessment of acceptability will be based on data captured in the acceptability and adherence questionnaires. Variables evaluating participants' willingness to use the vaginal ring will be adjusted by women's perceived risk of HIV and sexual practices. Variables evaluating consistent-use of the vaginal ring will also be used to adjust for possible confounding factors. Another aspect of comprehensive acceptability is to investigate factors influencing participants' attitudes and responses to the IP. The acceptability measures will be regressed over possible predictors via a logistic regression model at a 0.05 level of statistical significance. Additional exploratory and explanatory analysis will utilise the qualitative data from focus groups and individual interviews.

- **HIV-1 drug resistance**

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. The proportion of HIV-1 seroconverters with at least one HIV-1 drug resistant mutation will be presented overall, and by treatment arm, with corresponding 95% CIs. A logistic regression model will be developed to estimate the effect of the dapivirine ring on the odds of developing at least one HIV-1 resistance mutation, and will adjust for confounders that may distort the association between the dapivirine ring and HIV-1 resistance

mutations. Such confounders may include the number of sexual partners reported at baseline, type of contraception, or the diagnosis of genital infections. The distribution of HIV-1 resistance mutations may be presented graphically with a bar chart of relative frequencies, overall and by treatment arm.

It is possible that prolonged exposure to the IP and adherence to the IP may influence the development of resistant mutations. A box-plot displaying the distribution of days on IP may be presented for each treatment arm. The number of days of IP use prior to HIV-1 seroconversion as well as adherence to the IP may be evaluated as an independent predictor of acquiring a resistant mutation. The number of days of IP use may be included as a continuous covariate or parameterised as a categorical variable and included as a main effect in a logistic regression model for the outcome of developing at least one HIV-1 resistance mutation. The estimated odds ratio for the effect of the number of days of IP use, adjusted for treatment arm, will be displayed with 95% CIs.

### 9.5.3 Subgroup Analysis of participants of women over 40 years of age

IPM 027 will enrol participants over 40 years of age to assess the safety of dapivirine in a silicone elastomer vaginal matrix ring inserted once every 4 weeks in older women, when compared to a placebo vaginal ring. An assessment of the primary, secondary and exploratory endpoints will be performed in a subgroup of participants over 40 years of age.

A subgroup with approximately 200 participants over 40 years of age in the active arm, or approximately 300 participants in both arms, would be sufficient to detect at least one AE with a rate of 2% and at least three events if the AE rate was 5%. The table below presents the probabilities of detecting at least one, two, and three AEs of varying rates for a total of 150 and 200 participants over 40 years of age in the active arm.

AE rate	N=225 (150 on active)			N=300 (200 on active)		
	Probability* of detecting			Probability* of detecting		
	at least 1 event	at least 2 events	at least 3 events	at least 1 event	at least 2 events	at least 3 events
0.01	78%	44%	19%	87%	60%	32%
0.02	95%	80%	58%	98%	91%	76%
0.03	99%	94%	83%	100%	98%	94%
0.04	100%	98%	94%	100%	100%	99%
0.05	100%	100%	98%	100%	100%	100%
0.06	100%	100%	99%	100%	100%	100%

The subgroup analysis will not be powered to detect small differences in the safety profile between the active and placebo arms. However, with 300 participants in the subgroup, the trial has 94% power to detect a difference when the AE rate in the active arm is 20% and the AE rate in the placebo arm is 5%.

## **9.6 Data Safety Monitoring Board (DSMB)**

An independent DSMB will be established. The DSMB will meet via conference call at predetermined intervals during the trial; ad hoc calls may be convened if requested by the DSMB or IPM. DSMB members will include individuals not associated with this trial, but who have expertise in conducting clinical trials, experience working in developing countries, and/or a history of working in the microbicide arena. Prior to each DSMB meeting, the data management group will prepare a summary report of all AEs and SAEs for the DSMB to assess safety. The DSMB has the option to recommend pausing or stopping the trial at any point, if warranted, based on AEs observed during the trial, or other safety concerns identified during the course of the trial. DSMB members will remain blinded to the treatment groups unless it is necessary to unblind an individual or stop the trial for safety reasons.

A separate DSMB charter will describe the DSMB composition and its charges related to the trial.

This trial will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312), and in accordance with the ethical principles of the World Medical Association Declaration of Helsinki, the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the U.S. Code of Federal Regulations (CFR) Title 21 and applicable local regulatory requirements.

## **9.7 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 4-week 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.

# **10. INVESTIGATOR REQUIREMENTS**

## **10.1 Trial Initiation**

The trial can be initiated at the research centre once all relevant IRB/IEC and regulatory approvals have been obtained as per country requirements and IP shipment has been authorised by the Sponsor. Following Sponsor approval, IPM will notify the research centre in writing via letter correspondence to begin trial operations according to the protocol.

## **10.2 Institutional Review Board 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.

### **10.3 Trial Monitoring and Audits**

Trial monitors will regularly visit participating research centres to review all 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 Sponsor may request access to all trial documents for on-research centre audit or inspection.

### **10.4 Case Report Forms**

Case Report Forms (CRFs) will be supplied by IPM or its designee and will be handled in accordance with instructions from IPM.

All CRFs will be filled out completely by the designated trial staff. 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 initialled and dated. Erasures, overwriting, and correction fluid are NOT allowed on the CRFs.

### **10.5 Disclosure of Data**

Participant medical information is confidential and disclosure to third parties other than those described in Section 10.3 is strictly prohibited. All trial data will be stored securely at the trial research centre. All participant information including laboratory reports, forms, lists, logbooks, appointment books and administrative forms will be stored in locked file cabinets 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 the Sponsor, Sponsor's designated monitors, or regulatory authorities.

## 10.6 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 informed consent forms, 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. The Sponsor 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.

## 11. ETHICAL CONSIDERATIONS

### 11.1 Ethical Review

This protocol, research centre-specific informed consent forms, 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 the ethical principles of:

- World Medical Association Declaration of Helsinki<sup>13</sup>
- ICH GCP guidelines<sup>14</sup>
- 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*<sup>15</sup>.

### 11.2 Reporting and Management of Social Harms

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. The acceptability questionnaire also includes questions to assess the occurrence of social harms. Participants who experience social harms 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.



### **11.3 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, group level discussions, pre/post tests, distributed feedback forms, etc. Each research centre has a process for consulting with the community. The primary vehicle for this consultation is through formal structures such as the Community Advisory Boards/Groups/Committees. These systems have provided input into the protocol design and facilitated acceptance of the research and allowed investigators and communities to identify and respond rapidly to concerns raised.

## **12. 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 Sponsor's clinical trial agreement with the investigator. Authorship criteria will be based on contributions to the design, work, and analysis of the trial.

### 13. REFERENCES

1. AIDS at 30: Nations at the Crossroads; UNAIDS 2011.  
<http://www.unaids.org/unaidresources/aidsat30/aids-at-30.pdf>
2. Report on the Global AIDS Epidemic; UNAIDS 2010.  
<http://www.unaids.org/globalreport/>
3. Elias CJ, Coggins C. Female-controlled methods to prevent sexual transmission of HIV. AIDS 1996;10:S43-S51.
4. Abdool Karim Q, Abdool S S, Frohlich JA, et al. Effectiveness and safety of Tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Scienceexpress, 19 July 2010, 1126, science.1193748; p1-13.  
<http://www.sciencexpress.org>
5. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010;363:2587-99
6. [http://www.hptn.org/web%20documents/PressReleases/HPTN052PressReleaseF1NAL5\\_12\\_118am.pdf](http://www.hptn.org/web%20documents/PressReleases/HPTN052PressReleaseF1NAL5_12_118am.pdf)
7. [http://www.hptn.org/web%20documents/PressReleases/HPTN052PressReleaseF1NAL5\\_12\\_118am.pdf](http://www.hptn.org/web%20documents/PressReleases/HPTN052PressReleaseF1NAL5_12_118am.pdf)
8. Dapivirine Vaginal Ring Investigators Brochure
9. Pharmacia & Upjohn Estrin<sup>®</sup> Physician Leaflet.  
([http://www.pfizer.com/pfizer/download/uspi\\_estrin.pdf](http://www.pfizer.com/pfizer/download/uspi_estrin.pdf))
10. Warner Chilcott Femring<sup>®</sup> Full U.S. Prescribing Information.  
([http://www.warnerchilcott.com/pdfs/pi-femring\(physician\).pdf](http://www.warnerchilcott.com/pdfs/pi-femring(physician).pdf))
11. Warner Chilcott Femring<sup>®</sup> Patient Information Materials: Patient Acceptability.  
([http://www.warnerchilcott.com/pdfs/pi-femring\(patient\).pdf](http://www.warnerchilcott.com/pdfs/pi-femring(patient).pdf))
12. Woodsong C, Montgomery E, Masenga G, et al, Safety and acceptability of vaginal ring as microbicide delivery method in African women. Oral presentation, Microbicides 2010, May 23 – 26, Pittsburgh, Philadelphia.
13. World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects; WMA General Assembly, Seoul October 2008. <http://www.wma.net/e/policy/b3.htm>
14. Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance.  
([http://www.doh.gov.za/docs/policy/trials/trials\\_contents.html](http://www.doh.gov.za/docs/policy/trials/trials_contents.html))
15. Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa.  
([http://www.doh.gov.za/docs/policy/trials/trials\\_contents.html](http://www.doh.gov.za/docs/policy/trials/trials_contents.html))

## APPENDIX A: SCHEDULE OF CLINICAL PROCEDURES

Year 1 Visits	Screening 1	Screening 2	Enrolment <sup>b</sup>	4-weekly	12-weekly	24-weekly <sup>h</sup>	Last Product Use <sup>h</sup>	As Needed	Exit Visit
Trial Weeks <sup>a</sup>	Screening 2 must occur within 28 days of Screening 1			Weeks 4 - 52	Weeks 12, 24, 36, 48	Weeks 24, 48			
Informed Consent <sup>c</sup>	X		X						
Assign Participant Identification number	X								
Comprehension Assessment			X						
Demographics	X								
Medical History	X	X							
Concomitant Medication Evaluation	X	X		X	X	X	X		X
Inclusion/Exclusion Criteria	X	X							
Locator Information	X	X		X	X	X	X		X
Menses Information	X	X		X	X	X	X		
Physical Examination	X	X <sup>d</sup>					X	X <sup>d</sup>	
Adverse Event Evaluation			X	X	X	X	X	X	X
Pelvic Exam	X	X			X	X	X	X	
Vaginal Ring Dispensing and Insertion			X	X	X	X		X <sup>e</sup>	
Vaginal Ring Removal/Return				X	X	X	X	X <sup>e</sup>	
Provision and Collection of Diary Card			X	X	X	X			
Provision of Male Condoms	X	X		X	X	X	X	X	X
Collection of Diary Card				X	X	X	X		
Adherence Questionnaire				X	X	X	X		
Acceptability Questionnaire				X <sup>g</sup>		X	X		
Behavioural Questionnaire			X						
HIV/STI Risk Reduction Counselling	X	X		X	X	X	X		X
Vaginal Ring Adherence Counselling			X	X	X	X		X	
Contraceptive Counselling	X		X	X	X	X	X	X	X
HIV Pre- & Post-Test Counselling	X	X		X	X	X	X	X	X

<b>Year 2 Visits</b>				4-weekly	12-weekly	24-weekly	Last Product Use <sup>h</sup>	As Needed	Exit Visit
Trial Weeks <sup>a</sup>				Weeks 56 - 104	Weeks 60, 72, 84, 96	Weeks 72, 96			
Concomitant Medication Evaluation				X	X	X	X		X
Locator Information				X	X	X	X		X
Menses Information				X	X	X	X		
Physical Examination							X	X <sup>d</sup>	
Adverse Event Evaluation				X	X	X	X	X	X
Pelvic Exam					X	X	X	X	
Vaginal ring dispensing and insertion				X	X	X		X <sup>e</sup>	
Vaginal Ring Removal/Return				X	X	X	X	X <sup>e</sup>	
Provision and Collection of Diary Card				X	X	X			
Provision of Male Condoms				X	X	X	X	X	X
Adherence Questionnaire				X	X	X	X		
Acceptability Questionnaire						X	X		
HIV/STI Risk Reduction Counselling				X	X	X	X		X
Vaginal Ring Adherence Counselling				X	X	X		X	
Contraceptive Counselling				X	X	X	X	X	X
HIV Pre- & Post-Test Counselling				X	X	X	X	X	X

<sup>a</sup> Each trial week is equal to 7 days. All visits while on the investigational product may occur  $\pm$  7 days of scheduled visits.

<sup>b</sup> Enrolment may occur the same day as Screening 2.

<sup>c</sup> The informed consent will be signed prior to screening and again prior to enrolment.

<sup>d</sup> Directed examination determined by symptomatology.

<sup>e</sup> If a vaginal ring is removed for more than 24 hours a new ring will be dispensed.

<sup>f</sup> The diary card may be reviewed at 4-weekly visits as part of the adherence assessment. Participants may consult their diary cards during adherence counselling.

<sup>g</sup> The baseline acceptability questionnaire will be administered only at week 4.

<sup>h</sup> 6 – 10 participants will be invited to participate in an individual interview to be held during weeks 24 – 36. Each research centre will also conduct 2-3 focus groups with participants who have been recruited at the last product use visit. Additionally, 6 – 10 individual interviews with male partners will be conducted at each research centre.

## APPENDIX B: SCHEDULE OF LABORATORY PROCEDURES

Year 1 Visits	Screening 1	Screening 2	Enrolment	4-weekly	12-weekly	Annual	Last Product Use	As Needed	Exit Visit
Trial Weeks				Weeks 4 - 52	Weeks 12, 24, 36, 48	Week 52			
Urine Pregnancy Test <sup>n</sup>	X	X		X	X	X	X	X	
HIV Rapid Test	X	X		X	X	X	X		X
HIV-RNA PCR Test			X <sup>i,p</sup>	X <sup>i</sup>	X <sup>i</sup>	X <sup>i</sup>	X <sup>i</sup>		
Plasma Dapivirine Levels				X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		
Vaginal Fluid Dapivirine Levels				X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		
Plasma Viral Genotype Sample			X <sup>i,p</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		X <sup>i</sup>
HSV-2 Serology			X <sup>i,p</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		
Laboratory Testing for Safety Assessments <sup>k</sup>	X				X		X	X	
Vaginal Fluid pH and Vaginal Flora Sample			X		X		X		
Vaginal Fluid Viral Genotype Sample			X <sup>i</sup>					X <sup>j</sup>	X <sup>i</sup>
Cervicovaginal Sample Collection for STI Tests	X				X		X	X	
Cervical Sample Collection for Cytology <sup>o</sup>	X					X			
RPR <sup>m</sup>	X						X	X	
Final Laboratory results provided to participants									X

Year 2 Visits	Screening 1	Screening 2	Enrolment	4-weekly	12-weekly	Annual	Last Product Use	As Needed	Exit Visit
Trial Weeks				Weeks 56 - 104	Weeks 60, 72, 84, 96	Week 104			
Urine Pregnancy Test <sup>n</sup>				X	X	X	X	X	
HIV Rapid Test				X	X	X	X		X
HIV-RNA PCR Test				X <sup>i</sup>	X <sup>i</sup>	X <sup>i</sup>	X <sup>i</sup>		
Plasma Dapivirine Levels				X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		
Vaginal Fluid Dapivirine Levels				X <sup>i,j</sup>	X <sup>i</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		
Plasma Viral Genotype Sample				X <sup>i,j</sup>	X <sup>i</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		X <sup>i</sup>
HSV-2 serology				X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		
Laboratory Testing for Safety Assessments <sup>k</sup>					X		X	X	
Vaginal Fluid pH and Vaginal Flora Sample					X		X		
Vaginal Fluid Viral Genotype Sample								X	X <sup>i</sup>
Cervicovaginal Sample Collection for STI Tests					X		X	X	
Cervical Sample Collection for Cytology						X			
RPR <sup>m</sup>							X	X	
Final Laboratory results provided to participants									X

<sup>i</sup> Sample will be stored and will only undergo testing subsequently or after confirmation of seroconversion.

<sup>j</sup> Sample will be obtained and tested at the point of confirmed seroconversion.

<sup>k</sup> Urinalysis dipstick testing (Urine microscopy only if indicated), haematology (FBC with differential count and platelets), chemistry (electrolytes, calcium, urea, creatinine, AST, ALT, ALP, bilirubin).

<sup>l</sup> Blood and vaginal fluid samples for viral genotyping will also be collected at the scheduled exit visit following seroconversion.

<sup>m</sup> TPHA/TPPA should be performed if RPR positive.

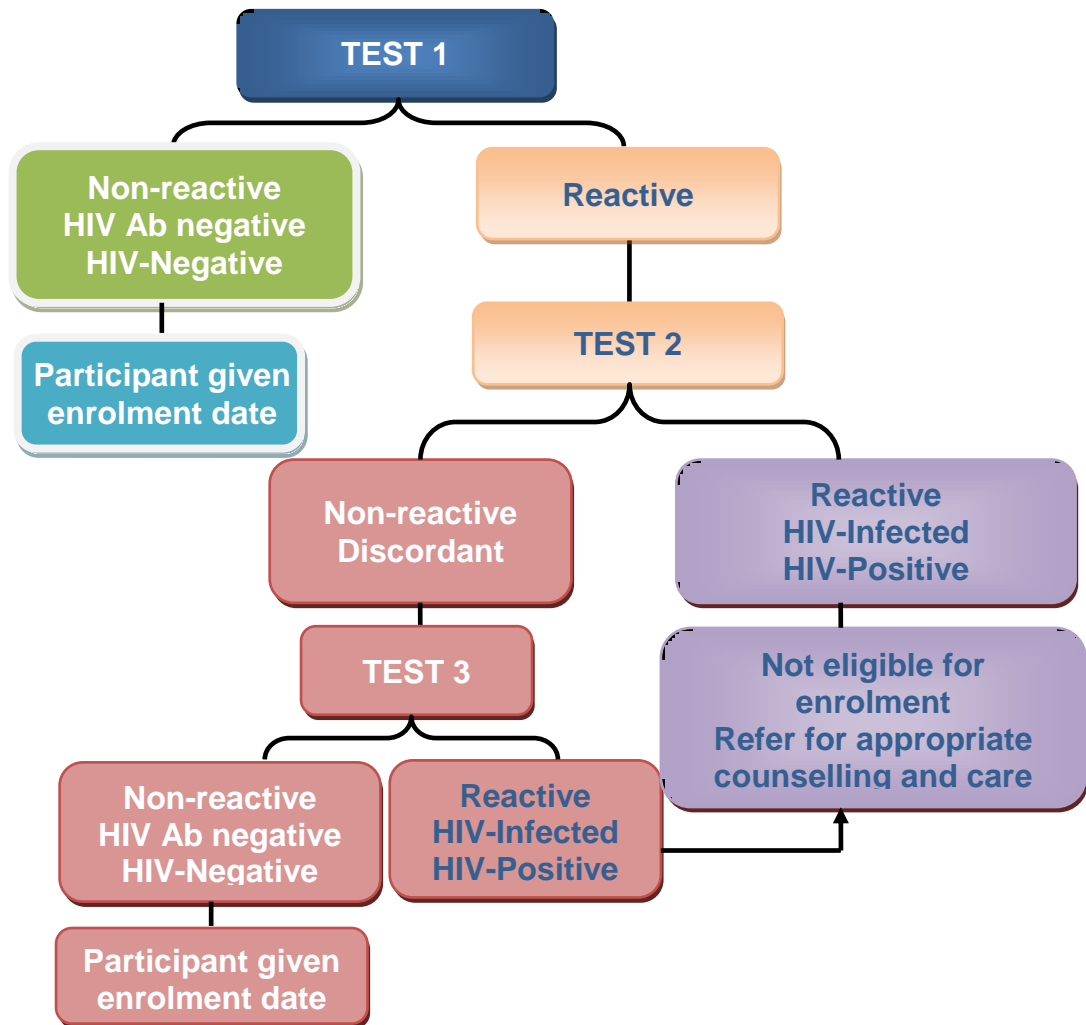
<sup>n</sup> A confirmatory serum pregnancy test may be requested if reason exists to suspect a false positive urine pregnancy test.

<sup>o</sup> For women with Grade 1 cervical cytology findings, cervical cytology will be repeated according to the local standard of care, or after 6 months; whichever is more conservative.

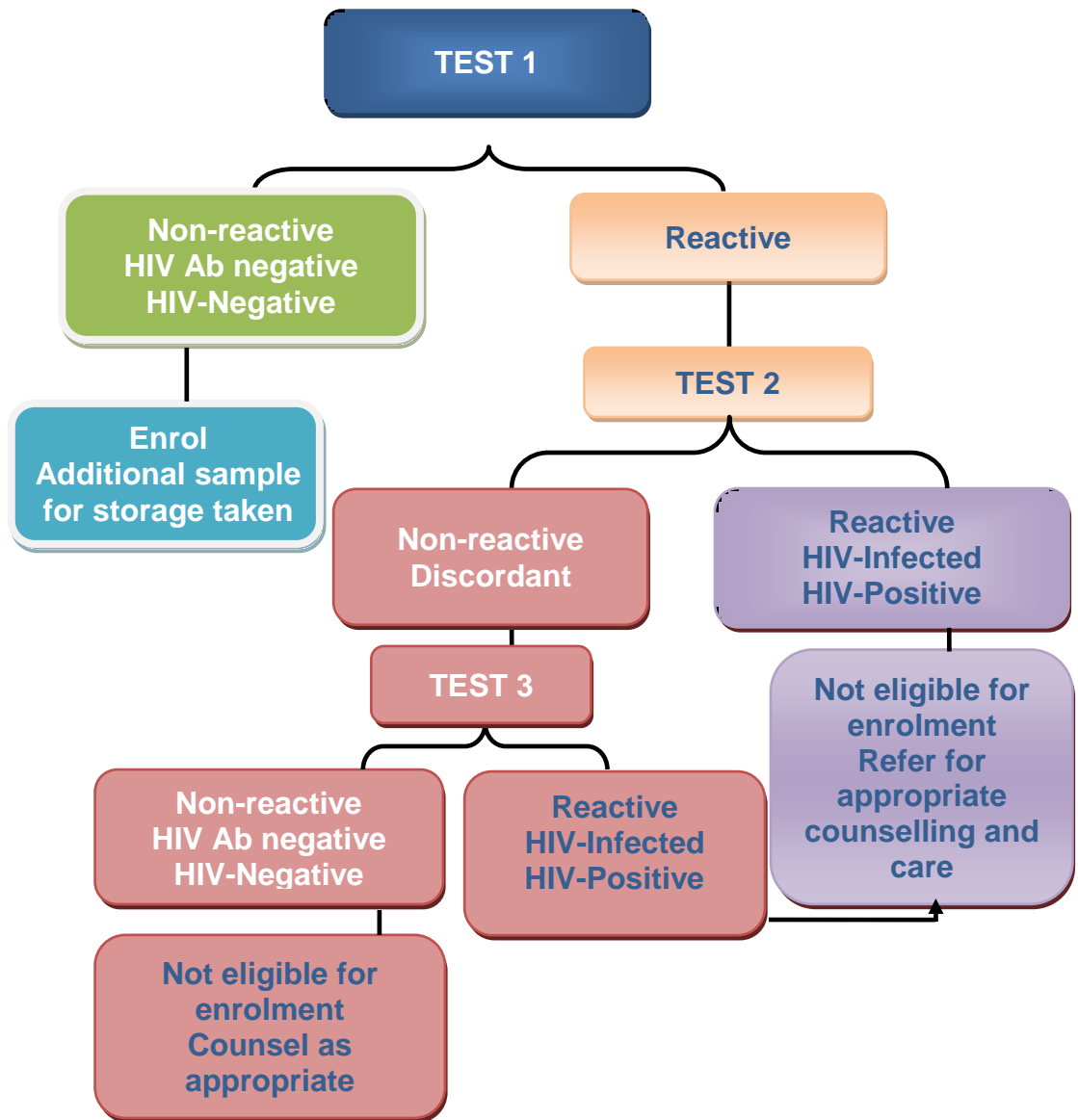
<sup>p</sup> Blood samples for HSV-2 serology, HIV viral genotyping and HIV-RNA PCR will be collected at screening 2 for research centres that use this option.

## APPENDIX C: HIV TESTING ALGORITHMS

Figure 1: Screening 1 Algorithm

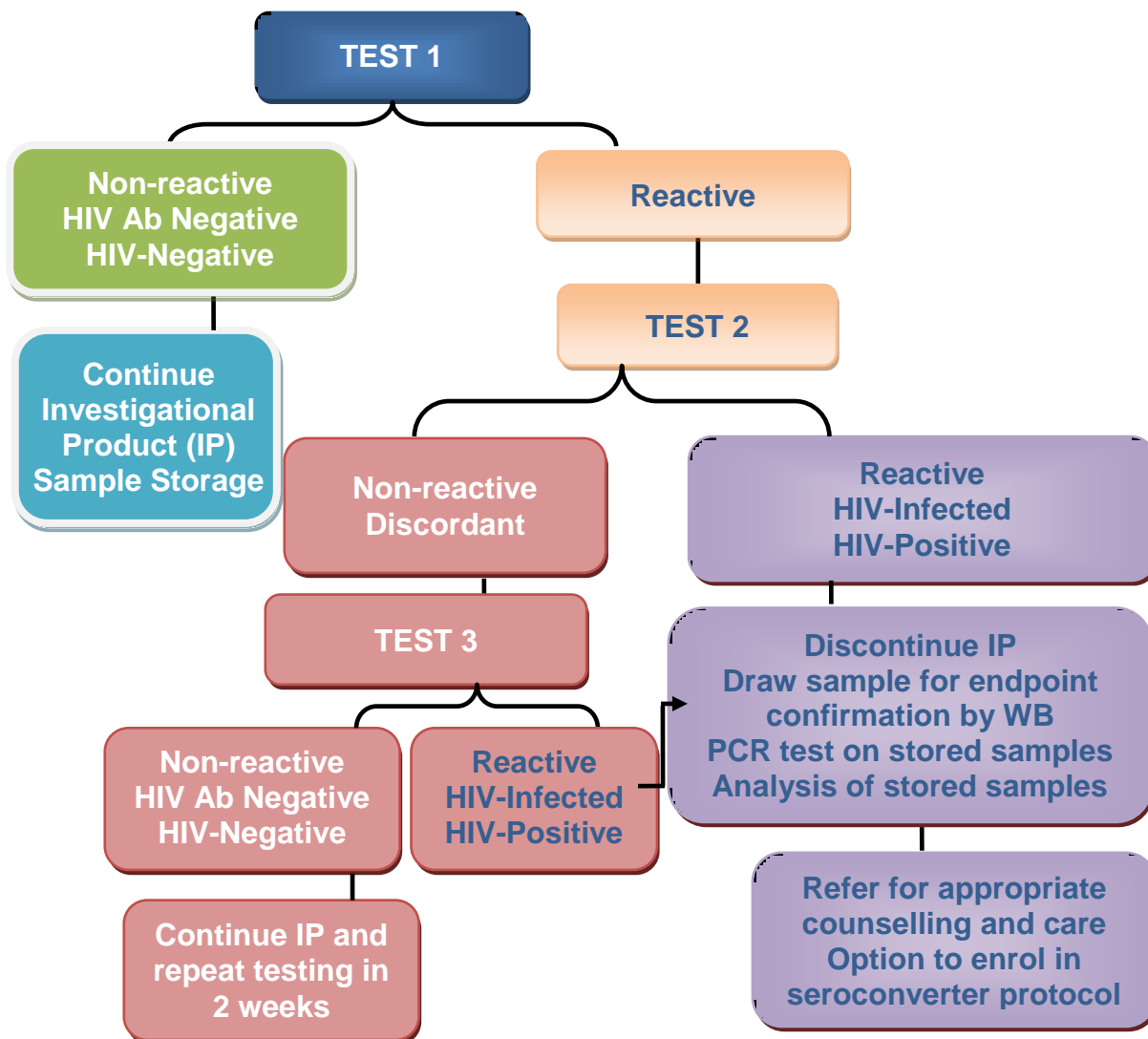


**Figure 2: Screening 2 and Enrolment Algorithm (should be conducted within 28 days [4 weeks] of screening unless otherwise stated within the protocol)**

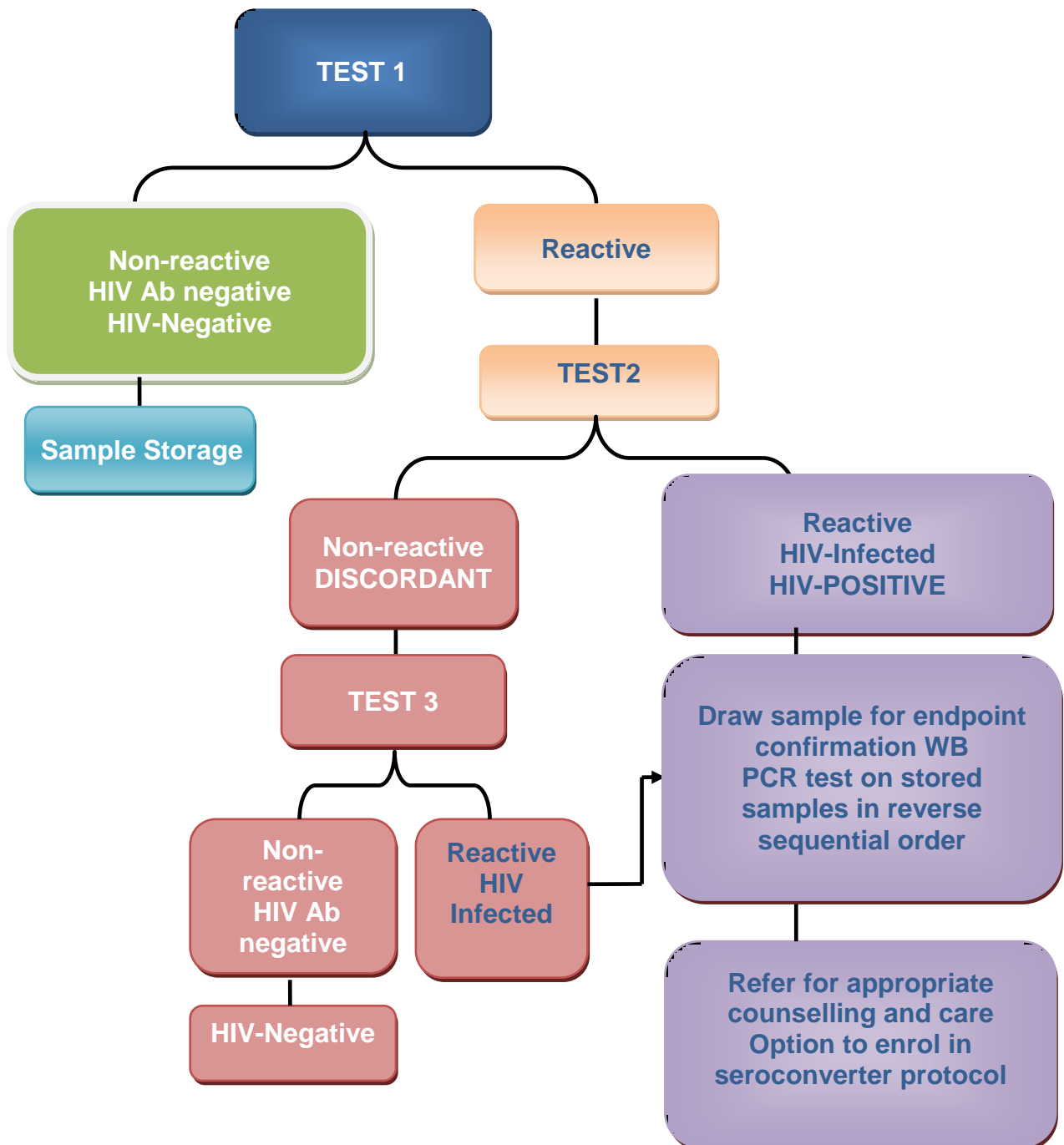




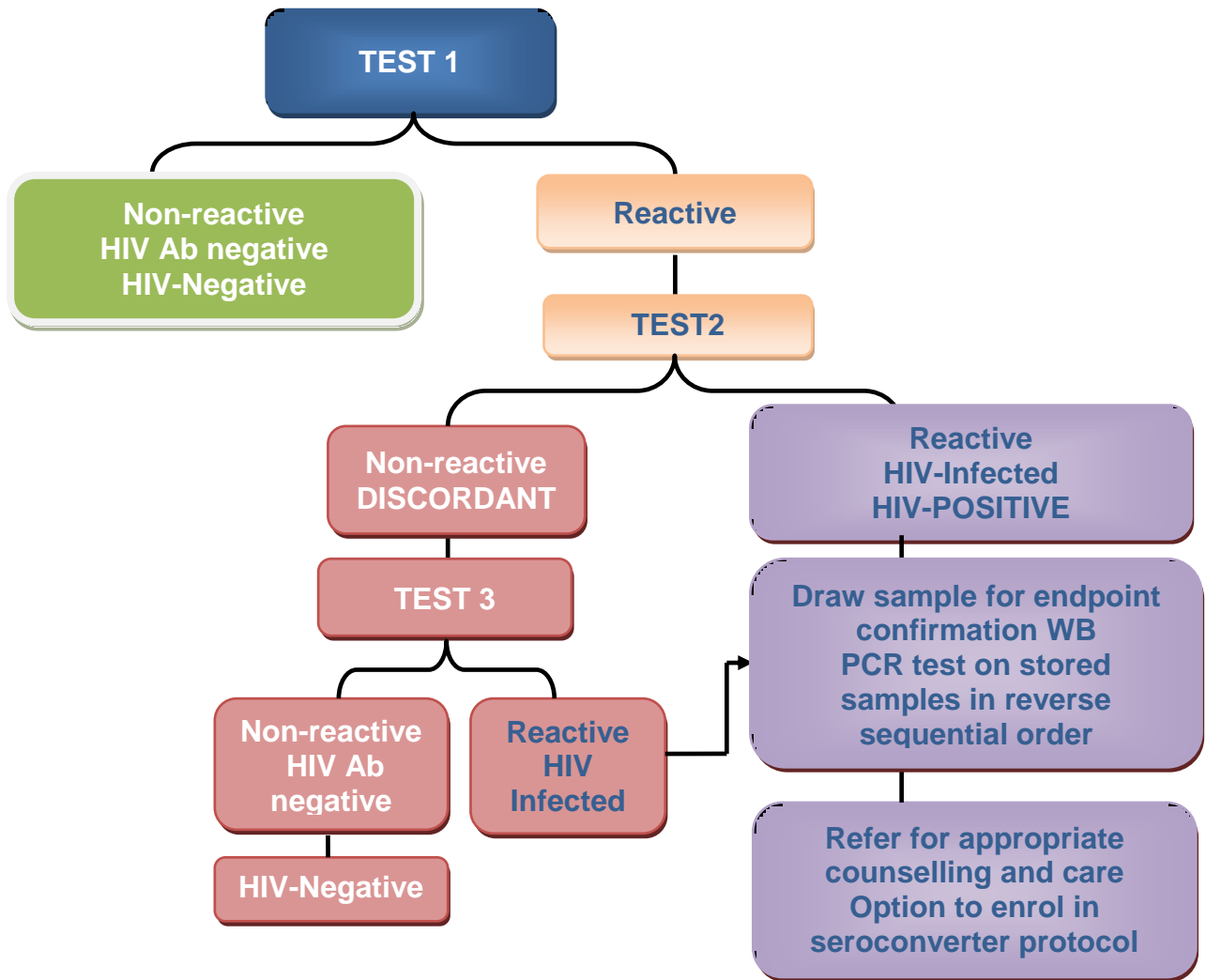
**Figure 3: Trial Visits Algorithm**



**Figure 4: Last Product Use Visit Algorithm**



**Figure 5: Exit Visit Algorithm: 6 weeks after product use**



### APPENDIX D: VISIT SCHEDULE AND 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
<b>Screening 1</b>	HIV rapid <sup>‡</sup> 5 mL	Haematology 5 mL	Chemistry 5 mL	RPR 5 mL		15 - 20 mL
<b>Screening 2 &amp; Enrolment</b>	HIV rapid <sup>‡</sup> 5 mL		Viral Genotyping <sup>#</sup> 10 mL	HSV-2 <sup>#</sup> 5 mL	HIV PCR <sup>#</sup> 5 mL	20 – 25 mL
<b>Monthly (4-weekly)</b>	HIV rapid 5 mL	Dapivirine levels <sup>#</sup> 6 mL	Viral genotyping <sup>#</sup> 10 mL	HSV-2 <sup>#</sup> 5 mL	HIV PCR <sup>#</sup> 5 mL	31 mL
<b>Quarterly (12-weekly)</b>	HIV rapid 5 mL	Haematology 5 mL Dapivirine levels <sup>#</sup> 6 mL	Chemistry 5 mL Viral genotyping <sup>#</sup> 10 mL	HSV-2 <sup>#</sup> 5 mL	HIV PCR <sup>#</sup> 5 mL	41 mL
<b>Last Product Use Visit</b>	HIV rapid 5 mL	Haematology 5 mL Dapivirine levels <sup>#</sup> 6 mL	Chemistry 5 mL Viral genotyping <sup>#</sup> - 10	RPR 5 mL HSV-2 <sup>#</sup> 5 mL	HIV PCR <sup>#</sup> 5 mL	46 mL
<b>Sero-converter tests<sup>+</sup></b>	Western blot 5 mL	Dapivirine levels 6 mL	Viral genotyping 10 mL	HSV-2 5 mL		26 mL

- \* If HIV rapid Test 1 is positive, Test 2 may be performed on the same sample.
- ‡ Depending on the research centre SOP on HIV testing, sampling may be performed by finger prick or venipuncture.
- # Stored plasma samples; tested retrospectively to evaluate different parameters at the time of seroconversion.
- + At the point of seroconversion, these samples will be collected and tested in addition to other visit-specific tests. No additional storage samples will be collected.

**IPM 027  
Protocol Version 1.0 Amendment 4.0  
21 August 2014**

**A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED  
SAFETY AND EFFICACY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN  
HEALTHY HIV-NEGATIVE WOMEN**

**SPONSOR:  
International Partnership for Microbicides  
8401 Colesville Road, Suite 200  
Silver Spring, MD 20910 U.S.A.**

**SIGNATURE PAGE**

**IPM 027**

**A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED  
SAFETY AND EFFICACY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN  
HEALTHY HIV-NEGATIVE WOMEN**

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 Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and all applicable regulations and guidelines.

\_\_\_\_\_  
Investigator Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Investigator Name (Printed)

\_\_\_\_\_  
Investigative 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. This trial will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

\_\_\_\_\_  
Chief Medical Officer Signature

\_\_\_\_\_  
Date

Annaléne Nel, MBChB, PhD

Chief Medical Officer Name (Printed)

\_\_\_\_\_  
Protocol Chair

\_\_\_\_\_  
Date

Prof. Saidi Kapiga, MD, MPH, ScD

Protocol Chair Name (Printed)

## TABLE OF CONTENTS

<b>ACRONYMS AND ABBREVIATIONS .....</b>	<b>6</b>
<b>IPM 027 SYNOPSIS .....</b>	<b>8</b>
<b>1. INTRODUCTION .....</b>	<b>19</b>
1.1 BACKGROUND.....	19
1.2 DAPIVIRINE VAGINAL RING.....	20
1.2.1 <i>Dapivirine</i> .....	20
1.2.2 <i>Nonclinical Research</i> .....	21
1.2.3 <i>Clinical Research</i> .....	22
1.2.4 <i>Formulation of a Silicone Elastomer Vaginal Matrix Ring Containing 25 mg of Dapivirine</i> .....	23
1.3 RATIONALE FOR PROTOCOL IPM 027 .....	23
<b>2. TRIAL OBJECTIVES.....</b>	<b>24</b>
2.1 TRIAL OBJECTIVES.....	24
2.2 TRIAL ENDPOINTS AND ASSESSMENTS.....	25
<b>3. OVERALL TRIAL DESIGN .....</b>	<b>26</b>
3.1 TRIAL DESIGN .....	26
3.2 TRIAL DURATION .....	29
3.3 TRIAL POPULATION .....	29
3.3.1 <i>Inclusion Criteria</i> .....	29
3.3.2 <i>Exclusion Criteria</i> .....	30
3.4 PARTICIPANT RECRUITMENT .....	31
3.4.1 <i>Pre-Screening</i> .....	31
3.4.2 <i>Participant Recruitment and Accrual</i> .....	31
<b>4. TRIAL VISITS AND PROCEDURES .....</b>	<b>31</b>
4.1 SCREENING VISITS.....	31
4.1.1 <i>Screening 1</i> .....	31
4.1.2 <i>Screening 2 (Within no more than 4 weeks [28 days] of Screening 1)</i> .....	33
4.2 ENROLMENT VISIT .....	33
4.3 TRIAL VISITS .....	34
4.3.1 <i>4-Weekly Trial Visits (Weeks 4 to 100)</i> .....	34
4.3.2 <i>12-Weekly Trial Visits (Weeks 12, 24, 36, 48, 60, 72, 84 and 96)</i> .....	35
4.3.3 <i>24-Weekly Trial Visits (Weeks 24, 48, 72 and 96)</i> .....	36
4.3.4 <i>Annual Visit (Week 52)</i> .....	36
4.3.5 <i>Last Product Use Visit (Week 104 or Early Discontinuation)</i> .....	37
4.4 EXIT VISIT (6 WEEKS AFTER THE LAST PRODUCT USE VISIT) .....	38
4.5 PARTICIPANT RETENTION .....	38
4.6 UNSCHEDULED VISITS.....	39
4.7 MISSED AND LATE VISITS .....	39
4.8 EARLY DISCONTINUATION VISIT .....	40
4.9 PREMATURE DISCONTINUATION OF THE TRIAL.....	41
<b>5. TRIAL PROCEDURE DETAILS .....</b>	<b>41</b>
5.1 INFORMED CONSENT.....	41
5.1.1 <i>Informed Consent Process</i> .....	41
5.1.2 <i>Comprehension Assessment Checklist</i> .....	42
5.2 HIV COUNSELLING.....	42
5.2.1 <i>HIV Pre- and Post-Test Counselling</i> .....	42
5.2.2 <i>HIV/STI Risk Reduction Counselling</i> .....	43
5.3 HIV TESTING AND MANAGEMENT .....	43
5.3.1 <i>Screening 1</i> .....	43

5.3.2	<i>Screening 2 and Enrolment</i>	43
5.3.3	<i>Trial Visits</i>	44
5.3.4	<i>Exit Visit</i>	45
5.4	MANAGEMENT OF CONTRACEPTION	46
5.5	PREGNANCY TESTING AND MANAGEMENT	47
5.6	DEMOGRAPHICS AND MEDICAL HISTORY	48
5.7	VITAL SIGNS AND PHYSICAL EXAMINATION	48
5.8	PELVIC EXAMINATION	49
5.9	SAFETY LABORATORY ASSESSMENTS	49
5.10	STI TESTING AND MANAGEMENT	49
5.10.1	<i>STI Testing</i>	49
5.10.2	<i>STI Management</i>	50
5.11	CERVICAL CYTOLOGY	50
5.12	VAGINAL RING INSERTION AND PLACEMENT CHECK AND RING REMOVAL	51
5.13	VAGINAL RING ADHERENCE COUNSELLING	51
5.14	QUESTIONNAIRES	51
5.14.1	<i>Baseline Behavioural Questionnaire</i>	51
5.14.2	<i>Adherence Questionnaire</i>	52
5.14.3	<i>Acceptability Questionnaire</i>	52
5.14.4	<i>Qualitative Interviews</i>	52
5.15	SAMPLE STORAGE AND ANALYSIS	52
5.16	METHOD OF TREATMENT ASSIGNMENT	53
5.17	REIMBURSEMENT	53
5.18	PARTICIPANT COMPENSATION	53
5.19	PARTICIPANT RESPONSIBILITY	53
5.20	STUDY OPERATIONS MANUAL	54
<b>6.</b>	<b>INVESTIGATIONAL PRODUCT</b>	<b>54</b>
6.1	INVESTIGATIONAL PRODUCT COMPOSITION	54
6.2	PACKAGING AND LABELLING	55
6.3	RANDOMISATION	55
6.4	BLINDING AND UNBLINDING	55
6.5	INVESTIGATIONAL PRODUCT STORAGE	55
6.6	INVESTIGATIONAL PRODUCT ADMINISTRATION	55
6.7	INVESTIGATIONAL PRODUCT EXPULSION OR LOSS	56
6.8	RETRIEVAL OF INVESTIGATIONAL PRODUCT	56
6.9	INVESTIGATIONAL PRODUCT ACCOUNTABILITY	56
6.10	CONCOMITANT MEDICATIONS AND PRODUCTS	57
<b>7.</b>	<b>ADVERSE EVENTS</b>	<b>57</b>
7.1	DEFINITION	57
7.2	ASSESSMENT OF ADVERSE EVENT SEVERITY	58
7.3	RELATIONSHIP TO INVESTIGATIONAL PRODUCT	58
7.4	SERIOUS ADVERSE EVENTS	59
7.4.1	<i>Serious Adverse Event Definition</i>	59
7.4.2	<i>Serious Adverse Event Contact Information</i>	60
7.4.3	<i>Sponsor Notification of SAEs to Regulatory Authorities</i>	60
7.4.4	<i>Research centre Notification of SAEs to Local Ethics Committee or Local Health or Regulatory Authorities</i>	60
7.5	IMMEDIATELY REPORTABLE EVENTS	61
7.6	SAFETY MONITORING	61
<b>8.</b>	<b>DATA MANAGEMENT</b>	<b>61</b>
8.1	DATA HANDLING AT RESEARCH CENTRES	61
8.2	SOURCE DATA VERIFICATION	62



<b>9. STATISTICAL METHODS .....</b>	<b>62</b>
9.1 GENERAL DESIGN .....	62
9.2 TRIAL ENDPOINTS .....	62
9.3 PRIMARY TRIAL HYPOTHESES .....	62
9.4 SAMPLE SIZE AND POWER CALCULATIONS .....	62
9.5 STATISTICAL ANALYSES .....	63
9.5.1 Primary Efficacy Analysis .....	64
9.5.2 Primary Safety Analysis .....	65
9.5.3 Secondary Analyses .....	65
9.6 INTERIM ANALYSIS .....	67
9.7 DATA AND SAFETY MONITORING BOARD (DSMB) .....	68
9.8 HANDLING OF MISSING DATA AND DROPOUTS .....	69
<b>10. INVESTIGATOR REQUIREMENTS .....</b>	<b>69</b>
10.1 TRIAL INITIATION .....	69
10.2 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE APPROVAL .....	69
10.3 TRIAL MONITORING AND AUDITS .....	69
10.4 CASE REPORT FORMS .....	70
10.5 DISCLOSURE OF DATA .....	70
10.6 RECORD RETENTION .....	70
<b>11. ETHICAL CONSIDERATIONS .....</b>	<b>70</b>
11.1 ETHICAL REVIEW .....	70
11.2 REPORTING AND MANAGEMENT OF SOCIAL HARMS .....	71
11.3 COMMUNITY ENGAGEMENT .....	71
<b>12. PUBLICATIONS .....</b>	<b>71</b>
<b>13. REFERENCES .....</b>	<b>72</b>
<b>APPENDIX A: SCHEDULE OF CLINICAL PROCEDURES .....</b>	<b>73</b>
<b>APPENDIX B: SCHEDULE OF LABORATORY PROCEDURES .....</b>	<b>75</b>
<b>APPENDIX C: HIV TESTING ALGORITHMS .....</b>	<b>77</b>
<b>APPENDIX D: VISIT SCHEDULE AND BLOOD VOLUMES .....</b>	<b>82</b>

## ACRONYMS AND ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARV	Antiretroviral
ASCUS	Atypical Squamous Cells of Undetermined Significance
AST	Aspartate aminotransferase
AUC	Area Under plasma concentration-time Curve
CDC	U.S. Centers for Disease Control and Prevention
CI	Confidence Interval
CRF	Case Report Form
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAPY	Di-aminopyrimidine
DSMB	Data and Safety Monitoring Board
FACTS	Follow on Africa Consortium for Tenofovir Studies
FBC	Full Blood Count
FDA	Food & Drug Administration (U.S.)
GCP	Good Clinical Practice
GEE	General Estimating Equation
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
HPTN	HIV Prevention Trials Network
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
IRE	Immediately Reportable Event
IUD	Intrauterine Device
MTD	Maximum Tolerated Dose
MTN	Microbicide Trials Network
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PCR	Polymerase Chain Reaction
PID	Participant Identification number
PMTCT	Prevention of Mother-to-Child Transmission of HIV
PrEP	Pre-Exposure Prophylaxis
RNA	Ribonucleic Acid
RPR	Rapid Plasma Reagin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STI	Sexually Transmitted Infection

TEAE	Treatment Emergent Adverse Event
TPHA	Treponema Pallidum Haemagglutination Test
TPPA	Treponema Pallidum Particle Agglutination Assay
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
USP	United States Pharmacopeia
VOICE	Vaginal and Oral Interventions to Control the Epidemic
WHO	World Health Organization

## IPM 027 SYNOPSIS

### A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED SAFETY AND EFFICACY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-NEGATIVE WOMEN

**BACKGROUND:** HIV/AIDS is the leading cause of death globally in women aged 15 to 44, and exerts an especially high toll in sub-Saharan Africa, where 60% of people living with HIV are women and girls. Developing new HIV prevention options that women can use remains a public health priority. The current generation of vaginal microbicide candidates, containing highly-specific antiretroviral (ARV) drugs, are currently undergoing extensive safety and efficacy trials. ARV-based microbicides specifically target HIV and can be designed in various forms (e.g. vaginal gels, rings, films, tablets) for more flexible dosing, including products for use around the time of sex, or daily or monthly products that could be used independent of sexual activity. Other recently completed and ongoing clinical trials are exploring whether oral daily ARVs taken as pre-exposure prophylaxis (PrEP) are safe and effective for HIV prevention.

Recent research confirms the potential of ARV-based HIV prevention. In July 2010, in an important milestone for HIV prevention, the CAPRISA 004 Phase IIB microbicide trial found a 39% lower HIV infection rate in women using 1% tenofovir gel as compared to the women using a placebo gel. 1% Tenofovir gel is the first ARV-based microbicide to be tested in an efficacy trial. It has been tested as a once-daily product in the MTN-003 (VOICE) Phase IIB trial, but the tenofovir gel arm was discontinued due to futility. A further confirmatory Phase III trial, FACTS 001, using the CAPRISA 004 BAT24 dosing regimen, started in 2011.

Successes with oral ARVs for prevention have also been observed. In November 2010, the iPrEx Phase III trial showed that oral Truvada® was 42% effective in reducing the risk of HIV infection among men who have sex with men. And in May 2011, results of the HPTN 052 “treatment for prevention” trial showed that immediate use of ARV therapy by HIV-positive individuals can reduce the risk of transmitting the virus to their uninfected partner by 96%. However, another recent Phase III trial, FEM-PrEP, which tested the effectiveness of daily oral Truvada® in 1,951 high-risk women in Africa, was stopped after an Independent Data Monitoring Committee determined that it was highly unlikely that the trial would be able to show that this strategy was effective. The efficacy of oral tenofovir tablets has also been tested in the MTN-003 (VOICE) Phase IIB trial, but the oral tenofovir arm was discontinued due to futility.

It appears that ARV approaches to prevention have the potential to transform the response to the HIV/AIDS pandemic. For women, in addition to confirmatory trials on tenofovir gel, 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 and improve upon the level of effectiveness seen in CAPRISA 004.

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. In addition, a product used independently of sex could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse. As seen in the CAPRISA 004 and iPrEx trials, higher adherence to the test product was associated with increased effectiveness of the product. It is likely that products that can be applied less frequently will be more acceptable and will achieve better adherence. Vaginal rings that need only be replaced monthly may therefore have benefits over dosage forms that need to be used more frequently. The dapivirine (25 mg) silicone elastomer vaginal matrix ring is IPM's lead candidate for advancement to clinical safety and efficacy testing.

Multiple Phase I and I/II clinical trials have evaluated the safety of dapivirine in vaginal rings and gels and in an oral formulation. These clinical trials support the favourable safety profile and tolerability of dapivirine in general, and specifically in vaginal delivery formulations. IPM 027 has been designed to evaluate the safety and to determine the efficacy of dapivirine administered in a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine (Ring-004), inserted once every 4 weeks, in healthy, HIV-negative, sexually active women – as compared with a placebo vaginal ring.

**OBJECTIVES:**

**The Primary Objectives are:**

1. To determine the efficacy of dapivirine administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks), in preventing HIV-1 infection among healthy, sexually active HIV-negative women.
2. To assess the safety of dapivirine administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks).

**The Secondary Objectives are:**

1. To determine the incidence of HIV-2 in the dapivirine and placebo vaginal ring groups.
2. To assess and compare the incidence of curable sexually-transmitted infections (STIs), and changes in vaginal flora in the dapivirine and placebo vaginal ring groups.

3. To determine the incidence of pregnancy in both trial arms.
4. To assess reported adherence to the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.
5. To assess reported acceptability of the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.
6. To assess the frequency and type of HIV-1 drug resistance in women who acquire HIV-1 infection while using the investigational product.

**The Exploratory Objectives are:**

1. To evaluate the association between HSV-2 and HIV-1 infection in both trial arms.
2. To explore the potential relationship between method of contraception, pregnancy incidence and HIV seroconversion in both trial arms.
3. To explore the relationship between drug concentrations and trial outcomes (HIV-1 seroconversion and viral resistance).
4. To explore the correlation of drug concentrations and self-reported adherence measures.

**ENDPOINTS AND ASSESSMENTS:**

**The primary endpoints are:**

- The incidence rate of HIV-1 seroconversion;
- All adverse events (AEs) (full descriptive evaluation).

**The primary endpoints will be assessed through:**

- Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C;
- Self-reports, physical examination, gynaecological assessments, including pelvic/speculum examination, laboratory tests and other indicated investigations. All AEs will be reported, regardless of grade or relatedness.

**The secondary endpoints are:**

- The incidence rate of HIV-2 seroconversion;

- The incidence of curable STIs (i.e. *N.gonorrhoea*, *C.trachomatis* and *T.vaginalis*), and changes in vaginal flora in each trial arm over the IP use period;
- The incidence of pregnancy in each trial arm over the IP use period;
- The proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period;
- The proportion of women who report the use of the vaginal ring as acceptable;
- The proportion of participants with HIV-1 drug resistance mutations among participants who acquire HIV-1.

**The secondary endpoints will be assessed through:**

- Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C;
- STI testing, vaginal flora and vaginal pH testing;
- Pregnancy testing;
- Questionnaires and qualitative data regarding sexual behaviour and adherence to the use of a vaginal ring inserted once every 4 weeks over the trial period;
- Questionnaires and qualitative data regarding the acceptability of the use of a vaginal ring inserted once every 4 weeks over the trial period;
- Viral genotyping methods.

**The exploratory endpoints are:**

- The proportion of HSV-2 among analysed samples;
- Incidence of pregnancy in correlation with HIV seroconversion rates and method(s) of contraception used by participants;
- Steady-state drug concentrations in blood and vaginal fluid;
- Steady-state drug concentrations in correlation with self-reported adherence as outlined above for the secondary objective.

**The exploratory endpoints will be assessed through:**

- HSV-2 testing;
- Pregnancy testing and HIV testing as outlined above for the secondary objective, and documentation of participant contraceptive method(s);
- Drug concentrations in blood and vaginal fluid;
- Vaginal fluid, plasma and/or ring residual drug concentrations and self-reported behavioural measures as outlined above for the secondary objective.

**TRIAL DESIGN:** IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled trial to assess the safety and efficacy of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks,

in healthy, sexually active HIV-negative women, when compared to a placebo vaginal ring. Approximately 1,950 participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.

**TRIAL DURATION:** Each participant will engage in the screening process for up to 4 weeks (28 days) prior to enrolment and will use the IP for a period of approximately 24 months (104 weeks).

Each participant will have an additional 6 weeks of follow-up after ring discontinuation, to assess safety and identify HIV seroconversions after product discontinuation.

**POPULATION:** Approximately 1,950 sexually active HIV-negative women, 18 – 45 years of age, who understand the trial and can provide informed consent, will be enrolled and randomised in a 2:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a placebo vaginal ring.

**INCLUSION CRITERIA:**

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

1. Women  $\geq 18$  and  $\leq 45$  years of age, at screening, who can provide informed consent;
2. Available for all visits and consent to follow all procedures scheduled for the trial;
3. Self-reported sexually active (defined as an average of at least one penetrative penile-vaginal coital act per month for the last 3 months prior to screening);
4. HIV-negative as determined by the HIV algorithm applied at screening and enrolment;
5. On a stable form of contraception as defined within section 5.4 and willing to continue on stable contraception for the duration of the clinical trial, unless post-menopausal or surgically sterilised;
6. Asymptomatic for genital infections at the time of enrolment (if a woman is diagnosed with any clinically significant curable STI, she must have initiated treatment at least 1 week prior to enrolment and have completed the full course of treatment);
7. 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;



8. Willing to refrain from participation in another research trial using drugs, vaccines, medical devices, microbicides or oral pre-exposure prophylaxis investigational drugs for the duration of the IPM 027 trial.

#### **EXCLUSION CRITERIA:**

Women who have any of the exclusion criteria below are not eligible:

1. Currently pregnant or last pregnancy within 3 months prior to screening or intends to become pregnant during trial participation;
2. Currently breast-feeding;
3. Non-therapeutic injection drug use in the 12 months prior to screening;
4. Participated in another research trial using drugs, medical devices, microbicides or oral pre-exposure prophylaxis agents within 60 days prior to screening;
5. Previously participated or currently participating in any HIV vaccine trial;
6. Untreated, clinically significant urogenital infections, e.g., urinary tract, or other sexually transmitted infections, or other gynaecological symptoms within 1 week prior to enrolment;
7. Has a Grade 2 or higher pelvic examination finding, according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; Addendum 1 Female Genital Grading Table for Use in Microbicide Studies;
8. History of significant urogenital or uterine prolapse, undiagnosed vaginal bleeding, diagnosed chronic and/or recurrent vulvovaginal candidiasis, urethral obstruction, incontinence or urge incontinence;
9. Any gynaecological surgery within 90 days prior to screening;
10. Any Grade 1 or higher baseline aspartate aminotransferase (AST), alanine transaminase (ALT), or platelet count, and any Grade 2 or higher baseline haematology, chemistry or urinalysis laboratory value according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events;
11. Any history of anaphylaxis or severe allergy resulting in angioedema; or a history of sensitivity/allergy to latex or a silicone elastomer;

12. Any history of diabetes mellitus and chronic use of oral corticosteroid therapy; and any uncontrolled serious chronic or progressive disease;
13. Cervical cytology at screening that requires cryotherapy, biopsy or treatment (other than for infection). Women with Grade 1 cervical cytology findings can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology);
14. Any condition(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 and enrolment: Potential participants who consent will be invited to screen for the trial. At screening 1, these potential participants will provide information on inclusion and exclusion criteria, including locator and menses information, demographic information, 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 condoms), contraceptive counselling and HIV pre- and post-test counselling, and tested for pregnancy, HIV, STIs and cervical cytology, as well as safety laboratory assessments. At screening 2, further information will be collected on medical history, concomitant medication, locator and menses information. Those women who meet specified inclusion criteria and no exclusion criteria, have a normal pelvic examination, negative pregnancy and HIV rapid tests, and consent to participate in the trial, will be invited to enrol in the trial. Eligible women will be randomly assigned in a 2:1 ratio to one of the two trial arms. At enrolment, each participant will receive a baseline behavioural questionnaire and a diary card to record sexual activity and ring experiences over the upcoming 4-week period. Blood samples will be collected for storage, and will be tested retrospectively for HIV-RNA PCR, HIV viral genotyping and HSV-2 serology subsequent to confirmed HIV-1 seroconversion. In addition, vaginal specimens will be taken prior to ring insertion to determine vaginal pH and assess vaginal flora.

At enrolment, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled visit.

Trial visits: Dapivirine or placebo vaginal rings will be inserted at 4-weekly intervals for the duration of the IP use trial period. Similar to the enrolment visit, at each regularly scheduled trial visit while on the IP, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled visit. All participants will receive pre- and post-test HIV counselling, HIV/STI risk reduction counselling, condom and vaginal ring adherence counselling, HIV and pregnancy testing, and collection

of locator, menses, and concomitant medication information. Male condoms will be provided at all visits as part of HIV/STI risk reduction counselling. Contraceptive counselling will be provided at all visits.

Blood and vaginal fluid samples will be collected for storage at all visits, including the last product use visit. These stored blood samples will be tested for HIV-RNA PCR and viral genotyping only in HIV-1 seroconverters, while HSV-2 serology, blood and vaginal fluid dapivirine concentration measurement will be conducted in confirmed HIV-1 seroconverters and a randomly selected control group of HIV-negative participants.

The rapid and confirmatory laboratory tests used in the HIV testing algorithm will be able to detect both subtypes, HIV-1 and HIV-2. At the point of HIV seroconversion, the IP will be discontinued, and additional samples will be collected and tested for viral genotyping (blood), dapivirine concentrations (blood and vaginal fluid) and HSV-2 serology (blood). In addition, blood samples for viral genotyping will also be collected at the scheduled exit visit, approximately 6 weeks following seroconversion. No further storage samples will be collected in these participants.

Adherence assessments will be conducted through an interviewer-administered questionnaire at all 4-weekly trial visits, except the exit visit. Participants will be provided with diary cards at all 4-weekly visits except the last product use and exit visits. The participant may consult the diary card during the adherence assessments and the adherence counselling sessions at each 4-weekly visit. The cards will be collected at each visit. Acceptability questionnaires will be administered at the second trial visit (week 4), and at 24-weekly intervals thereafter, until the last product use visit.

Twenty-four (24) to 42 weeks after research centre activation, each research centre will conduct 6 – 10 qualitative individual interviews with participants, and 6 – 10 qualitative individual interviews with male partners. These interviews will provide data on acceptability, sexual behaviour and adherence issues. The recruitment and sampling strategy will be specified in the Statistical Analysis Plan (SAP).

AEs will be assessed at all visits post-randomisation. In addition, safety laboratory assessments, pelvic examination, vaginal pH and vaginal flora as well as STI tests will be performed at 12-weekly intervals. Cervical cytology will be repeated at the end of the first and second year of IP use. Residual dapivirine levels in returned rings will be measured for a selected group of participants at predetermined time-points.

Last product use visit: At the last product use visit, participants will return the last used rings; report any medical problems and/or concomitant medications since the last visit; provide locator and menses information; receive pre- and post-test HIV counselling, contraceptive counselling and HIV/STI risk-reduction counselling

(including provision of male condoms); complete vaginal ring use, adherence and acceptability questionnaires; undergo a physical examination as well as a pelvic examination for evaluation of STIs and changes in vaginal flora; have a specimen collected for cervical cytology; and provide blood and vaginal fluid specimens for storage, and specimens for pregnancy and HIV testing, and safety laboratory assessments.

Each research centre will conduct 2 – 3 focus groups with participants who have been recruited for these groups at the last product use visit. Additionally, 6 – 10 qualitative individual interviews with male partners will be conducted at each research centre. These interviews will provide data on acceptability and adherence issues. The recruitment and sampling strategy will be specified in the SAP.

Exit visit - 6 weeks after ring discontinuation: Participants may be notified of any abnormal findings and asked to return to the research centre prior to the exit visit, as needed for treatment and/or referral. On the day of the scheduled exit visit, participants will return to the research centre to receive results from their pelvic examination/STI testing and safety laboratory assessments done at the last product use visit, and treatment or referral as needed. AEs and concomitant medications will also be recorded at this visit.

Participants will receive pre- and post-test counselling for HIV and undergo final HIV testing. HIV/STI risk reduction counselling (including provision of male condoms) and contraceptive counselling will also be provided at the exit visit. If a clinically significant gynaecological or other related AE remains unresolved at the time of trial completion, a clinical assessment will be made by the research centre's investigator or designated qualified physician and the IPM Clinical Physician or designee to determine whether continued follow-up of the AE is warranted.

Participants will then be considered to have completed trial participation, and informed that they may be re-contacted at a future date to be provided information about trial results, including individual unblinding.

## **STATISTICAL CONSIDERATIONS:**

General: IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled trial to assess the safety and efficacy of dapivirine in a silicone elastomer vaginal matrix ring, to be conducted at approximately 7 clinical research centres. Individuals meeting all inclusion criteria and no exclusion criteria will be randomised in a 2:1 (dapivirine:placebo) ratio to either the investigational product or placebo. Randomisation will be stratified by research centre at the time of enrolment, using a pre-specified block size, and will be determined via the use of an automated randomisation system to ensure balance of the treatment assignments.

Sample Size and Power Calculations:

IPM 027 will randomise approximately 1,950 HIV-negative women in a 2:1 ratio such that 1,300 participants will be assigned to the investigational product and 650 participants will be assigned to the placebo ring. The increased sample size will mitigate the potential negative impact of product non-adherence on the trial outcome and sustain the power of the trial for the primary objectives.

Under this design, a total of 96 HIV-1 seroconversions are expected and will provide 81% power to detect a 50% reduction in the rate of HIV-1 seroconversions in the active arm, assuming an annual HIV-1 seroconversion rate of 4% in the placebo arm.

Statistical Analyses: The analysis of the primary efficacy endpoint (HIV-1 seroconversion rate) will be performed on the modified Intent-to-Treat (m-ITT) population, which will include all participants who were HIV-1 negative at the time of enrolment, analysed according to the treatment arm to which they were randomised, regardless of adherence to the product. A per-protocol analysis may also be performed on a subset of participants who did not experience a major protocol violation.

The primary efficacy analysis will provide an estimate of the HIV-1 seroconversion rates for the treatment and placebo arms, with 95% confidence intervals (CIs). The log-rank test, stratified by research centre, will formally evaluate at a 5% significance level the null hypothesis that the probability of an HIV-1 seroconversion occurring at any time point is the same for the active and placebo arms. Kaplan-Meier curves will also be presented, stratified by research centre.

For the safety analysis, a descriptive analysis of all AEs will be presented in tables and listings. Fisher's Exact test will be performed to compare the proportion of participants in the active and placebo arms, with regard to all Grade 3 and 4 AEs, all SAEs, and AEs leading to IP discontinuation, at a 0.05 significance level.

The analysis of the social and behavioural secondary endpoints will focus on the assessment of acceptability of the vaginal ring, adherence to the use of the vaginal ring, as well as investigation of possible factors influencing adherence of women participating in the trial. Data for vaginal ring acceptability, sexual behaviour, condom use and vaginal ring use will be collected by self-report through interviewer-administered questionnaires, focus groups and individual interviews. Comparison between the two treatment arms will be conducted and will take into account the repeated measures by using a general estimating equation (GEE) framework.

Appropriate statistical analyses of the exploratory endpoints will be performed.

The Data and Safety Monitoring Board (DSMB) will perform thorough reviews of the data at pre-specified time points during the

trial duration. They may recommend the early termination of the trial or modification due to evidence of safety concerns among participants. An interim analysis to assess for possible futility or efficacy will be conducted when approximately 50% of the expected trial endpoints have been observed. An additional interim analysis/analyses may be requested by the DSMB.

## 1. INTRODUCTION

### 1.1 Background

According to UNAIDS, the estimated number of people living with HIV worldwide in 2010 (30 years after the HIV/AIDS epidemic first started) was 34 million<sup>1</sup>. In 2009, 2.6 million people became newly infected with HIV and 1.8 million lost their lives to AIDS<sup>2</sup>. Over 95 percent of new infections are occurring in developing countries, specifically sub-Saharan Africa, where new infections threaten the sustainability of expanded access to HIV/AIDS treatment. According to UNAIDS, for every 3 people placed on antiretroviral treatment in 2010, 5 others become newly infected worldwide<sup>1</sup>. The ongoing development of safe and effective HIV prevention technologies that can be made easily accessible to developing countries remains a public health priority.

“AIDS at 30: Nations at the Crossroads”, the report published by UNAIDS in 2011, shows that women and girls continue to be affected disproportionately by HIV in sub-Saharan Africa, where they account for 60% of people living with HIV<sup>1</sup>. Unprotected heterosexual intercourse is currently the leading mode of HIV transmission among women. Correct and consistent use of latex condoms is one proven method of preventing HIV transmission; however, condoms are widely regarded as inadequate prevention options for women, because many women are unable to negotiate condom use with their partners. Most current HIV prevention methods require the consent (as well as some action or behaviour change) of the male partner<sup>3</sup>.

Developing HIV prevention options that women can use remains a global concern, given the high rates of HIV infection among women. Vaginal microbicides, which are self-initiated, would offer women a critically needed new tool to prevent HIV. Microbicide candidates, based on antiretroviral (ARV) drugs that specifically target HIV, are planned to undergo extensive safety and efficacy trials. 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 July 2010, an important milestone for HIV prevention came from the CAPRISA 004 Phase IIB microbicide trial, which found a 39% lower HIV infection rate in women using 1% tenofovir gel within 12 hours before and after sex (i.e. two applications per sex act), as compared to the women using a placebo gel. In women who reported using the gel with more than 80% of sex acts, the protection level was even higher, at 54%<sup>4</sup>. Tenofovir gel is the first ARV-based microbicide to be tested in an efficacy trial. It has been tested as a once-daily product in the MTN-003 (VOICE) Phase IIB trial in Africa, but the tenofovir gel arm was discontinued due to futility. A further confirmatory Phase III trial, FACTS 001, using the same BAT24 dose regimen as in the CAPRISA 004 trial, started in 2011.

Successes with oral ARVs for prevention have also been observed. In November 2010, the iPrEx Phase III trial showed that oral Truvada® was 42% effective in reducing the risk of HIV infection among men who have sex with men<sup>5</sup>. And in May 2011, results of the HPTN 052 “treatment for prevention” trial showed that immediate use of ARV therapy by HIV-positive individuals can reduce the risk of transmitting the virus to their uninfected partner by 96%<sup>6</sup>.

However, another recent Phase III trial, FEM-PrEP, which tested the effectiveness of daily oral Truvada® in preventing HIV transmission in 1,951 high-risk women in Africa, was

stopped after an Independent Data Monitoring Committee (IDMC) determined that it was highly unlikely that the trial would be able to show that this strategy was effective. In this trial, 56 new HIV infections were equally distributed among women who received Truvada® and those who received placebo<sup>7</sup>. The reasons for this failure are still being investigated. Similarly, the efficacy of oral tenofovir tablets was evaluated in the MTN-003 (VOICE) Phase IIB trial, but after an independent interim review of the data it was concluded that the trial will not be able to demonstrate that tenofovir tablets are effective in preventing HIV infection, and the oral tenofovir arm was consequently discontinued.

It appears that ARV approaches to prevention have the potential to transform the response to the HIV/AIDS epidemic. For women, in addition to confirmatory work on tenofovir gel, further research is needed on microbicides that contain different ARV compounds in different formulations and using different dosing strategies, to provide options and improve upon the level of effectiveness seen in CAPRISA 004.

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. In addition, a product used independently of sex could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse. As seen in the CAPRISA 004 trial, higher adherence to product may translate into higher effectiveness of the product. It is likely that products that can be applied less frequently will be more acceptable and will achieve better adherence. Vaginal rings that need only be replaced monthly may therefore have benefits over dosage forms that need to be used more frequently. The dapivirine (25 mg) silicone elastomer vaginal ring is IPM's lead candidate for advancement to clinical safety and efficacy testing.

Multiple Phase I and I/II clinical trials have evaluated the safety of dapivirine in vaginal rings, gels and in an oral formulation. These clinical trials support the favourable safety profile and tolerability of dapivirine in general and specifically in vaginal delivery formulations.

## 1.2 Dapivirine Vaginal Ring

### 1.2.1 Dapivirine

Dapivirine is a substituted di-aminopyrimidine (DAPY) derivative and one of a new generation of non-nucleoside reverse transcriptase inhibitors (NNRTIs). NNRTIs bind to the HIV reverse transcriptase (RT) enzyme preventing viral replication and therefore production of infectious virus. Dapivirine was originally developed by 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 also 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.



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

- Clinical trials have demonstrated sustained delivery of high levels of dapivirine throughout the cervicovaginal vault for up to 1 month;
- Since the ring is able to deliver drug for at least 1 month, the burden of user adherence is lower than for once daily products;
- Product acceptability studies and the experience gained from marketed vaginal ring products have established a high level of acceptance and adherence from women using vaginal rings with similar physical characteristics;
- The overall cost for the ring is relatively low;
- Minimal storage space is required for the ring when compared with once daily products;
- Vaginal rings can be used more discreetly than daily or pre-coital products.

The safety and tolerability of dapivirine have been evaluated by IPM and Tibotec Pharmaceuticals in both animal and human studies via the oral and vaginal routes. Below is a summary of the data collected through these studies. Detailed information on dapivirine is available in the Dapivirine Vaginal Ring Investigator's Brochure<sup>8</sup> (IB).

### 1.2.2 Nonclinical Research

The potential of dapivirine as a microbicide for prevention of sexual transmission of HIV has been assessed and confirmed in different *in vitro*, *ex vivo* and *in vivo* models:

- 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<sub>50</sub> values ranging from 0.9 nM (0.3 ng/mL) against laboratory isolates to less than 100 nM (32.9 ng/mL) for HIV-1 isolates encoding one or more known NNRTI resistance mutations. Dapivirine is equally active against both CCR5 tropic and CXCR4 tropic strains of HIV-1.
- *In vitro* studies in monocyte-derived dendritic cells and autologous CD4+ T-cells, which are important cells in mucosal transmission, indicated that dapivirine is able to prevent viral replication at 10 nM (3.3 ng/mL). Long-term treatment with dapivirine aborted HIV-1 replication in cells infected with cell-free virus at 10 nM (3.3 ng/mL), or those infected by cell-to-cell transmission at 100 nM (32.9 ng/mL).
- In a cervical explant model using tissue from hysterectomised women, dapivirine potently inhibited HIV infection of tissue (IC<sub>50</sub> = 1.5 nM [0.49 ng/mL]), with > 99% inhibition at 10 nM (3.3 ng/mL). Furthermore, dapivirine inhibited the transfer of HIV from migratory dendritic cells to permissive T-cells with an IC<sub>50</sub> of 0.1 nM (0.03 ng/mL), and at 100 nM (32.9 ng/mL) transfer was completely inhibited.
- In an *in vivo* hu-SCID mouse model in which mice were treated with dapivirine gels (2.25 to 225 µM [0.7 to 74.1 µg/mL]) vaginally, and then challenged vaginally with human peripheral blood lymphocytes infected with either R5 or X4 virus, the gels demonstrated 70 – 100% protection.

The toxicity of dapivirine has been evaluated in a comprehensive program of preclinical studies. These are described in the IB and included chronic vaginal toxicity studies in rabbits using gel formulations of dapivirine. No local or systemic toxicity was observed following repeat administration at up to 20 mg/mL for 14 days, up to 5 mg/mL (0.5%) for 13 weeks or up to 2 mg/mL (0.2%) for 39 weeks. Furthermore, vaginal reproductive toxicity studies in rats and rabbits using dapivirine gel at up to 2.0 mg/mL (0.2%) did not identify any adverse effects on the maternal animals or the developing embryo/foetus.

A study was conducted in sheep to evaluate Ring-004 containing 25 mg dapivirine for potential local and systemic toxicity and compare the findings with those in animals receiving dapivirine gel. There were no treatment related findings in sheep that received up to 3 rings (each ring for a period of 30 days, after which the ring was removed and replaced with a fresh ring) or daily 2 mg/mL (0.2%) gel (dose volume = 2.5 mL) for a total exposure of 90 days.

The no adverse effect level (NOAEL) in rats and dogs following oral administration was 20 mg/kg/day. The  $C_{max}$  at the NOAEL was 0.39  $\mu\text{g/mL}$  in rats and 1.21  $\mu\text{g/mL}$  in dogs; which is, respectively, more than 990 and 3000 times the maximum mean plasma concentration (0.392 ng/mL) in women using Ring-004. AUC at the NOAEL was 4.80  $\mu\text{g.h/mL}$  in rats and 12.98  $\mu\text{g.h/mL}$  in dogs, which is over 570 and 1500 times, respectively, the mean AUC (8.379 ng.h/mL) in women using Ring-004.

### 1.2.3 Clinical Research

To date, 25 Phase I and Phase I/II clinical trials of dapivirine have been conducted: six trials of dapivirine vaginal rings in 393 participants (222 using dapivirine rings and 183 using placebo rings); eight 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. The data analysis of three of these trials, one vaginal ring trial (IPM 015) and two vaginal gel trials (IPM 014A and IPM 020) is ongoing, and no results are available as yet.

In a safety and pharmacokinetic trial in healthy HIV-negative women to assess delivery of dapivirine from both the matrix and reservoir vaginal rings containing 25 mg of dapivirine (IPM 018), the mean maximum dapivirine concentration in cervicovaginal fluids was 2.866 mg/g, and in one subject a concentration of 11 mg/g was detected. These levels were associated with the matrix configuration (much lower levels were observed for the reservoir ring) and occurred at about 24 hours post ring insertion, after which they decreased rapidly. Since the highest gel concentration of dapivirine previously evaluated in vaginal toxicity studies was approximately 2 mg/mL, an additional 14-day vaginal study in rabbits was performed at concentrations up to 20 mg/mL. Again, no evidence of local or systemic toxicity was observed.

The maximum tolerated dose (MTD) was established in oral trials as 350 mg for a single dose and 300 mg when administered twice daily for 14 days. The highest daily dose of dapivirine delivered from a vaginal gel to date (Gel 4759 and Gel 4789, approximately 1250  $\mu\text{g/day}$  for 84 days) is 280 times lower than the MTD for a single dose of oral dapivirine (350 mg) and 480 times lower than the MTD for multiple doses of oral dapivirine (300 mg b.i.d. for 14 days). The drug load for the dapivirine vaginal ring is 25 mg, which is also much lower than the oral MTD. Studies measuring the amount of residual dapivirine in the vaginal ring post-use indicate that < 10 mg of the total drug load is released over a 28-day period of ring use.

No drug-related serious adverse events (SAEs) have been reported to-date and no trials were stopped for safety reasons. Adverse events (AEs) documented in 5 or more participants (>2%) after oral exposure to dapivirine were headache, dizziness, nausea, diarrhoea, fatigue, tremor, somnolence, flatulence, and vomiting. Most of these treatment emergent adverse events (TEAEs) were Grade 1 or Grade 2 and most (≥80%) were considered to be drug-related. Grade 3 TEAEs included headache, dizziness, injury, nausea, tremor, paraesthesia, disturbance in attention, abrasion, AST increased, ALT increased, polyuria, fever, diarrhoea, and vomiting. Elevated liver function was documented in laboratory tests. These increases in AST and ALT were transient and did not result in any liver impairment related to use of the investigational product. AEs which have been documented in at least 5% of participants in all dapivirine ring and dapivirine gel trials include headache, vaginal haemorrhage (“vaginal bleeding”)<sup>1</sup>, lower abdominal pain, metrorrhagia, and vulvovaginal/genital pruritus. Events that were considered related to the dapivirine vaginal ring include headache, fatigue, vulvovaginal or genital pruritus, vulvovaginal discomfort, abdominal pain, urinary incontinence, nausea, and vaginal or genital discharge.

A complete summary of the safety data from preclinical studies and previous clinical trials of dapivirine via the oral and vaginal routes and the different dosage forms are contained in the Dapivirine Vaginal Ring IB.

#### **1.2.4 Formulation of a Silicone Elastomer Vaginal 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 drug substance dispersed in a platinum-cured silicone matrix. The dimensions of the ring are 56 mm and 7.7 mm – the outer diameter and cross-sectional diameter, respectively. Details regarding the formulation and dimensions are provided in the IB. The dapivirine silicone elastomer vaginal matrix ring is designed to provide sustained release over a minimum of 28 days.

### **1.3 Rationale for Protocol IPM 027**

Based on *in vitro*, *in vivo*, and *ex vivo* studies described in the Dapivirine Vaginal Ring IB, dapivirine shows great promise as a topical microbicide to prevent HIV-1 infection.

In order for a microbicide to be most effective, it is essential that it is used correctly and consistently. It is likely that products that can be applied less frequently, and have a minimal effect on the vaginal environment during sex will be more acceptable to women and their male partners and will achieve better user-adherence. Vaginal rings that need only be replaced every month may have benefits over dosage forms that need to be used more frequently.

Silicone elastomer vaginal rings have already been developed and approved as delivery methods for medications. For example, Pfizer (formerly Pharmacia and Upjohn Company) has marketed Estring<sup>®</sup> (estradiol vaginal ring), a vaginal ring that is also made from

---

<sup>1</sup> Based on the MedDRA version that was used, the following Lower Level Terms would have coded to a Preferred Term of “vaginal haemorrhage”: vaginal bleeding, bloody vaginal discharge, vaginal haemorrhage, vaginal ecchymosis, and vaginal petechiae.

silicone elastomer and contains estradiol used to treat local symptoms of urogenital atrophy, since 1993. Prior to the launch of Estring<sup>®</sup>, the biological safety of the silicone elastomer was studied in various *in vitro* and *in vivo* test models. The results show that the silicone elastomer is non-toxic, non-pyrogenic, non-irritating, and non-sensitising<sup>9</sup>.

Femring<sup>®</sup> (estradiol acetate vaginal ring), a hormone replacement product approved in June 2003 by the United States (U.S.) Food and Drug Administration (FDA), is another silicone ring that treats menopause-induced vasomotor symptoms (e.g., hot flashes) and symptoms of vulvar and vaginal atrophy (e.g., dryness)<sup>10</sup>. Although these rings are not exactly the same as the IPM ring, the extensive clinical trial and post-marketing experience gained from these products provides further assurance of the safety of silicone elastomer rings as vaginal drug delivery devices. An acceptability trial of the silicone elastomer ring used in Femring<sup>®</sup> (but containing no drug) among postmenopausal women in the U.S. demonstrated very high acceptability and ease of use<sup>11</sup>. IPM recently evaluated the acceptability and safety of a similar placebo vaginal ring in the IPM 011 study (n=170). This study confirmed that the placebo ring was safe and acceptable to users and their male partners<sup>12</sup>.

IPM 027 has been designed to evaluate the safety and determine the efficacy of dapivirine (25 mg) in a silicone elastomer vaginal matrix ring (Ring-004), inserted once every 4 weeks in healthy, HIV-negative sexually active women, as compared with a placebo vaginal ring.

## **2. TRIAL OBJECTIVES**

### **2.1 Trial Objectives**

#### Primary Objectives

1. To determine the efficacy of dapivirine administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks), in preventing HIV-1 infection among healthy, sexually active HIV-negative women.
2. To assess the safety of dapivirine administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks).

#### Secondary Objectives

1. To determine the incidence of HIV-2 in the dapivirine and placebo vaginal ring groups.
2. To assess and compare the incidence of curable sexually-transmitted infections (STIs), and changes in vaginal flora in the dapivirine and placebo vaginal ring groups.
3. To determine the incidence of pregnancy in both trial arms.

4. To assess reported adherence to the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.
5. To assess reported acceptability of the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.
6. To assess the frequency and type of HIV-1 drug resistance in women who acquire HIV-1 infection while using the investigational product.

### Exploratory Objectives

1. To evaluate the association between HSV-2 and HIV-1 infection in both trial arms.
2. To explore the potential relationship between method of contraception, pregnancy incidence and HIV seroconversion in both trial arms.
3. To explore the relationship between drug concentrations and trial outcomes (HIV-1 seroconversion and viral resistance).
4. To explore the correlation of drug concentrations and self-reported adherence measures.

## **2.2 Trial Endpoints and Assessments**

### **The primary endpoints are:**

- The incidence rate of HIV-1 seroconversion;
- All adverse events (AEs) (full descriptive evaluation).

The primary endpoints will be assessed through:

- Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C;
- Self-reports, physical examination, gynaecological assessments, including pelvic/speculum examination, laboratory tests and other indicated investigations. All AEs will be reported, regardless of grade or relatedness.

### **The secondary endpoints are:**

- The incidence rate of HIV-2 seroconversion;
- The incidence of curable STIs (i.e. *N.gonorrhoea*, *C.trachomatis* and *T.vaginalis*), and changes in vaginal flora in each trial arm over the IP use period;
- The incidence of pregnancy in each trial arm over the IP use period;
- The proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period;

- The proportion of women who report the use of the vaginal ring as acceptable;
- The proportion of participants with HIV-1 drug resistance mutations among participants who acquire HIV-1.

The secondary endpoints will be assessed through:

- Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C;
- STI testing, vaginal flora and vaginal pH testing;
- Pregnancy testing;
- Questionnaires and qualitative data regarding sexual behaviour and adherence to the use of a vaginal ring inserted once every 4 weeks over the trial period;
- Questionnaires and qualitative data regarding the acceptability of use of a vaginal ring inserted once every 4 weeks over the trial period;
- Viral genotyping methods.

**The exploratory endpoints are:**

- The proportion of HSV-2 among analysed samples;
- Incidence of pregnancy in correlation with HIV seroconversion rates and method(s) of contraception used by participants;
- Steady-state drug concentrations in blood and vaginal fluid;
- Steady-state drug concentrations in correlation with self-reported adherence as outlined above for the secondary objective.

The exploratory endpoints will be assessed through:

- HSV-2 testing;
- Pregnancy testing and HIV testing as outlined above for the secondary objective, and documentation of participant contraceptive method(s);
- Drug concentrations in blood and vaginal fluid;
- Vaginal fluid, plasma and/or ring residual drug concentrations and self-reported behavioural measures as outlined above for the secondary objective.

### **3. OVERALL TRIAL DESIGN**

#### **3.1 Trial Design**

IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled trial to assess the safety and efficacy of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks in healthy, sexually active HIV-negative women, when compared to a

placebo vaginal ring. The trial will be conducted at approximately 7 clinical research centres in sub-Saharan Africa. Approximately 1,950 participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.

Each participant will engage in the screening period of up to 4 weeks (28 days) prior to enrolment, and will use the IP for an estimated period of 24 months (104 weeks). Each participant will have an additional 6 weeks of follow-up after ring discontinuation to assess for safety and identify HIV seroconversions after product discontinuation.

### **Screening and enrolment**

Potential participants who consent will be invited to screen for the trial. At screening 1, these potential participants will provide information on inclusion and exclusion criteria, including locator, demographic and menses information, 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 condoms), contraceptive counselling and HIV pre- and post-test counselling, and tested for pregnancy, HIV, STIs and cervical cytology, as well as safety laboratory assessments. At screening 2, further information will be collected on medical history, concomitant medication, locator and menses information. Those women who meet specified inclusion criteria and no exclusion criteria, have a normal pelvic examination, negative pregnancy and HIV rapid tests, and consent to participate in the trial, will be invited to enrol in the trial. Eligible women will be randomly assigned in a 2:1 ratio to one of the two trial arms. At enrolment, each participant will receive a baseline behavioural questionnaire and a diary card to record sexual activity and ring experiences over the upcoming 4-week period. Blood samples will be collected for storage. These stored samples will be tested retrospectively for HIV-RNA PCR, HIV viral genotyping and HSV-2 serology subsequent to confirmed HIV-1 seroconversion; HIV-RNA PCR and HIV viral genotyping will be tested only in HIV-1 seroconverters, while HSV-2 serology will be tested in HIV-1 seroconverters and also in a randomly selected control group of HIV-negative participants. In addition, vaginal specimens will be taken prior to ring insertion to determine vaginal pH and assess vaginal flora.

At enrolment, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled visit. After initial ring insertion at enrolment, women will remain in the research centre under observation for 30 minutes to be assessed for immediate reactions.

### **Trial visits (during investigational product use)**

Dapivirine or placebo vaginal rings, according to the allocated randomisation group, will be inserted at 4-weekly intervals for the duration of the IP use period. Similar to enrolment, at each regularly scheduled trial visit while on the IP, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled trial visit. All participants will receive pre- and post-test HIV counselling, HIV/STI risk reduction counselling, condom and vaginal ring adherence counselling, HIV and pregnancy testing, and collection of locator, menses, and concomitant medication information. Male condoms will be provided at all visits as part of HIV/STI risk reduction counselling. Contraceptive counselling will be provided at all visits. Blood samples and vaginal fluid samples will be collected for storage at all visits. These stored blood samples will be tested for HIV-RNA PCR and viral genotyping only in HIV-1 seroconverters, while HSV-2 serology, blood and vaginal fluid dapivirine concentration measurement will be conducted in these seroconverters and a randomly selected control group of HIV-negative participants.

The rapid and confirmatory laboratory tests used in the HIV testing algorithm will detect both subtypes, HIV-1 and HIV-2. At the point of HIV seroconversion, the IP will be discontinued, and additional samples will be collected and tested for viral genotyping (blood), dapivirine concentrations (blood and vaginal fluid) and HSV-2 serology (blood). In addition, blood samples for viral genotyping will also be collected at the scheduled exit visit approximately 6 weeks following seroconversion. No further storage samples will be taken in these participants.

Adherence assessments will be conducted through an interviewer-administered questionnaire at all 4-weekly trial visits, except the exit visit. Participants will be provided with a diary card at each 4-weekly visit except the last product use and exit visits. The diary card will be self-administered, and record the participant's sexual activity and ring use during the 4-week period. The diary card is meant to be completed daily by the participant, and returned to the research centre at each 4-weekly visit, to serve as a memory aid for participants to review during adherence counselling, and the adherence questionnaires. Acceptability questionnaires will be administered at the second trial visit (week 4), and 24-weekly intervals from week 24 thereafter, until the last product use visit.

Twenty-four (24) to 42 weeks after research centre activation, each research centre will conduct 6 – 10 qualitative individual interviews with participants, and 6 – 10 qualitative individual interviews with male partners. These interviews will provide data on acceptability, sexual behaviour and adherence issues. The recruitment and sampling strategy will be specified in the SAP.

AEs will be assessed at all visits post-randomisation. In addition, safety laboratory assessments, pelvic examination, vaginal pH and vaginal flora as well as STI tests will be performed at 12-weekly intervals. Cervical cytology will be repeated at the end of the first and second year of IP use. Residual dapivirine levels in returned rings will be measured for a selected group of participants at pre-determined time-points.

#### **Last product use visit**

At the last product use visit, participants will return the last used rings; report any medical problems and/or concomitant medications since the last visit; provide locator and menses information; receive pre- and post-test HIV counselling, contraceptive counselling and HIV/STI risk-reduction counselling (including provision of male condoms); complete vaginal ring use, adherence and acceptability questionnaires; undergo a physical examination as well as a pelvic examination for evaluation of STIs and changes in vaginal flora; have a specimen collected for cervical cytology; and provide blood and vaginal fluid specimens for storage, and specimens for pregnancy and HIV testing and safety laboratory assessments.

Each research centre will conduct 2 – 3 focus groups with participants who have been recruited for these groups at the last product use visit. Additionally, 6 – 10 qualitative individual interviews with male partners will be conducted at each research centre. These interviews will provide data on acceptability and adherence issues. The recruitment and sampling strategy will be specified in the SAP.

#### **Exit visit (6 weeks after ring discontinuation)**

Participants may be notified of any abnormal findings and asked to return to the research centre prior to the exit visit, as needed for treatment and/or referral. On the day of the scheduled exit visit, participants will return to the research centre to receive results from their pelvic examination/STI testing and safety laboratory assessments done at the last



product use visit, and treatment or referral as needed. AEs and concomitant medications will also be recorded at this visit.

Participants will receive pre- and post-test counselling for HIV and undergo final HIV testing. HIV/STI risk reduction counselling (including provision of male condoms) and contraceptive counselling will also be provided at the exit visit. If a clinically significant gynaecological or other related AE remains unresolved at the time of trial completion, a clinical assessment will be made by the research centre's investigator or designated qualified physician and the IPM Clinical Physician or designee to determine whether continued follow-up of the AE is warranted.

Participants will then be considered to have completed trial participation, and informed that they may be re-contacted at a future date to be provided information about trial results, including individual unblinding.

### **3.2 Trial Duration**

Each participant will be followed on the IP over a period of approximately 24 months (104 weeks).

Each participant will have an additional 6 weeks of follow-up after ring discontinuation. In total, each participant will complete approximately 25.5 months on the trial after enrolment.

### **3.3 Trial Population**

Approximately 1,950 sexually active HIV-negative women, 18 – 45 years of age, who understand the trial and can provide informed consent, will be enrolled and randomised in a 2:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a placebo vaginal ring.

#### **3.3.1 Inclusion Criteria**

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

1. Women  $\geq 18$  and  $\leq 45$  years of age, at screening, who can provide informed consent;
2. Available for all visits and consent to follow all procedures scheduled for the trial;
3. Self-reported sexually active (defined as an average of at least one penetrative penile-vaginal coital act per month for the last 3 months prior to screening);
4. HIV-negative as determined by the HIV algorithm applied at screening and enrolment;
5. On a stable form of contraception as defined within section 5.4 and willing to continue on stable contraception for the duration of the clinical trial, unless post-menopausal or surgically sterilised;

6. Asymptomatic for genital infections at the time of enrolment (if a woman is diagnosed with any clinically significant treatable STI, she must have initiated treatment at least 1 week prior to enrolment and have completed the full course of treatment);
7. 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;
8. Willing to refrain from participation in another research trial using drugs, vaccines, medical devices, microbicides or oral pre-exposure prophylaxis investigational drugs for the duration of the IPM 027 trial.

### 3.3.2 Exclusion Criteria

Women who have any of the exclusion criteria below are not eligible:

1. Currently pregnant or last pregnancy within 3 months prior to screening or intends to become pregnant during trial participation;
2. Currently breast-feeding;
3. Non-therapeutic injection drug use in the 12 months prior to screening;
4. Participated in another research trial using drugs, medical devices, microbicides or oral pre-exposure prophylaxis agents within 60 days prior to screening;
5. Previously participated or currently participating in any HIV vaccine trial;
6. Untreated, clinically significant urogenital infections, e.g., urinary tract, or other sexually transmitted infections, or other gynaecological symptoms within 1 week prior to enrolment;
7. Has a Grade 2 or higher pelvic examination finding, according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; Addendum 1 Female Genital Grading Table for Use in Microbicide Studies;
8. History of significant urogenital or uterine prolapse, undiagnosed vaginal bleeding, diagnosed chronic and/or recurrent vulvovaginal candidiasis urethral obstruction, incontinence or urge incontinence;
9. Any gynaecological surgery within 90 days prior to screening;
10. Any Grade 1 or higher baseline aspartate aminotransferase (AST), alanine transaminase (ALT), or platelet count, and any Grade 2 or higher baseline haematology, chemistry or urinalysis laboratory value according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events;
11. Any history of anaphylaxis or severe allergy resulting in angioedema; or a history of sensitivity/allergy to latex or a silicone elastomer;

12. Any history of diabetes mellitus and chronic use of oral corticosteroid therapy; and any uncontrolled serious chronic or progressive disease;
13. Cervical cytology at screening that requires cryotherapy, biopsy or treatment (other than for infection). Women with Grade 1 cervical cytology findings can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology);
14. Any condition(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.

### **3.4 Participant Recruitment**

#### **3.4.1 Pre-Screening**

Research Centres may use formal or informal pre-screening tools in the community and in the research centre in order to pre-identify basic eligibility requirements of potential participants before actually screening for the trial. Formal IRB/IEC-approved pre-screens may include actual clinical procedures such as HIV, STI and pregnancy tests. Informal pre-screens may include recruiter/outreach worker potential participant checklists that identify basic eligibility criteria such as age, contraception, participant location within the area for the given time of the trial, ownership of a legal identification card, etc. The pre-screening methods may vary between centres according to target populations.

#### **3.4.2 Participant Recruitment and Accrual**

It is anticipated that eligible participants will be enrolled over a 6-month period (excluding the trial initiation and screening period) at each research centre. At regular intervals, the Principal Investigators, in consultation with the Sponsor will assess progress in recruitment and retention at each of the research centres and may reallocate enrolment numbers and targets across the research centres, as deemed necessary to achieve the enrolment targets. The enrolment period may be extended at the discretion of the Sponsor in order to ensure sufficient participant numbers are reached to complete the trial accrual targets.

## **4. TRIAL VISITS AND PROCEDURES**

### **4.1 Screening Visits**

#### **4.1.1 Screening 1**

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

- a. Explain screening and trial procedures to the potential participant.
- b. If the potential participant agrees to be screened, obtain written informed consent (screening consent). Illiterate participants may provide a thumbprint or mark witnessed and signed by a person independent from trial staff.
- c. Assign a unique Participant Identification number to the potential participant. A confidential master log of screening participants, with demographic and locator information will be maintained.
- d. Conduct a preliminary 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 menses information, relevant medical history, and concomitant medication taken within the last 30 days (Refer to Section 5.6 for more details about relevant medical history).
- h. Perform urine pregnancy and urinalysis dipstick testing (microscopy only if indicated). Refer pregnant women to local prenatal clinic for support services (Refer to Sections 5.5 and 5.9).
- i. Provide HIV/STI risk-reduction counselling (including provision of male condoms) and contraceptive counselling. (Refer to Sections 5.2.2 and 5.4).
- j. Provide HIV pre- and post-test counselling. (Refer to Section 5.2.1).
- k. Perform HIV rapid testing as detailed in Section 5.3.
- l. Perform general physical examination (Refer to Section 5.7 for a description of the elements required in the general physical examination).
- m. Perform pelvic examination (Refer to Section 5.8). If 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.*
- n. Collect cervicovaginal swabs for STI testing and a specimen for cervical cytology (Refer to Sections 5.10 and 5.11).
- o. Collect blood samples by venipuncture for syphilis testing (RPR), and the following safety laboratory tests (Blood volumes specified in Appendix D):
  - haematology (FBC with differential and platelet count),
  - chemistry (sodium, potassium, phosphate, chloride, calcium, urea, creatinine, total bilirubin, ALT, AST and

*ALP). (Refer to Section 5.9).*

- p. Invite potential participant to return to the research centre within no more than 4 weeks for the screening 2 and enrolment visit.

#### **4.1.2 Screening 2 (Within no more than 4 weeks [28 days] of Screening 1)**

- a. Obtain locator and menses information.
- b. Obtain and record any medical problems and concomitant medication since the screening visit. *NOTE: Record any conditions as part of the relevant Medical History (Refer to Section 5.6).*
- c. Perform urine pregnancy testing. If a woman is pregnant, she is not eligible for the trial. Refer pregnant women to the local prenatal clinic for support services (Refer to Section 5.5).
- d. Provide HIV/STI risk-reduction counselling; including provision of male condoms (Refer to Section 5.2.2).
- e. Provide HIV pre- and post-test counselling. (Refer to Section 5.2.1).
- f. Perform HIV rapid testing as detailed in Section 5.3. **NOTE:** *Research centres using venipuncture for HIV testing at screening 2 may opt to collect the enrolment storage samples (as described below) at the same time the screening 2 HIV test sample is drawn. If this option is taken, storage samples for participants who do not enrol will be destroyed according to local SOPs.*
- g. If the HIV and pregnancy tests are negative, perform a pelvic examination (Refer to Section 5.8). **NOTE:** *The potential participant must be asymptomatic for genital infections (and have initiated treatment for any STI diagnosed during screening at least 1 week prior to enrolment and have completed the full course of treatment) and have a normal pelvic examination at the time of enrolment.*
- h. If all inclusion criteria and none of the exclusion criteria are met, invite the woman to enrol immediately. **NOTE:** *At the discretion of the investigator or designee, each potential participant may be retested once for safety laboratory tests before enrolment, within the 4-week screening period.*

#### **4.2 Enrolment Visit**

**NOTE:** *If the potential participant is menstruating at this visit, the entire visit should be rescheduled for two days after completion of menses, but must be completed within 4 weeks of screening 1. The enrolment visit may occur on the same day as screening 2 or subsequently; provided it is still within 4 weeks of screening 1.*

- a. If a potential participant agrees to enrol in the trial, obtain written informed consent (enrolment consent). Illiterate participants may provide a thumbprint or

mark witnessed and signed by a person independent from trial staff. A comprehension assessment checklist will be used to support the enrolment consent process.

- b. Administer the baseline behavioural questionnaire.
- c. Provide and explain the use of the diary card to the participant.
- d. Dispense one vaginal ring to the participant according to the unique participant identification number assigned at screening 1.
- e. Collect specimen for assessment of vaginal flora and vaginal pH. **NOTE:** *At the discretion of the investigator or designee, this specimen may be collected at the same time the screening 2 pelvic examination is performed.*
- f. Instruct the participant to insert the vaginal ring (Refer to Section 5.12). Perform brief digital examination to verify the vaginal ring has been properly placed.
- g. After ring insertion, the participant will remain in the research centre under observation for 30 minutes to be observed for immediate reactions (immediate reactions will be recorded as AEs).
- h. Provide adherence counselling, including contraceptive adherence, adherence to trial visit schedule and requirements and vaginal ring adherence. (Refer to Sections 5.4 and 5.13). Participants will be instructed to keep the ring inserted for a period of 28 consecutive days (4 weeks). 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. Adherence counselling will include information on actions that should be taken in the event of expulsion or removal.
- i. Collect a blood specimen by venipuncture for HSV-2 serology, HIV viral genotyping and HIV-RNA PCR sample storage (Blood volume specified in Appendix D). **NOTE:** *Research centres using venipuncture for HIV testing at screening 2 may have opted to collect these storage samples at the same time as the screening 2 HIV test sample.*
- j. Schedule the next visit.

### 4.3 Trial Visits

#### 4.3.1 4-Weekly Trial Visits (Weeks 4 to 100)

**(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  $\pm 7$  days. Although the visit window is  $\pm 7$  days, consecutive visits should be no less than 21 days and no more than 35 days apart.)**

**NOTE:** *Additional procedures for participants who test HIV-positive are described in Section 5.3 of the protocol.*

- a. Update locator and menses information as necessary.

- b. Obtain and record any AEs and concomitant medications since the last visit.
- c. Collect and review the diary card and provide a new diary card. Administer the adherence questionnaire.
- d. Provide adherence counselling, including contraceptive adherence, adherence to trial visit schedule and requirements and vaginal ring adherence. (Refer to Sections 5.4 and 5.13). Participants will be instructed to keep the ring inserted for a period of 28 consecutive days (4 weeks). 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. Adherence counselling will include further details on actions that should be taken in the event of expulsion or removal.
- e. Administer the acceptability questionnaire (**NOTE: ONLY at the second trial visit (week 4) after enrolment, and at 24-weekly intervals thereafter, starting at week 24 until the last product use visit**).
- f. Provide HIV/STI risk reduction counselling; including provision of male condoms (Refer to Section 5.2.2).
- g. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).
- h. Perform HIV rapid testing as detailed in Section 5.3. (Additional procedures for participants who test HIV-positive are also described in Section 5.3 of the protocol).
- i. Perform urine pregnancy testing.
- j. Collect blood specimens by venipuncture for storage (Blood volume specified in Appendix D).
- k. Instruct the participant to remove the vaginal ring. Perform IP accountability.
- l. Collect vaginal fluid samples for storage (Refer to Section 5.15). **NOTE: For dapivirine concentration measurements, blood and vaginal fluid samples should preferably be collected prior to removal of the vaginal ring.**
- m. Dispense a new vaginal ring and instruct participant to self-insert the new ring.
- n. Perform brief digital examination to ensure the ring is properly placed (Refer to Section 5.12).
- o. Schedule the next visit.

#### **4.3.2 12-Weekly Trial Visits (Weeks 12, 24, 36, 48, 60, 72, 84 and 96)**

**(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of  $\pm 7$  days. Although the visit window is  $\pm 7$  days, consecutive visits should be no less than 21 days and no more than 35 days apart.)**

**NOTE:** Participants will 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.

- a. Complete all 4-weekly trial visit procedures as detailed above. **NOTE:** A new vaginal ring will only be dispensed to the participant after vaginal fluid sampling for dapivirine concentration measurements and the pelvic examination have been conducted. Pelvic examination is described below.
- b. Perform pelvic examination (Refer to Section 5.8) and collect specimen for assessment of vaginal flora and vaginal pH, and cervicovaginal swabs for STI testing (Refer to Section 5.10). If 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 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.
- c. Obtain urine and blood specimens for safety laboratory assessments as listed in Section 4.1.1 (Blood volume specified in Appendix D).

#### 4.3.3 24-Weekly Trial Visits (Weeks 24, 48, 72 and 96)

**(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of  $\pm 7$  days. Although the visit window is  $\pm 7$  days, consecutive visits should be no less than 21 days and no more than 35 days apart.)**

**NOTE:** Participants will 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.

- a. Complete all 4-weekly and 12-weekly trial visit procedures as detailed above.
- b. Administer the acceptability questionnaire.
- c. Invite 6 – 10 participants to participate in an individual interview to be held at each research centre during weeks 24 – 42.
- d. Request permission from participants that have completed week 24 to recruit their male partner for an individual interview until 6 – 10 male partner interviews have been conducted at each research centre.

#### 4.3.4 Annual Visit (Week 52)

**(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of  $\pm 7$  days. Although the visit window is  $\pm 7$  days, consecutive visits should be no less than 21 days and no more than 35 days apart.)**

- a. Complete all 4-weekly trial visit procedures as detailed above.



- b. Collect a specimen for cervical cytology.

#### 4.3.5 Last Product Use Visit (Week 104 or Early Discontinuation)

**(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of  $\pm 7$  days. Although the visit window is  $\pm 7$  days, consecutive visits should be no less than 21 days and no more than 35 days apart.)**

**NOTE:** *These trial procedures will also apply when two positive HIV rapid tests or a positive urine pregnancy test is obtained, or when IP is permanently discontinued. The applicable visit will be considered the last product use visit for the participant.*

- a. Update locator and menses information as necessary.
- b. Obtain and record any AEs and concomitant medications since the last visit.
- c. Collect the diary card.
- d. Administer the adherence questionnaire.
- e. Administer the acceptability questionnaire.
- f. Provide HIV/STI risk-reduction counselling (including dispensing of condoms) and contraceptive counselling (Refer to Sections 5.2.2 and 5.4).
- g. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).
- h. Perform HIV rapid testing as detailed in section 5.3. (Additional procedures for participants who test HIV-positive are also described in Section 5.3 of the protocol)
- i. Perform pregnancy testing and urinalysis dipstick testing (microscopy only if indicated).
- j. Collect blood specimen by venipuncture for syphilis testing (RPR) and safety laboratory tests (haematology and chemistry). Blood volume is specified in Appendix D.
- k. Collect blood specimen by venipuncture for sample storage (Blood volume specified in Appendix D).
- l. Perform physical examination.
- m. Collect vaginal fluid sample for storage. **NOTE:** *For dapivirine concentration measurements, blood and vaginal fluid samples should preferably be collected prior to removal of the vaginal ring.*
- n. Instruct the participant to remove the last vaginal ring. Perform IP accountability.
- o. Perform pelvic examination (Refer to Section 5.8) and collect specimen for assessment of vaginal flora and vaginal pH, and cervicovaginal swabs for STI testing (Refer to Section 5.10). If pelvic examination indicates abnormal findings,

e.g., any symptoms or evidence of genital infections, abrasions, ulcerations, etc., provide or refer for appropriate treatment.

- p. Collect a specimen for cervical cytology. **NOTE:** *It is not recommended that cervical cytology be repeated within six weeks of a previous sample.*
- q. Schedule the exit visit.
- r. Each research centre will conduct 2 – 3 focus groups with participants who have been recruited for these groups at the last product use visit. Additionally, 6 – 10 individual interviews with male partners will be conducted at each research centre.

#### **4.4 Exit Visit (6 weeks after the Last Product Use Visit)**

**(The scheduled visit has a window period of  $\pm$  7 days.)**

**NOTE:** *If the outcome of confirmatory tests is pending, the exit visit may be conducted more than 6 weeks 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 5.3 (No further HIV counselling and testing will be done unless indicated for additional confirmatory testing).*

- a. Update locator information as necessary.
- b. Obtain and record any AEs and concomitant medications since the last visit.
- c. Provide final safety and STI laboratory results to participant.
- d. Provide HIV/STI risk-reduction counselling; including provision of male condoms (Refer to Section 5.2.2).
- e. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).
- f. Perform HIV rapid testing as detailed in Section 5.3.
- g. Exit the participant from the trial.

#### **4.5 Participant Retention**

The target retention rate during the trial is > 90% per annum. Retention rates will be monitored and tracked and any required action will be taken to address below-target retention rates. Once a participant is enrolled in the trial, trial staff will make every reasonable effort to retain her in the trial. This may include obtaining and checking locator information, home visits, issuing telephonic and in-person reminders of scheduled visits, and maintaining a schedule of enrolled participants as part of a strategy to achieve the target.

#### **4.6     Unscheduled Visits**

Unscheduled visits may be performed at any time during the trial for HIV or pregnancy testing, or if the participant is experiencing any problems, e.g., vaginal complaints, difficulties with re-inserting the ring in cases of accidental expulsion or removal, or accidental loss of the ring. 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. Laboratory testing may be performed during unscheduled visits, 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 clinic for a scheduled visit during the trial window, e.g., within  $\pm$  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 and applicable CRFs.

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 3 by the time the trial window has begun for Visit 4, i.e., within 7 days from Visit 4, Visit 3 will be considered missed. Trial procedures will be performed as scheduled for the current visit (e.g. Visit 4 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 4-weekly visits where a new vaginal ring would be inserted, the research centre could dispense an additional ring(s) on a case-by-case basis following discussion by the investigator with the IPM Clinical Project Manager or designee. The participant would then self-insert the new ring on the day that her 4-weekly visit was due to take place. The research centre will contact the participant telephonically, if possible, to remind her to remove the current ring and insert the new ring. The adherence questionnaire will be administered over the telephone and research centre staff will enquire about adverse events and concomitant medication; other information will be collected as appropriate.

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 be put back on her original visit schedule.

If a 12-weekly or 24-weekly visit is missed, safety laboratory assessments and STI testing should be performed at the next visit.

#### 4.8 Early Discontinuation Visit

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 fails to follow protocol requirements which are deemed to be serious enough by the investigator to warrant a discontinuation, e.g., in the absence of an AE or discomfort, participant refuses to keep vaginal ring inserted for duration of the trial.
- Participant is lost to follow-up, i.e., research centre is unsuccessful (following reasonable attempts as defined in the local SOP) in contacting participant or bringing the participant back to the research centre and she misses 3 consecutive visits.
- Participant is confirmed to be pregnant.
- Participant tests HIV-positive according to the HIV-testing algorithm in Appendix C.
- If for safety reasons the investigator considers it in the best interest of the participant to discontinue her from the trial. Genital AEs that may warrant permanent IP discontinuation are described in the Clinical Management of Genital Diagnoses section of the Study Operations Manual. For laboratory investigations, any of the following abnormal parameters may apply:
  - Haemoglobin < 9.0 g/dL **or** < 1.40 mmol/L
  - Absolute Neutrophil Count (ANC): < 1000/mm<sup>3</sup> **or** < 1.0 x 10<sup>9</sup>/L
  - Absolute Lymphocyte Count (ALC): ≤ 500/mm<sup>3</sup> **or** ≤ 0.5 x 10<sup>9</sup>/L
  - Platelets: ≤ 90,000 ≥ 550,000/mm<sup>3</sup> **or** ≤ 90 x 10<sup>9</sup> ≥ 550 x 10<sup>9</sup>/L
  - Creatinine: > 1.4 x ULN
  - AST: > 3.0 x ULN
  - ALT: > 3.0 x ULN
- At the discretion of the investigator, Sponsor, IRB/IEC or the government health agency.

**NOTE:** The DSMB may provide recommendations to the Sponsor or to the investigators regarding participants who should be discontinued, or allowed to continue in the trial.

The date and reason for permanent trial discontinuation will be noted in the source documents and applicable CRFs. All participants who prematurely discontinue 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 6 weeks after product discontinuation can be completed.

Participants who miss three (3) consecutive trial visits and cannot be contacted during this time will be considered lost to follow-up and will be permanently discontinued from the trial. Reasonable contact attempts will be made according to the locator information provided by the participant and local SOPs, and final 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 clinic chart (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 communication with the IPM Clinical

Project Manager, depending on the reason for the missed visits. Participants who discontinue early from the trial will not be replaced.

#### **4.9 Premature Discontinuation of the Trial**

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

### **5. TRIAL PROCEDURE DETAILS**

#### **5.1 Informed Consent**

##### **5.1.1 Informed Consent Process**

The informed consent documents will describe the purpose of the trial, the procedures to be followed, and the risks and benefits of participation. Two consent forms will be administered at screening 1 and at enrolment: a screening consent form and an enrolment consent form.

The informed consent process will include adequate time for each potential participant to have any trial 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 screening consent form. The form will be signed and dated by the person administering the consent process as delegated by the Principal Investigator according to Research Centre SOP. If a potential participant is functionally illiterate, the 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 observer. After the potential participant has verbally consented and provided a thumbprint or mark which is witnessed by the impartial observer, this independent observer will sign and date the consent form as a witness.

Prior to enrolment, eligible participants who agree to participate in the trial will sign and date the enrolment consent form. It will be signed and countersigned in the same manner as the screening consent form.

The signed and dated consent forms will be retained at the research centre. A copy of the signed and dated consent forms will be offered to the participant. If the participant is not willing to receive the forms, the second copy will be retained at the research centre. Likewise, during the trial, signed and dated consent document 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 forms.

Documentation of the participant's refusal to accept a copy of the informed consent 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 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 consent documents or addenda to the original consent documents in a timely manner and will be signed and dated by the participant in the same manner described above.

### **5.1.2 Comprehension Assessment Checklist**

Trial staff will assess the candidate participant's understanding of informed consent information prior to obtaining a signature on the informed consent form at Screening 1 and Enrollment. At enrolment, 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 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.

## **5.2 HIV Counselling**

### **5.2.1 HIV Pre- and Post-Test Counselling**

At screening and all trial visits where HIV testing is performed, pre- and post-test counselling will be provided according to the CDC Revised 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.

### 5.2.2 HIV/STI Risk Reduction Counselling

HIV/STI risk reduction guidelines will be developed in conjunction with local voluntary counselling and testing (VCT) guidelines. Counselling will be provided at both screening visits, and all trial visits including the exit visit. Efforts will be made to ensure standardisation of risk reduction counselling at the trial clinics.

**NOTE:** *Risk reduction counselling will include recommendation of male condom use. Participants will be provided with a supply of male non-spermicidal condoms during each trial visit. The use of female condoms is not encouraged in this trial, in order to protect the integrity of the lower genital tract and reduce the possibility of AEs due to agents other than the investigational product.*

## 5.3 HIV Testing and Management

### 5.3.1 Screening 1

The details of the HIV rapid testing kits will be specified in the Laboratory Manual. At screening 1, potential participants will be tested for HIV using a highly sensitive antibody Rapid test (Test 1). If the test result is non-reactive, the participant could potentially be enrolled in the trial if she is otherwise eligible. If Test 1 is reactive, the potential participant will be retested using a highly specific HIV antibody Rapid test (Test 2). If Test 2 is reactive, the woman is considered to be HIV-infected and not eligible for enrolment. Initial counselling services will be provided at the research centre and women 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 2 is non-reactive, (yielding discordant results from Test 1), a highly specific HIV antibody Test 3 will be performed for all discordant results. If Test 3 is reactive then the potential participant is considered to be HIV-infected and is not eligible for enrolment. If Test 3 is non-reactive, the person is considered to be potentially HIV-negative and can be given a date for enrolment into the trial. Refer to Appendix C: HIV Testing Algorithms.

**NOTE:** *For the purposes of HIV rapid testing at screening, blood may be obtained by finger prick or venous sampling. However, if Test 2 is required, this must be done on a venous sample. 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 027 HIV testing algorithm, as part of the screening process and documented as such.*

### 5.3.2 Screening 2 and Enrolment

On the scheduled day of possible enrolment, as part of the screening 2 procedure, the participant will be tested for HIV and will only be enrolled if the result is considered to be HIV-negative and the participant is otherwise eligible. Test 1 will be performed. If the test is 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-negative and eligible for enrolment. After enrolment, a blood sample will be obtained by venipuncture to be sent for sample storage locally or at a central laboratory, for potential HIV-RNA PCR testing if the participant seroconverts (blood volume specified in Appendix D). Research centres using venipuncture for HIV testing at screening 2 may opt to collect the storage samples at the same time the screening 2 HIV test sample is drawn. If this option is taken, storage samples for participants who do not enrol will be destroyed according to local SOPs.

If HIV Test 1 is reactive, the potential participant will be retested using Test 2, which must be done with a venous sample. If Test 2 is reactive, the woman will be considered HIV-infected 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. If Test 2 is non-reactive the result is discordant. Rapid Test 3 will be performed for all discordant rapid tests. If Test 3 is reactive then the potential participant is considered to be HIV-infected and not eligible for enrolment. If Test 3 is non-reactive, the person is considered to be probably HIV-negative BUT the participant is NOT eligible for enrolment. She will be counselled and referred to the local health facilities for appropriate follow-up. The participant can return to the research centre for rescreening after 8 weeks for one more cycle of HIV testing. Refer to Appendix C: HIV Testing Algorithms.

### 5.3.3 Trial Visits

Both the 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 C) will be applied for all 4-weekly trial visits, including the last product use visit. HIV-testing while the participant is enrolled in the trial will be performed on blood samples obtained by venipuncture (blood volumes specified in Appendix D).

If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative and continue using the IP. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2 (done on the same blood sample). If Test 2 is reactive, IP will be withheld until HIV infection has been confirmed. Trial procedures relevant to the last product use visit 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. If a pelvic examination was performed within the previous 12 weeks, it may be repeated at the investigator's discretion prior to re-introduction of IP. If confirmatory test(s) indicate(s) that the participant is HIV infected, the participant will be permanently discontinued from IP.

Additional testing will be performed on stored samples of seroconverters as described in Section 5.15. Nucleic acid-amplification testing (NAAT) by an HIV-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.

If Test 2 is non-reactive, the result is discordant and 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 last product use visit 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. If a pelvic examination was performed within the previous 12 weeks, it may be repeated at the investigator's discretion prior to re-introduction of IP. If confirmatory test(s) indicate(s) that the participant is HIV infected, the participant will be permanently discontinued from IP. Nucleic acid-amplification testing (NAAT) by an HIV-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 probably HIV-negative. The participant will continue on the IP and be requested to return for repeat testing after two weeks. In such cases the research centre will notify the IPM Clinical Physician 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, the process of repeat testing after 2 weeks may continue for a third cycle.

All enrolled participants will, in addition, have blood taken at each trial visit to be stored locally or at a central laboratory, for possible HIV-RNA PCR 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 the PCR test result is negative. This will be done to approximate the period of HIV infection. If the enrolment HIV-RNA PCR test result is positive, the participant is not considered to have been infected while using the IP.

Additional blood (blood volume as specified in Appendix D) 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 5.15.

Any participant who is confirmed HIV-infected while on the trial will be permanently discontinued from the IP. Trial procedures relevant to the last product use visit as detailed in Section 4.3.5 will be performed, and an exit visit will be scheduled approximately 6 weeks 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-positive but cannot be confirmed as HIV-infected, the participant will be discontinued from IP and the protocol-required procedures as stipulated for 4-, 12- and 24-weekly visits will be performed at the Investigator's discretion. Samples for measurement of dapivirine levels will no longer be collected and adherence and acceptability questionnaires will not be completed. Additional testing to demonstrate HIV infection may be performed. Participants will be followed up until the exit visit according to the original enrolment date.

#### **5.3.4 Exit Visit**

##### **For participants confirmed as HIV-negative prior to the exit visit**

At the exit visit, the participants will be tested using the same testing algorithm. If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2. If Test 2 is reactive,

additional confirmatory testing will be performed by Western Blot and other confirmatory tests, where appropriate. Samples for possible viral genotype analysis and HIV-RNA PCR testing will be collected. Once HIV infection has been confirmed, this will be considered an HIV seroconversion after product discontinuation. This 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 an HIV-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.

If Test 2 is non-reactive, the result is discordant. HIV Rapid Test 3 will be performed for discordant rapid test results. If Test 3 is reactive then the participant will be considered to be HIV-infected. Additional confirmatory testing will be performed by Western Blot and other confirmatory tests, where appropriate. Samples for possible viral genotype analysis and HIV-RNA PCR 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-negative and will be counselled appropriately. Refer to Appendix C: HIV Testing Algorithms, and Appendix D: Visit Schedule and Blood Volumes.

#### **For participants confirmed as HIV-infected prior to the exit visit**

As stated in Section 5.3.3 above, an exit visit will be scheduled approximately 6 weeks following confirmed HIV-seroconversion and IP discontinuation. Blood samples for viral genotyping will be collected from these participants. Additional trial procedures for exit visits scheduled following HIV seroconversion are described in Section 4.4 (No further HIV counselling and testing will be done unless indicated for additional confirmatory testing).

***NOTE:*** Up to 15% of all HIV rapid test samples will be retested at a central laboratory, for quality control purposes. Details of this testing will be provided in the Laboratory Manual. The Laboratory Manual will also provide details of the IPM specified Test 1; Test 2 and Test 3.

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 (PMTCT) services.

The research centres will inform IPM Medical Safety of any new HIV infections within 24 hours of diagnosis. The applicable regulatory authorities and ethics committees who require expedited notification of HIV seroconversions 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.

## **5.4 Management of Contraception**

To meet eligibility criteria, unless postmenopausal with no history of menses for one year prior to screening, participants must be on stable contraception prior to screening and

enrolment, have demonstrated adherence to her chosen method of contraception and have no significant resultant problems.

Stable contraception is defined, for the purposes of the trial, as surgical sterilisation at least 3 months prior to enrolment OR one of the following:

Participants who have used contraceptives for at least the preceding year should be on the same contraceptive method:

- Oral contraceptive regimen for at least 2 months prior to enrolment, OR
- Transdermal contraceptive patch for at least 2 months prior to enrolment, OR,
- Long-acting injectable progestins for at least 2 consecutive injections, OR,
- Subcutaneous implant inserted at least 3 months prior to enrolment, OR
- An IUD inserted at least 3 months prior to enrolment.

Participants who have newly commenced contraceptive use or have recommenced contraceptive use after a period of greater than 6 months should be on the same contraceptive method:

- Oral contraceptive regimen for at least 3 months prior to enrolment, OR
- Transdermal contraceptive patch for at least 3 months prior to enrolment, OR,
- Long-acting injectable progestins for at least 6 months, OR,
- Subcutaneous implant inserted at least 3 months prior to enrolment, OR
- An IUD inserted at least 3 months prior to enrolment.

In order to address challenges that participants may experience in consistently obtaining reliable contraception, research centres will provide participants with contraceptives from enrolment for the duration of the trial. The contraceptives provided will be consistent with what is available locally and what the participant had been using prior to enrolment. Alternatively, participants will be referred to the local family planning clinic if a referral system has been implemented. Under supervision of the investigator or designated qualified personnel, the participant may switch from one contraceptive method to another, provided that stable contraception is maintained.

Contraceptive counselling will be provided at screening and all trial visits; including the last product use and exit 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 5.5.

## 5.5 Pregnancy Testing and Management

A urine pregnancy test will be performed at all scheduled trial visits while the participant is using the IP 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.

If a participant tests positive for pregnancy while on the IP, ring use will be discontinued immediately. Trial procedures relevant to the last product use visit will be performed. 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 24 hours of confirming a positive pregnancy test. A confirmatory serum pregnancy test may be requested at the discretion of the investigator or a designated qualified 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.

An exit visit will be scheduled approximately 6 weeks following a positive pregnancy test and IP discontinuation. Trial procedures for exit visits are described in Section 4.4. If the participant indicates a change in pregnancy status or the participant's clinical history indicates a change in her pregnancy status, a urine pregnancy test may be performed. If the urine pregnancy test is negative, the investigator can consider recommencing IP. The participant must have a negative pregnancy test prior to re-introduction of IP. 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 Prevention of Mother-to-Child Transmission (PMTCT) services. Should a participant have a positive pregnancy test in an instance where she was determined to be HIV-positive 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.

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.

## **5.6 Demographics and Medical History**

At screening 1, basic demographic information will be obtained. At both screening 1 and 2, relevant medical history will also be collected, 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.

## **5.7 Vital Signs and Physical Examination**

A general physical examination will be conducted at screening 1 and the last product use visit, and will include weight, vital signs, 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 screening 1. A symptom-directed physical examination will be conducted at screening 2 and as needed throughout the trial.

## 5.8 Pelvic Examination

A pelvic examination will be performed at screening 1 and 2 and at 12-weekly trial visits, including the last product use visit, 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 will be investigated and the source identified. A follow-up pelvic examination will be performed to ensure resolution of the condition.

## 5.9 Safety Laboratory Assessments

Safety laboratory assessments will be conducted at screening 1 and at all 12-weekly trial visits thereafter; until the last product use visit. These safety tests will include urine obtained for urinalysis dipstick testing (urine microscopy as indicated only) and blood drawn by venipuncture for laboratory testing (haematology, chemistry, including renal and liver functions). Haematology will include full blood counts, differential, and platelet count. Chemistry tests will include electrolytes (sodium, potassium, chloride, phosphate and calcium), renal functions (urea and creatinine), liver functions (total bilirubin, AST, ALT, and ALP). Details of blood volumes are specified in Appendix D. At the discretion of the investigator or designee, each potential participant may be retested once for safety laboratory tests.

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

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

## 5.10 STI Testing and Management

### 5.10.1 STI Testing

Cervicovaginal samples will be collected for STI testing at screening 1 and at 12-weekly visits. All participants will be evaluated for *Trichomonas vaginalis* (TV), *Neisseria gonorrhoea* (NG) and *Chlamydia trachomatis* (CT). Pelvic samples will also be collected for assessment of vaginal flora and vaginal fluid pH at enrolment and 12-weekly visits.

At screening 1 and at the last product use visit, blood will be collected by venipuncture for Syphilis (RPR) testing (Blood volume specified in Appendix D). TPHA/TPPA will be performed if RPR reactive.

Blood samples will be stored at enrolment and at every scheduled trial visit for HSV-2 serology. Testing will be conducted in HIV-1 seroconverters and a randomly selected control group of HIV-negative participants. In addition, a blood sample for HSV-2 serology will be collected at the point of confirmed seroconversion.

Additional descriptive information regarding specimen collection to test for STIs and vaginal flora, and processing for all tests will be detailed in the Laboratory Manual.

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

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

### 5.10.2 STI Management

Participants will be treated at the research centre or referred to a local health facility; according to local STI Treatment Guidelines. During routine trial visits, all participants who present with STIs will be managed syndromically; however, cervicovaginal swabs will also be collected from these participants, at the Investigator's discretion or when required by local standard of care, in order to document the aetiological diagnosis. Aetiological management may be applicable following 12-weekly STI testing, according to the aetiological diagnosis.

The *Clinical Management of Genital Diagnoses* will be detailed in the Study Operations Manual for guidelines to determine whether the vaginal ring requires temporary or permanent removal, as well as follow-up recommendations. To ensure that participants are not treated with topical urogenital treatments, they will be instructed to seek treatment at the research centre and not from local physicians, should they experience any symptoms between scheduled visits. All cases of symptomatic vulvovaginal candidiasis will be treated with oral fluconazole.

### 5.11 Cervical Cytology

A cervical cytology sample will be collected at screening 1, week 52 and at the last product use visit. Women with Grade 1 abnormal cervical cytology findings at screening can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology). Cervical cytology will be repeated according to the local standard of care, or after 6 months; whichever is more conservative.

Women with Grade 1 cervical cytology findings at week 52 will continue using the IP, and cervical cytology will be repeated according to the local standard of care, or after 6 months; whichever is more conservative.

Women with Grade 2 or 3 cervical cytology findings at week 52 will discontinue IP use and will be referred for appropriate medical services. These referral systems 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.

## **5.12 Vaginal Ring Insertion and Placement Check and Ring Removal**

At the enrolment and 4-weekly trial visits, participants will insert their vaginal rings under clinic supervision. The participant will be instructed to wash her hands thoroughly, 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 wash her hands thoroughly again. A brief digital examination will be performed immediately after by an appropriately qualified and trained trial staff member as designated by the investigator, to verify proper placement of the ring. The verification of the placement of the ring at subsequent visits will be done at the discretion of the designated trial staff. If upon digital examination the ring is not inserted correctly, the investigator or nurse will allow the participant additional attempts to re-insert the ring properly or provide assistance as required to put the ring in place. At all trial visits when a pelvic examination is performed, the participant will remove the ring prior to the examination.

If the participant requests help with either removal or re-insertion of the vaginal ring, or after she has made several attempts to remove/re-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 Study Operations Manual.

## **5.13 Vaginal Ring Adherence Counselling**

At all 4-weekly trial visits except the last product use and exit visits, participants will receive vaginal ring adherence counselling. Research centre staff will counsel participants to refrain from removing the ring (except as directed during clinic visits) and to avoid using concomitant vaginal products or other objects. However, tampon use is permitted.

Research centre staff will also provide instructions for re-insertion 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.

If, for any reason, the participant is non-adherent in her 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 in the source documents and applicable CRFs. The behavioural questionnaires will document the reason for non-adherence and additional adherence counselling will be provided.

## **5.14 Questionnaires**

### **5.14.1 Baseline Behavioural Questionnaire**

The baseline behavioural questionnaire will be administered at the enrolment visit. This questionnaire includes behavioural, acceptability and adherence questions about sexual behaviour, vaginal practices and anticipated adherence and acceptability issues.

### **5.14.2 Adherence Questionnaire**

Trained staff will administer adherence questionnaires at 4-weekly visits, from week 4, until the last product use visit. Adherence questionnaires include questions about ring use. The diary cards will serve as a memory aid for the participant during the adherence questionnaire session, and will be collected at each 4-weekly visit.

### **5.14.3 Acceptability Questionnaire**

Trained staff will administer an acceptability questionnaire at week 4 and at 24-weekly intervals, starting from week 24 until last product use visit. Acceptability questionnaires will include questions about use of the vaginal ring, vaginal practices, sexual behaviour, worries and concerns about ring use, male partner issues, and willingness to use a proven effective vaginal ring.

### **5.14.4 Qualitative Interviews**

Qualitative interviews (focus groups and individual interviews) will be conducted at two points in the trial: 24 – 42 weeks after research centre activation, and following last product use visits. Focus groups and individual interviews will be conducted with a sample of trial participants, and individual interviews will be conducted with a sample of participant's male partners. These interviews will provide further information on acceptability and adherence for the exploratory objectives.

## **5.15 Sample Storage and Analysis**

Blood and vaginal fluid samples will be collected for storage locally or at a central laboratory at all trial visits, to be tested subsequent to confirmed HIV-1 seroconversion. Blood samples for HSV-2 serology, HIV viral genotyping and HIV-RNA PCR will be stored from enrolment (or screening 2 for research centres that use this option). Testing will be conducted on stored samples from confirmed HIV-1 seroconverters and specifically for dapivirine concentration measurements and HSV-2 serology from both HIV-1 seroconverters and a random sample of HIV-negative participants. For dapivirine concentration measurements, blood 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 (which forms part of the Study Operations Manual).

As described in Section 5.3.3 above, additional blood (blood volume as specified in Appendix D) and vaginal fluid samples will also be obtained for analysis at the point of HIV seroconversion according to the HIV testing algorithm described in Section 5.3. The blood samples will be tested retrospectively for HIV-RNA PCR, HSV-2 serology and viral genotyping, while both blood and vaginal fluid will be tested for dapivirine concentrations. Plasma and vaginal fluid drug concentrations will be used to evaluate the relationship between drug concentrations and HIV seroconversion. HSV-2 serology and dapivirine concentration analyses will be conducted in HIV-1 seroconverters and a randomly selected control group of HIV-negative participants.

All specimens will be collected and analysed according to methods described in the Laboratory Manual and standard operating procedures (SOPs) for proper collection, processing, labelling, and transport of specimens to the laboratories conducting the



assays. Where possible and appropriate, stored specimens will be re-tested to assess validity of unusual or unexpected assay results.

Any residual specimens will be destroyed at the end of the trial after all protocol-required and quality control testing has been completed.

### **5.16 Method of Treatment Assignment**

Participants who meet all of the trial inclusion criteria and no exclusion criterion at baseline will be randomly assigned in a 2:1 ratio to one of two groups receiving either the vaginal ring containing dapivirine or the placebo vaginal ring, respectively. Randomisation will be stratified by research centre at the time of enrolment, using a pre-specified block size, and will be determined via the use of an automated randomisation system to ensure balance of the treatment assignments. Both groups will use a 4-weekly administered ring continuously for the duration of trial participation and have a follow-up visit 6 weeks after ring removal.

A master randomisation list for the trial will be generated which links each participant identification number to a trial treatment assignment (dapivirine ring or placebo ring). At each research centre, as each new participant enters the trial, a unique participant identification number will be assigned to that participant using an automated response system.

### **5.17 Reimbursement**

Participants will be reimbursed for any travel costs incurred as per local regulations. Reimbursements will be made after the completion of each trial visit. Upfront reimbursement for travel expenses may be made if this has been approved by the relevant ethics committee. Research centre specific reimbursement amounts will be documented in the trial informed consent approved by the applicable IRB/IEC.

### **5.18 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.

### **5.19 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.

## 5.20 Study Operations Manual

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

## 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 drug substance dispersed in a platinum-cured silicone matrix. The dimensions of the ring are 56 mm and 7.7 mm – the outer diameter and cross sectional diameter, respectively. The dapivirine silicone elastomer vaginal matrix ring is designed to provide sustained release over a minimum of 28 days.

The placebo ring composition is the same as the dapivirine ring with the exception of the absence of dapivirine, and inclusion of titanium dioxide USP colourant. Pharmacopoeial grade titanium dioxide is included as a colourant to maintain blinded conditions during clinical evaluation. Details regarding the composition of the dapivirine and placebo rings are included in the IB.

Silicone elastomer vaginal rings have already been developed and approved as delivery methods for medications. For example, Pfizer (formerly Pharmacia and Upjohn Company) has marketed Estring<sup>®</sup> (estradiol vaginal ring), a vaginal ring that is also made from silicone elastomer and contains estradiol used to treat local symptoms of urogenital atrophy, since 1993. Prior to the launch of Estring<sup>®</sup>, the biological safety of the silicone elastomer was studied in various *in vitro* and *in vivo* test models. The results show that the silicone elastomer is non-toxic, non-pyrogenic, non-irritating, and non-sensitising<sup>9</sup>. Femring<sup>®</sup> (estradiol acetate vaginal ring), a hormone replacement product approved in June 2003 by the United States (U.S.) Food and Drug Administration (FDA) treats menopause-induced vasomotor symptoms (e.g., hot flushes) and symptoms of vulvar and vaginal atrophy (e.g., dryness)<sup>9</sup>. Although these rings are not exactly the same as the IPM ring, the extensive clinical trial and post-marketing experience gained from these products provides further assurance of the safety of silicone elastomer rings as vaginal drug delivery devices.

The Dapivirine 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. 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 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 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 Randomisation**

A randomisation schedule will be generated and validated according to specifications required for IPM's process of packaging and dispensing. The schedule will contain participant identification numbers and treatment assignment. At each research centre, each enrolled participant will be assigned a participant identification number using an automated response system.

## **6.4 Blinding and Unblinding**

The Principal Investigator or his/her designee will be able to unblind each enrolled participant, through the automated system, if necessary. If during the course of the trial a medical emergency requires knowledge of the test agent used by a particular participant, the trial blind or code may be broken for that specific participant, after discussion with IPM's Clinical Physician or designee whenever possible. Any unblinding of participant treatment assignments will be justified and explained in the source documents and applicable CRF and reporting forms. If the blinding code is broken by the Principal Investigator or his/her designee, the participant will be withdrawn from the trial and followed up if appropriate. The blinding and unblinding process will be performed by the automated response system.

## **6.5 Investigational Product Storage**

The recommended storage condition for the dapivirine and placebo rings is 15°C to 30°C. 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.

The investigator (or pharmacist) will maintain an inventory and acknowledge receipt of all shipments of IP. The automated response system will also be used to confirm receipt of and activate kits for use.

## **6.6 Investigational Product Administration**

Participants will self-insert a new vaginal ring at enrolment and each 4-weekly visit through the period of trial participation. Designated trial staff will perform a brief digital examination at each 4-weekly trial visit, at their discretion, to ensure the ring is properly placed. Participants should continue ring use through menses.

In the event that a participant will be away and unable to attend one of the 4-weekly visits where a new vaginal ring would be inserted, the research centre could dispense an additional ring(s), which the participant should then self-insert on the day that her 4-

weekly visit was due to take place. Management thereof will be on a case by case basis following discussion by the investigator with the IPM Clinical Physician or designee.

### **6.7 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 it. If the vaginal ring is expelled and cannot be successfully reinserted, the ring should be appropriately rinsed and stored in the bag provided for this purpose, until the earliest possible opportunity the participant can return for reinsertion of a new ring at the clinic. If a second expulsion occurs before the next scheduled visit, and a second replacement of a ring (with a new ring) needs to be considered, the IPM Clinical Physician should be consulted with regard to appropriate follow-up action.

The participant 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 return to the clinic. Also in cases where a ring is removed due to a genital AE, a new ring will be dispensed and inserted. Visits associated with expulsion or loss of rings will be regarded as unscheduled visits and management thereof will be on a case by case basis following discussion by the investigator with the IPM Clinical Physician or designee, unless the visit is within the 7-day window period of the next scheduled visit.

### **6.8 Retrieval of Investigational Product**

All participants who prematurely discontinue 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.

### **6.9 Investigational Product 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.

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 ring 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 levels.

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

## 6.10 Concomitant Medications and Products

All prescription and non-prescription medications, including any treatment for STIs and other reproductive tract infections, will be collected and recorded on the source documents and applicable CRFs.

All cases of symptomatic candidiasis will be treated with oral fluconazole. Oral therapy will also be prescribed for the treatment of STIs and other reproductive tract infections. Concomitant use of non-trial vaginal products, practices or use of other devices including but not limited to spermicides, diaphragms, contraceptive vaginal rings, female condoms, vaginally applied medication, menstrual cups, cervical caps, douches, lubricants, etc., will be discouraged. Participants will be instructed to avoid these medications and practices in order to protect the integrity of the lower genital tract and reduce the possibility of AEs due to agents other than the investigational product. **NOTE:** *Tampons are not included in this list and may be used for the duration of the trial.*

## 7. ADVERSE EVENTS

### 7.1 Definition

An adverse event (AE) is any untoward medical occurrence during the course of a trial in a participant who received an investigational product at any dose, which does not necessarily have a causal relationship with the investigational product. 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 investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational medicinal product). Final determination of whether an event is considered unexpected will be made by IPM, but 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 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 (treatment assignment) at Visit 1 will be reported as a pre-existing condition under Medical History. All AEs occurring during the trial will be recorded in the source documents and applicable CRFs.

If possible, a specific disease or syndrome rather than individual associated signs and symptoms should be recorded by the investigator. 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 is identified, or until the investigator does not expect any improvement or worsening of condition/symptoms. If a related AE remains unresolved at the participant's last trial 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 Study Operations Manual.

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 or causal relationship to the investigational product administration. The AE is clearly explained by another cause (concurrent disease, concomitant medication, environmental or toxic factors, etc.).

- **Related**

There is a reasonable causal relationship between the investigational product and the AE. 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 Events**

### **7.4.1 Serious Adverse Event Definition**

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that at any dose meets any of the following criteria:

- 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 inpatient hospitalisation or prolongation of existing hospitalisation.  
This criterion applies if the event requires inpatient hospitalisation and results in an overnight stay in hospital or, in the opinion of the investigator, prolongs an existing hospitalisation. A hospitalisation (including hospitalisation for an elective procedure or routinely scheduled treatment) 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.
- Is an important and significant medical event that may not be immediately life threatening or result in death or hospitalisation but, based upon appropriate medical judgment, may jeopardise the participant or require intervention to prevent one of the other outcomes listed above. e.g., bronchospasm requiring intensive treatment in an emergency room or at home.

**NOTE:** *An SAE need not be severe in nature to meet any of the above criteria.*

All SAEs that occur from the time the participant is enrolled (receives treatment assignment) through the duration of the trial, whether considered to be associated with investigational product or not, must be reported to the IPM Medical Safety Physician or designee within 24 hours of the research centre becoming aware of the event. All SAEs should be reported using the designated Immediately Reportable Event (IRE) Report Form.

The IRE Report Form will be completed with all available information at the time of reporting. The investigator is required to write a detailed written report and complete SAE follow-up in a timely manner until the SAE returns to baseline, the participant returns to normal health or until the investigator does not expect further improvement or worsening of the event. Medical records may be requested by IPM or designee to assist in assessing relatedness and severity of the SAE, and for possible submission to Regulatory or Health authorities. To maintain confidentiality, the participant's name will be blacked out and replaced with the Participant Identification Number and initials on any medical records submitted.

More details on SAE reporting requirements are described in a separate Safety Reporting Plan.

#### **7.4.2 Serious Adverse Event Contact Information**

SAEs will be reported to IPM or designee within 24 hours of the research centre becoming aware of the event. If the SAE is related, and life-threatening or fatal, IPM Medical Safety should 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](mailto:safetyreports@ipmglobal.org). Contact details of relevant safety personnel are provided in the Safety Reporting Plan.

IPM or designee will process all safety reports. The Medical Safety team will review all SAEs and generate the necessary queries.

#### **7.4.3 Sponsor Notification of SAEs to Regulatory Authorities**

All SAEs will be reported according to the guidelines of the local ethics and regulatory authorities in the countries in which IPM clinical trials are being conducted. Any unexpected SAE which is deemed to be Related to the investigational product will be considered "associated with the use of the investigational product" and thus IPM will notify appropriate regulatory authorities of the event in an expedited manner unless policies of local regulatory authorities mandate such reporting by the trial research centres.

Any unexpected SAE deemed to be Not Related will not be reported to regulatory authorities in an expedited manner unless otherwise requested by the local authorities.

#### **7.4.4 Research centre Notification of SAEs to Local Ethics Committee or Local Health or Regulatory Authorities**

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



## 7.5 Immediately Reportable Events

In addition to the SAEs the following events will be considered Immediately Reportable events (IRE) and will be reported to IPM within 24 hours:

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

## 7.6 Safety Monitoring

The IPM 027 trial team will monitor safety and participant recruitment throughout the trial for all participants. Safety data from the trial will be evaluated at predetermined regular intervals by an independent Data and Safety Monitoring Board (DSMB). The DSMB has the option to recommend stopping the trial at any point, if warranted, based on AEs observed during the trial or other concerns regarding participant safety or trial conduct.

Close monitoring by the DSMB will be necessary to evaluate trial progress and respond to occurrences of toxicity in a timely manner. Rates of accrual, data queries, trial product adherence, follow-up, and AE incidence will be monitored by the DSMB on a regular basis. The DSMB will meet via conference call at predetermined intervals during the trial; ad hoc calls may be convened if requested by the DSMB or IPM. A separate DSMB charter will describe the DSMB composition and its charges related to the trial.

## 8. DATA MANAGEMENT

### 8.1 Data Handling at Research Centres

All trial data will first be collected on designated source documents and then recorded on Case Report Forms (CRFs) with the exception of the Behavioural, Acceptability and Adherence questionnaires, 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 Study Operations Manual. Qualitative data (focus groups and individual interviews) will be audio-recorded, password protected, and transcribed, following standardised procedures to be specified by IPM.

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.

## **8.2 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 available for review to the Sponsor or representative(s), IRB, IEC and other regulatory inspectors to ensure that the collected data is consistent with the CRFs and has been completely and accurately reported as required by the trial protocol.

## **9. STATISTICAL METHODS**

### **9.1 General Design**

IPM 027 has been designed to assess the safety and efficacy of dapivirine administered in a silicone elastomer vaginal ring (Ring-004) containing 25 mg of dapivirine and inserted once every 4 weeks, among approximately 1,950 healthy, HIV-negative, sexually active women aged 18 – 45 years – as compared with a placebo vaginal ring.

Individuals meeting all inclusion criteria and no exclusion criteria will be randomised in a 2:1 ratio to either the investigational product or a placebo vaginal ring. To maintain the treatment ratio within each research centre, randomisation, via an automated randomisation system, will be stratified by research centre, using a pre-specified block size.

Participants will be followed on IP over a period of approximately 24 months (104 weeks). Each participant will have an additional 6 weeks of follow-up after ring discontinuation.

### **9.2 Trial Endpoints**

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

### **9.3 Primary Trial Hypotheses**

#### **Primary efficacy hypothesis**

IPM 027 is designed to test the efficacy of the investigational product in preventing HIV-1 infection as compared with placebo. The null hypothesis is that the rate of HIV-1 seroconversion is not different among participants assigned the dapivirine vaginal ring compared with participants assigned to the placebo ring.

#### **Primary safety analysis**

The primary safety analysis is descriptive in nature. Tabular summaries and listings will be provided and will include all participants who have received the IP.

### **9.4 Sample Size and Power Calculations**

IPM 027 will be conducted in a sample of approximately 1,950 HIV-negative women in a 2:1 ratio, such that 1,300 participants will be assigned to the investigational product and 650 participants will be assigned to the placebo ring. The sample size for this trial was determined based on the primary efficacy endpoint, the incidence rate of HIV-1 seroconversions, in the two treatment arms.

The statistical assumptions used in determining this sample size therefore include:

- proportional hazards among the two groups,
- microbicide efficacy of  $\geq 50\%$  in preventing HIV-1 infection,
- randomisation ratio of 2:1 (dapivirine vaginal ring vs. placebo ring),
- a two-sided log-rank test statistic, with  $\alpha = 0.05$ ,
- $> 4\%$  average annual HIV incidence in the placebo arm (assumes a reduction in incidence in the trial population due to risk reduction counseling), and
- $\leq 10\%$  loss-to-follow-up rate over the duration of the trial period.

The increased sample size will mitigate the potential negative impact of product non-adherence on the trial outcome and sustain the power of the trial for the primary objectives.

Below is a table which provides the estimated power to detect 40%, 50% and 60% microbicide efficacy with a sample size of 1,950 and under the assumptions as stated above.

<b>Microbicide efficacy</b>	<b># Expected HIV- 1 seroconversions</b>	<b>Power</b>
40%	104	61%
50%	96	81%
60%	88	94%

A trial with the proposed design will provide 81% power to detect a 50% reduction in the rate of HIV-1 seroconversions in the active arm, assuming an annual HIV-1 seroconversion rate of 4% in the placebo arm, and a 10% lost-to-follow-up rate.

Moreover, in a trial with this number of participants assigned to the investigational product, there is a 95% probability of detecting an AE occurring at a rate of 0.3% or higher.

## **9.5 Statistical Analyses**

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

As stated in the ICH E9 guidance document, “the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject rather than the actual treatment given”<sup>13</sup>. The intent-to-treat (ITT) population is defined as all participants randomised to either treatment, and under their planned treatment assignment. However, due to the time between HIV-1 infection and the ability to detect antibodies, it is possible that participants who tested negative at screening were infected with HIV. Therefore, the primary analysis will be conducted using a modification of the intent-to-treat (ITT)

principle. The modified intent-to-treat (m-ITT) population will exclude all participants that were determined at any point during or after the trial to have been HIV-infected based on the stored HIV-RNA PCR sample taken at the time of enrolment.

As it is possible that the inclusion of non-adherent participants or participants removed from the trial product may artificially lower the rates of safety outcomes, additional analyses will be conducted on the per-protocol population, where time off-product is removed from the analysis. 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 written in a SAP, which will be finalised prior to unblinding of trial data.

For the secondary analyses, the incidence density rates of HIV-2 seroconversions, curable STIs, changes in vaginal flora and pregnancies will be compared between treatment groups. Additional analyses will be performed to evaluate adherence and acceptability to 4-weekly use of the vaginal ring over the IP use period as well as additional predictors of adherence (including sexual behaviour and condom use of women using a vaginal ring). The frequency of HIV-1 drug resistance in women who seroconvert while using the IP will also be assessed. The data will be presented using appropriate statistical measures including, but not limited to: mean, standard deviation, median, and interquartile range for continuous data; and the frequency and relative frequency for categorical data. When appropriate, 95% confidence intervals will be presented.

### **9.5.1 Primary Efficacy Analysis**

As stated earlier, the primary analysis will be performed on the m-ITT population, i.e., all trial participants that were HIV-1 negative at enrolment and were randomised to either the trial product or placebo. The primary efficacy analysis of the primary endpoint will be the comparison of the incidence rate of HIV-1 seroconversion, as determined by the HIV testing algorithm in Appendix C, between the active and placebo arms. For participants who were reported to HIV-1 seroconvert at the exit visit, HIV-RNA PCR tests will be performed on stored samples in reverse sequential order to estimate the time point of HIV infection. If the infection is determined to have been acquired while the participant was on product, the seroconversion will be included in the primary analysis. However, if the infection is determined to have been acquired during the time between the last product visit and the exit visit, the seroconversion will not be included in the primary analysis.

The primary analysis will include the estimation of the incidence density rate of HIV-1 seroconversion, with corresponding 95% CIs. The formal statistical test used to evaluate the efficacy of the dapivirine ring will evaluate the null hypothesis of no difference in the population survival curves (i.e. the probability of an HIV-1 seroconversion occurring at any time point is the same for the active and placebo arms) via a log-rank test stratified by research centre and evaluated at a 5% significance level. This analysis will be accompanied with Kaplan-Meier survival curves of the two trial arms for visual inspection of the proportional hazards assumption. Trial participants will be followed on the IP for 24 months, and will be tested for HIV-1 infection at 4-weekly visits. Participants that are not diagnosed with HIV-1 at the end of the trial participation period will be censored at the earliest date of any of the following events: completion of investigational product use, trial drop-out, a positive pregnancy test followed by permanent product discontinuation, or death.

### 9.5.2 Primary Safety Analysis

A descriptive analysis of all AEs will be presented in tables and listings. Data will be presented by MedDRA System Organ Class (SOC) and Preferred term (PT), by treatment arm. Fisher's Exact test will be performed to compare the proportion of participants in the active and placebo arms, with regard to all Grade 3 and 4 AEs, all SAEs, and AEs leading to IP discontinuation, at a 0.05 significance level. Similar analyses will be conducted on the m-ITT and Per-Protocol populations.

As this is a randomised trial, it is anticipated that the two groups will be comparable at baseline with respect to pre-existing conditions, and furthermore, that women with pre-existing conditions will be treated and evaluated before being enrolled into the trial. For this reason, no baseline adjustments are planned prospectively, but the data will be thoroughly reviewed to assess any potentially relevant baseline imbalances. Chi-square tests of association will be used to evaluate differences in categorical variables between the two groups under a 0.05 alpha level. For categorical variables with small sample size (< 30), Fisher's Exact test may be used. Continuous data may be compared between the two treatment arms using Student t-tests or Wilcoxon signed rank tests. Comparisons between measurements taken during the trial and prior to or at enrolment may also be made; comparisons of continuous data will be performed using paired t-tests and comparisons of categorical data will be performed using McNemar's test.

The safety profile is not expected to differ across research centres and it is unlikely that the difference in the safety profile between the active and control arms is affected by the research centre. However, for each analysis subsequently discussed, research centres will be evaluated via inclusion as a main effect and with a treatment-by-centre interaction term in appropriate regression models. Although balance of baseline characteristics is expected across trial arms, a Poisson regression model may be used to provide risk ratios adjusted for imbalance in any baseline characteristics.

### 9.5.3 Secondary Analyses

- **Incidence rate of HIV-2 seroconversion**

The incidence density rates of HIV-2 seroconversion in the active and placebo arms will be provided with 95% CIs. The log-rank test will be used to test the null hypothesis that there is no difference between the population survival curves (i.e. the probability of an HIV-2 seroconversion occurring at any time point is the same for the active and placebo arms), and will be stratified by research centre and evaluated at a 5% significance level.

- **Curable STIs**

The incidence density rates of first occurrence of curable STIs (i.e. *N.gonorrhoea*, *C.trachomatis* and *T.vaginalis*) will be compared between treatment groups. For each treatment group, the numerator will include the number of participants that were diagnosed with at least one curable STI and the denominator will include the total number of STI-free days that each participant contributed to the trial (i.e., from enrolment to their first STI or trial completion, whichever occurs first). The application of General Estimating Equations (GEE) will be used to evaluate the trends in curable STIs during the trial period. In addition, the Kaplan-Meier survival curves describing the time until the first occurrence of a curable STI in each treatment arm will be provided. Cox proportional hazards will be used to estimate the median time to the first occurrence of a curable STI between the treatment groups.

- **Changes in vaginal flora**

The incidence density rates of first occurrence of vaginal flora changes will be compared between treatment groups. For each treatment group, the numerator will include the number of participants that were diagnosed with vaginal flora changes and the denominator will include the total number days with no vaginal flora changes that each participant contributed to the trial (i.e., from enrolment to their first incident of vaginal flora changes or trial completion, whichever occurs first). The application of GEE will be used to evaluate the trends in vaginal flora changes during the trial period. In addition, the Kaplan-Meier survival curves describing the time until the first occurrence of vaginal flora changes in each treatment arm will be provided. Cox proportional hazards will be used to estimate the median time to the first occurrence of changes in vaginal flora between the treatment groups.

- **Incidence of pregnancy**

The incidence density rates of pregnancies will be compared between treatment groups. For each treatment group, the numerator will include the number of participants that had a positive urine pregnancy test during the trial period and the denominator will include the total number of days that each participant contributed to the trial (i.e., from enrolment to pregnancy or trial completion, whichever occurs first). In addition, Cox proportional hazards will be used to estimate the median time to pregnancy between the two treatment groups.

- **Adherence to the ring regimen**

Definitions for adherence to the ring regimen may be categorised by the percent of days that the participant reportedly wore the ring out of the total number of days that the participant was expected to wear the ring. Such categorisations will be further defined in the SAP. In addition, a dichotomous variable will be created to define “adherent participants” based on a predefined cut-off percent of adherence deemed acceptable. This percent will be described more fully in the SAP. The proportion of participants that are not adherent to the ring regimen will be compared in each treatment group. For each treatment group, the numerator will include the number of participants who were not adherent during the trial period and the denominator will include the total number of days that each participant contributed to the trial (i.e., from enrolment to becoming non-adherent or to trial completion, whichever occurs first). The application of GEE will be used to evaluate the trends in missed days of the ring regimen during the trial period. In addition, Cox proportional hazards will be used to compare the time to the first missed day of the ring regimen between the two treatment groups. Additional exploratory and explanatory analysis will utilise the qualitative data from focus groups and individual interviews.

Multiple methods of data collection will be utilised to examine adherence; comparisons across the different methods will be explored and will be provided in greater detail in the SAP.

- **Acceptability of the ring regimen**

Two types of acceptability assessments will be performed; these are referred to as (1) simple approximation of acceptability and (2) comprehensive assessment of acceptability. These assessments will be fully described in the SAP.

For both types of assessments, cross-tabulations and simple descriptive statistics will be calculated for socio-demographic variables and psychosocial variables collected in the acceptability and adherence questionnaires. If between-group differences arise and/or there are differential rates of drop-out on potentially confounding characteristics, the variable(s) will be included as covariates in the analyses. If numerous confounders are identified, a propensity scoring approach will be used to adjust for confounding.

Simple approximation of acceptability will be assessed by analysis of stated willingness to use the vaginal ring if proven effective against HIV infection, and reported consistent use of the vaginal ring during the trial. A participant will be classified as having found the vaginal ring acceptable if she responds positively to questions about willingness to use and consistent use. Logistic regression analysis will be performed to examine the relationship between this acceptability and other variables of interest.

Comprehensive assessment of acceptability will be based on data captured in the acceptability and adherence questionnaires. Variables evaluating participants' willingness to use the vaginal ring will be adjusted by women's perceived risk of HIV and sexual practices. Variables evaluating consistent-use of the vaginal ring will also be used to adjust for possible confounding factors. Another aspect of comprehensive acceptability is to investigate factors influencing participants' attitudes and responses to the IP. The acceptability measures will be regressed over possible predictors via a logistic regression model at a 0.05 level of statistical significance. Additional exploratory and explanatory analysis will utilise the qualitative data from focus groups and individual interviews.

- **HIV-1 drug resistance**

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. The proportion of HIV-1 seroconverters with at least one HIV-1 drug resistant mutation will be presented overall, and by treatment arm, with corresponding 95% CIs. A logistic regression model will be developed to estimate the effect of the dapivirine ring on the odds of developing at least one HIV-1 resistance mutation, and will adjust for confounders that may distort the association between the dapivirine ring and HIV-1 resistance mutations. Such confounders may include the number of sexual partners reported at baseline, type of contraception, or the diagnosis of genital infections. The distribution of HIV-1 resistance mutations may be presented graphically with a bar chart of relative frequencies, overall and by treatment arm.

It is possible that prolonged exposure to the IP and adherence to the IP may influence the development of resistant mutations. A box-plot displaying the distribution of days on IP may be presented for each treatment arm. The number of days of IP use prior to HIV-1 seroconversion as well as adherence to the IP may be evaluated as an independent predictor of acquiring a resistant mutation. The number of days of IP use may be included as a continuous covariate or parameterised as a categorical variable and included as a main effect in a logistic regression model for the outcome of developing at least one HIV-1 resistance mutation. The estimated odds ratio for the effect of the number of days of IP use, adjusted for treatment arm, will be displayed with 95% CIs.

## **9.6 Interim Analysis**

Regular safety reviews will be conducted by the Data and Safety Monitoring Board (DSMB) at predetermined intervals during the trial (refer to Section 9.7). An interim efficacy analysis is planned when approximately 50% of the expected trial endpoints have

occurred. The interim analysis will be performed by an independent statistician that is otherwise not involved in the trial and will include descriptive statistics of baseline variables, safety data (i.e., AEs), and STI and HIV incidence. To maintain the proposed Type I error rate ( $\alpha = 0.05$ ), which will be inflated due to multiple testing of the efficacy hypothesis, the interim and final analyses will be adjusted using a Lan-DeMets spending function with O'Brien-Fleming grouped sequential stopping boundary<sup>14, 15</sup>.

In addition, the DSMB may recommend early termination of the trial on the basis of: 1) safety concerns, or 2) demonstrating futility:

- 1) Safety concern – an increased risk of safety outcomes in the dapivirine ring arm as compared to the placebo ring arm.
- 2) Demonstrating futility – evidence that the trial is highly unlikely to show that the new intervention is superior, given current evidence and the added information that would become available if the trial continued.

An additional interim analysis/analyses may be requested by the DSMB.

A separate SAP for the interim analysis/analyses will be drafted after the protocol is finalised. This plan will provide specific details about:

- 1) the parameterisation of variables,
- 2) the statistical assumptions required,
- 3) the statistical methods to be employed,
- 4) specifications of the stopping boundaries used in the interim analysis, and
- 5) the Type I error at the interim look.

The Sponsor will review and approve the SAP for any interim analysis before any analyses are undertaken.

## **9.7 Data and Safety Monitoring Board (DSMB)**

An independent DSMB will be established. The DSMB will meet via conference call at predetermined intervals during the trial; *ad hoc* calls or face-to-face meetings may be convened if requested by the DSMB or IPM. DSMB members will include individuals not associated with this trial, but who have expertise in conducting clinical trials, experience working in developing countries, and/or a history of working in the microbicide arena. Prior to each DSMB meeting, the data management group will prepare a summary report of all AEs and SAEs for the DSMB to assess safety. The DSMB has the option to recommend pausing or stopping the trial at any point, if warranted, based on AEs observed during the trial, or other safety concerns identified during the course of the trial. DSMB members will remain blinded to the treatment groups unless it is necessary to unblind an individual or stop the trial for safety reasons.

A separate DSMB charter will describe the DSMB composition and its charges related to the trial.

This trial will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312), and in accordance with the ethical principles of the World Medical Association Declaration of Helsinki, the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the U.S. Code of Federal Regulations (CFR) Title 21 and applicable local regulatory requirements.



## **9.8 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 4-week 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.

## **10. INVESTIGATOR REQUIREMENTS**

### **10.1 Trial Initiation**

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

### **10.2 Institutional Review Board 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.

### **10.3 Trial Monitoring and Audits**

Trial monitors will regularly visit participating research centres to review all 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 Sponsor may request access to all trial documents for on-research centre audit or inspection.

## **10.4 Case Report Forms**

Case Report Forms (CRFs) will be supplied by IPM or its designee and will be handled in accordance with instructions from IPM.

All CRFs will be filled out completely by the designated trial staff. 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 initialled and dated. Erasures, overwriting, and correction fluid are NOT allowed on the CRFs.

## **10.5 Disclosure of Data**

Participant medical information is confidential and disclosure to third parties other than those described in Section 10.3 is strictly prohibited. All trial data will be stored securely at the trial 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 the Sponsor, Sponsor's designated monitors, regulatory authorities, or local IRBs/IECs.

## **10.6 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 informed consent forms, 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. The Sponsor 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.

# **11. ETHICAL CONSIDERATIONS**

## **11.1 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 the ethical principles of:

- World Medical Association Declaration of Helsinki<sup>16</sup>
- ICH GCP guidelines<sup>17</sup>
- 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*<sup>18</sup>.

### **11.2 Reporting and Management of Social Harms**

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. The acceptability questionnaire also includes questions to assess the occurrence of social harms. Participants who experience social harms 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.

### **11.3 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, group level discussions, pre/post tests, distributed feedback forms, etc. Each research centre has a process for consulting with the community. The primary vehicle for this consultation is through formal structures such as the Community Advisory Boards/Groups/Committees. These systems have provided input into the protocol design and facilitated acceptance of the research and allowed investigators and communities to identify and respond rapidly to concerns raised.

## **12. 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 Sponsor's clinical trial agreement with the investigator. Authorship criteria will be based on contributions to the design, work, and analysis of the trial.

### 13. REFERENCES

1. AIDS at 30: Nations at the Crossroads; UNAIDS 2011.  
<http://www.unaids.org/unaidresources/aidsat30/aids-at-30.pdf>
2. Report on the Global AIDS Epidemic; UNAIDS 2010.  
<http://www.unaids.org/globalreport/>
3. Elias CJ, Coggins C. Female-controlled methods to prevent sexual transmission of HIV. AIDS 1996;10:S43-S51.
4. Abdool Karim Q, Abdool S S, Frohlich JA, et al. Effectiveness and safety of Tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Scienceexpress, 19 July 2010, 1126, science.1193748; p1-13.  
<http://www.sciencexpress.org>
5. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010;363:2587-99
6. [http://www.hptn.org/web%20documents/PressReleases/HPTN052PressReleaseF1NAL5\\_12\\_118am.pdf](http://www.hptn.org/web%20documents/PressReleases/HPTN052PressReleaseF1NAL5_12_118am.pdf)
7. [http://www.hptn.org/web%20documents/PressReleases/HPTN052PressReleaseF1NAL5\\_12\\_118am.pdf](http://www.hptn.org/web%20documents/PressReleases/HPTN052PressReleaseF1NAL5_12_118am.pdf)
8. Dapivirine Vaginal Ring Investigators Brochure
9. Pharmacia & Upjohn Estrin<sup>®</sup> Physician Leaflet.  
([http://www.pfizer.com/pfizer/download/uspi\\_estrin.pdf](http://www.pfizer.com/pfizer/download/uspi_estrin.pdf))
10. Warner Chilcott Femring<sup>®</sup> Full U.S. Prescribing Information.  
([http://www.warnerchilcott.com/pdfs/pi-femring\(physician\).pdf](http://www.warnerchilcott.com/pdfs/pi-femring(physician).pdf))
11. Warner Chilcott Femring<sup>®</sup> Patient Information Materials: Patient Acceptability.  
([http://www.warnerchilcott.com/pdfs/pi-femring\(patient\).pdf](http://www.warnerchilcott.com/pdfs/pi-femring(patient).pdf))
12. Woodsong C, Montgomery E, Masenga G, et al, Safety and acceptability of vaginal ring as microbicide delivery method in African women. Oral presentation, Microbicides 2010, May 23 – 26, Pittsburgh, Pennsylvania.
13. ICH (1998) International Conference on Harmonization. Guideline E9 on Statistical Principles for Clinical Trials.
14. Lan KKG and DeMets DL, 1983. Discrete sequential boundaries for clinical trials. Biometrika, 70: 659-663.
15. O'Brien PC and Fleming TR, 1979. A multiple testing procedure for clinical trials. Biometrics, 35: 549-556.
16. World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects; WMA General Assembly, Seoul October 2008. <http://www.wma.net/e/policy/b3.htm>
17. Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance.  
([http://www.doh.gov.za/docs/policy/trials/trials\\_contents.html](http://www.doh.gov.za/docs/policy/trials/trials_contents.html))
18. Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa.  
([http://www.doh.gov.za/docs/policy/trials/trials\\_contents.html](http://www.doh.gov.za/docs/policy/trials/trials_contents.html))

## APPENDIX A: SCHEDULE OF CLINICAL PROCEDURES

Year 1 Visits	Screening 1	Screening 2	Enrolment <sup>b</sup>	4-weekly	12-weekly	24-weekly <sup>h</sup>	Last Product Use <sup>h</sup>	As Needed	Exit Visit
Trial Weeks <sup>a</sup>	Screening 2 must occur within 28 days of Screening 1			Weeks 4 - 52	Weeks 12, 24, 36, 48	Weeks 24, 48			
Informed Consent <sup>c</sup>	X		X						
Assign Participant Identification number	X								
Comprehension Assessment			X						
Demographics	X								
Medical History	X	X							
Concomitant Medication Evaluation	X	X		X	X	X	X		X
Inclusion/Exclusion Criteria	X	X							
Locator Information	X	X		X	X	X	X		X
Menses Information	X	X		X	X	X	X		
Physical Examination	X	X <sup>d</sup>					X	X <sup>d</sup>	
Adverse Event Evaluation			X	X	X	X	X	X	X <sup>f</sup>
Pelvic Exam	X	X			X	X	X	X	
Vaginal Ring Dispensing and Insertion			X	X	X	X		X <sup>e</sup>	
Vaginal Ring Removal/Return				X	X	X	X	X <sup>e</sup>	
Provision and Collection of Diary Card			X	X	X	X			
Provision of Male Condoms	X	X		X	X	X	X	X	X
Collection of Diary Card				X	X	X	X		
Adherence Questionnaire				X	X	X	X		
Acceptability Questionnaire				X <sup>g</sup>		X	X		
Behavioural Questionnaire			X						
HIV/STI Risk Reduction Counselling	X	X		X	X	X	X		X
Vaginal Ring Adherence Counselling			X	X	X	X		X	
Contraceptive Counselling	X		X	X	X	X	X	X	X
HIV Pre- & Post-Test Counselling	X	X		X	X	X	X	X	X

Year 2 Visits				4-weekly	12-weekly	24-weekly	Last Product Use <sup>h</sup>	As Needed	Exit Visit
Trial Weeks <sup>a</sup>				Weeks 56 - 100	Weeks 60, 72, 84, 96	Weeks 72, 96	Week 104/ Early discontinuation		
Concomitant Medication Evaluation				X	X	X	X		X
Locator Information				X	X	X	X		X
Menses Information				X	X	X	X		
Physical Examination							X	X <sup>d</sup>	
Adverse Event Evaluation				X	X	X	X	X	X <sup>f</sup>
Pelvic Exam					X	X	X	X	
Vaginal Ring Dispensing and Insertion				X	X	X		X <sup>e</sup>	
Vaginal Ring Removal/Return				X	X	X	X	X <sup>e</sup>	
Provision and Collection of Diary Card				X	X	X			
Provision of Male Condoms				X	X	X	X	X	X
Adherence Questionnaire				X	X	X	X		
Acceptability Questionnaire						X	X		
HIV/STI Risk Reduction Counselling				X	X	X	X		X
Vaginal Ring Adherence Counselling				X	X	X		X	
Contraceptive Counselling				X	X	X	X	X	X
HIV Pre- & Post-Test Counselling				X	X	X	X	X	X

<sup>a</sup> Each trial week is equal to 7 days. All visits while on the investigational product may occur  $\pm$  7 days of scheduled visits.

<sup>b</sup> Enrolment may occur the same day as Screening 2.

<sup>c</sup> The informed consent will be signed prior to screening and again prior to enrolment.

<sup>d</sup> Directed examination determined by symptomatology.

<sup>e</sup> If a vaginal ring is removed for more than 24 hours a new ring will be dispensed.

<sup>f</sup> The diary card may be reviewed at 4-weekly visits as part of the adherence assessment. Participants may consult their diary cards during adherence counselling.

<sup>g</sup> The baseline acceptability questionnaire will be administered only at week 4.

<sup>h</sup> 6 – 10 participants will be invited to participate in an individual interview to be held during weeks 24 – 42. Each research centre will also conduct 2 – 3 focus groups with participants who have been recruited at the last product use visit. Additionally, 6 – 10 individual interviews with male partners will be conducted at each research centre.

<sup>i</sup> If IP was permanently discontinued due to a laboratory AE, safety assessment(s) should be performed at the exit visit if the laboratory abnormality has not resolved.

## APPENDIX B: SCHEDULE OF LABORATORY PROCEDURES

Year 1 Visits	Screening 1	Screening 2	Enrolment	4-weekly	12-weekly	Annual	Last Product Use	As Needed	Exit Visit
Trial Weeks				Weeks 4 - 52	Weeks 12, 24, 36, 48	Week 52			
Urine Pregnancy Test <sup>n</sup>	X	X		X	X	X	X	X	
HIV Rapid Test	X	X		X	X	X	X		X
HIV-RNA PCR Test			X <sup>i,p</sup>	X <sup>i</sup>	X <sup>i</sup>	X <sup>i</sup>	X <sup>i</sup>		
Plasma Dapivirine Levels				X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		
Vaginal Fluid Dapivirine Levels				X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		
Plasma Viral Genotype Sample			X <sup>i,p</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		X <sup>i</sup>
HSV-2 Serology			X <sup>i,p</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		
Laboratory Testing for Safety Assessments <sup>k</sup>	X				X		X	X	
Vaginal Fluid pH and Vaginal Flora Sample			X		X		X		
Cervicovaginal Sample Collection for STI Tests	X				X		X	X	
Cervical Sample Collection for Cytology <sup>o</sup>	X					X	X <sup>q</sup>		
RPR <sup>m</sup>	X						X	X	
Final Laboratory results provided to participants									X

Year 2 Visits	Screening 1	Screening 2	Enrolment	4-weekly	12-weekly	Last Product Use	As Needed	Exit Visit
Trial Weeks				Weeks 56 - 100	Weeks 60, 72, 84, 96	Week 104/ Early discontinuation		
Urine Pregnancy Test <sup>n</sup>				X	X	X	X	
HIV Rapid Test				X	X	X		X
HIV-RNA PCR Test				X <sup>i</sup>	X <sup>i</sup>	X <sup>i</sup>		
Plasma Dapivirine Levels				X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		
Vaginal Fluid Dapivirine Levels				X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		
Plasma Viral Genotype Sample				X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		X <sup>l</sup>
HSV-2 serology				X <sup>i,j</sup>	X <sup>i,j</sup>	X <sup>i,j</sup>		
Laboratory Testing for Safety Assessments <sup>k</sup>					X	X	X	
Vaginal Fluid pH and Vaginal Flora Sample					X	X		
Cervicovaginal Sample Collection for STI Tests					X	X	X	
Cervical Sample Collection for Cytology						X <sup>q</sup>		
RPR <sup>m</sup>						X	X	
Final Laboratory results provided to participants								X

<sup>i</sup> Sample will be stored and will only undergo testing subsequently or after confirmation of seroconversion.

<sup>j</sup> Sample will be obtained at the point of two positive HIV rapid tests, and tested subsequently or after confirmation of seroconversion.

<sup>k</sup> Urinalysis dipstick testing (Urine microscopy only if indicated), haematology (FBC with differential count and platelets), chemistry (electrolytes, calcium, urea, creatinine, AST, ALT, ALP, bilirubin).

<sup>l</sup> Blood samples for viral genotyping will only be collected at the scheduled exit visit following seroconversion.

<sup>m</sup> TPHA/TPPA should be performed if RPR positive.

<sup>n</sup> A confirmatory serum pregnancy test may be requested if reason exists to suspect a false positive urine pregnancy test.

<sup>o</sup> For women with Grade 1 cervical cytology findings, cervical cytology will be repeated according to the local standard of care, or after 6 months; whichever is more conservative.

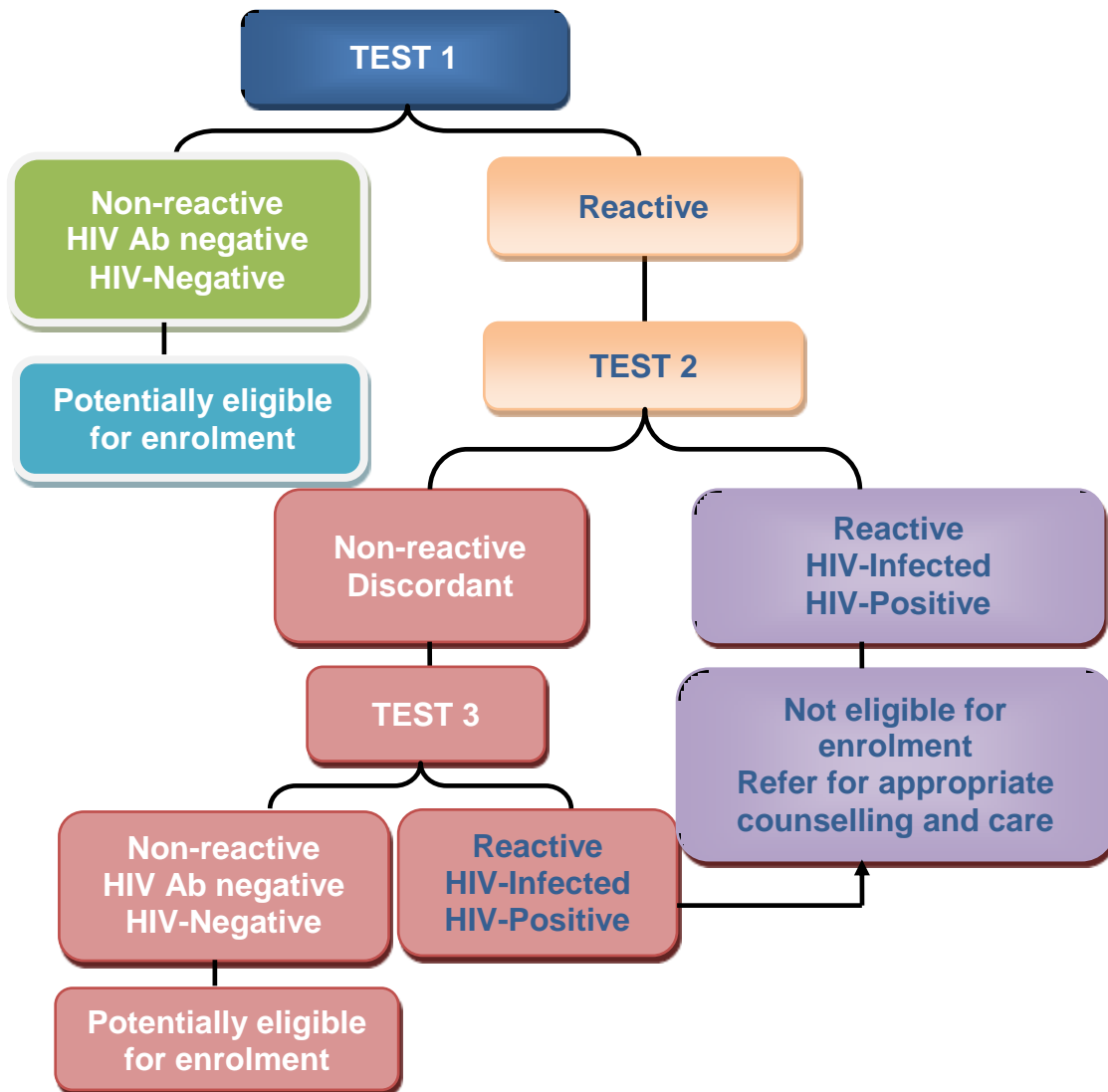
<sup>p</sup> Blood samples for HSV-2 serology, HIV viral genotyping and HIV-RNA PCR will be collected at screening 2 for research centres that use this option.

<sup>q</sup> It is not recommended that cervical cytology be repeated within six weeks of a previous sample.

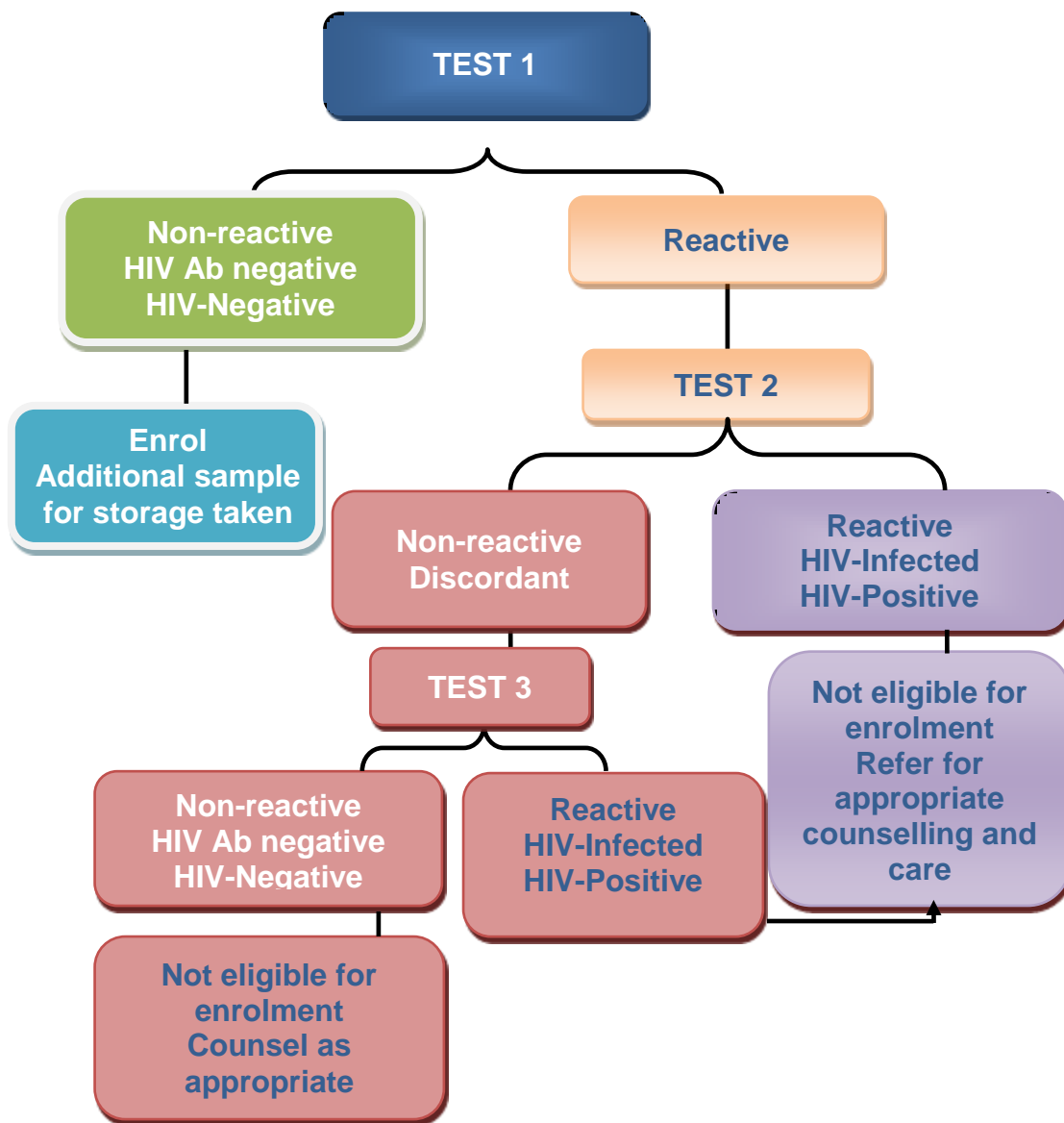


## APPENDIX C: HIV TESTING ALGORITHMS

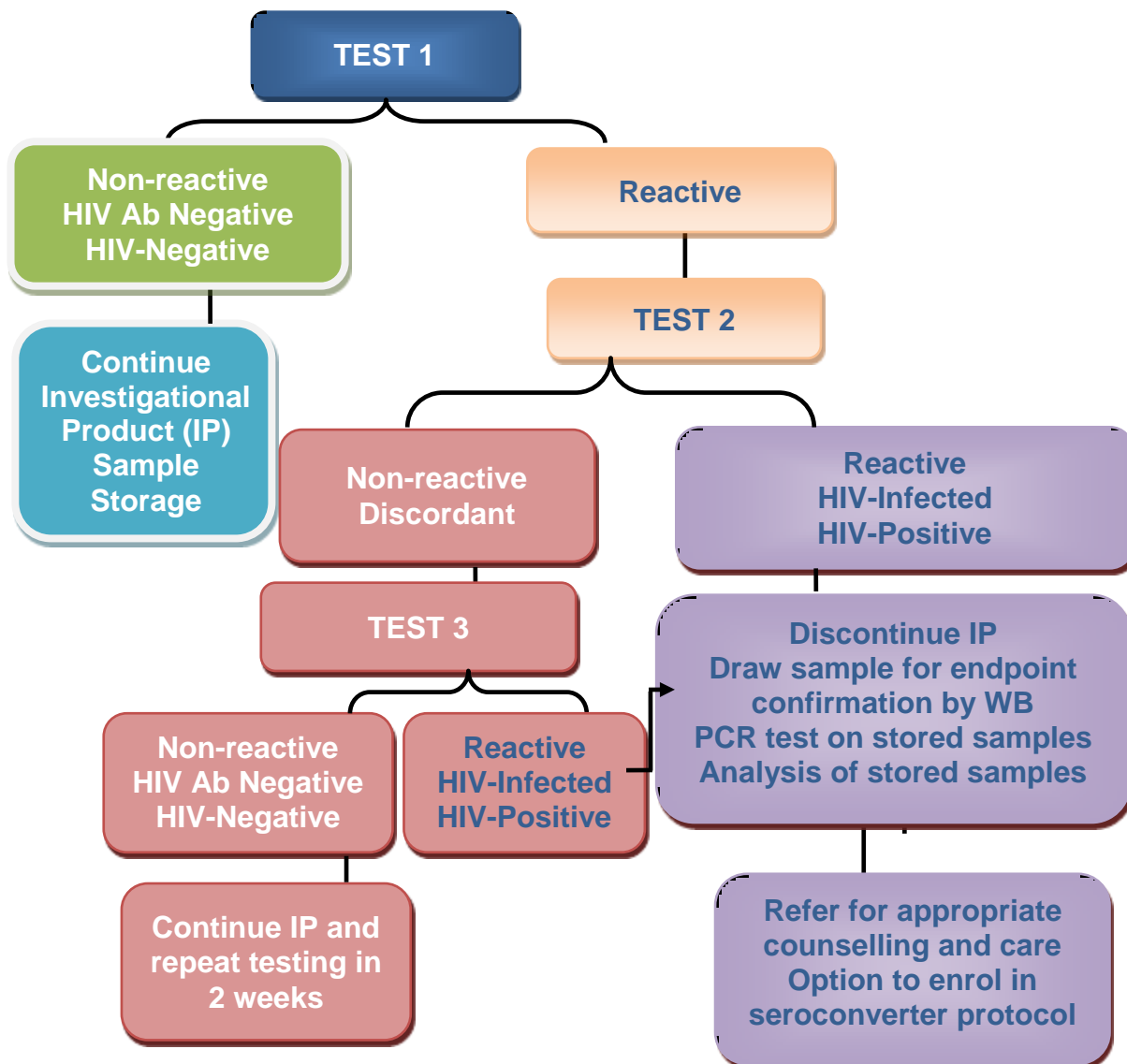
Figure 1: Screening 1 Algorithm



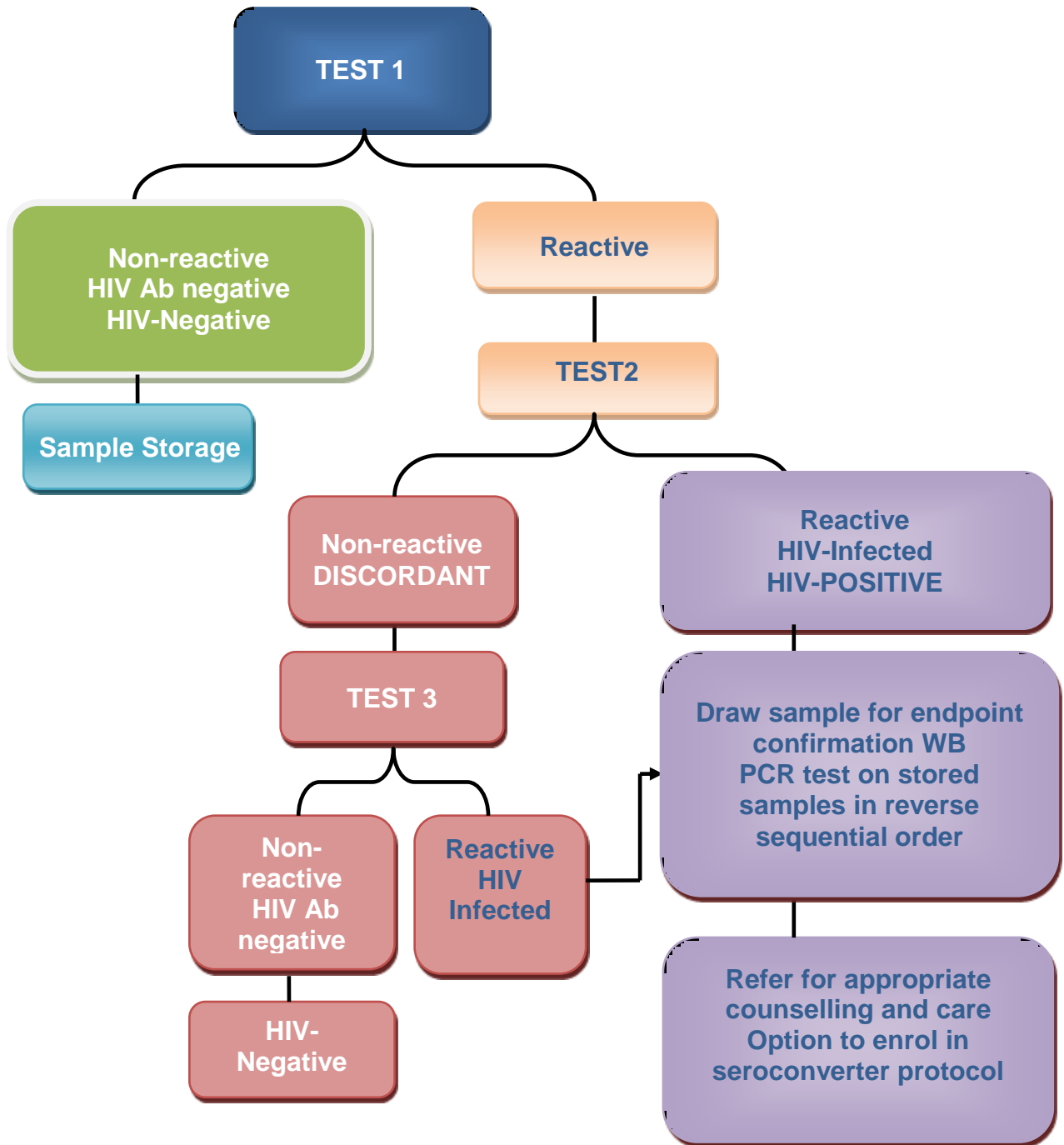
**Figure 2: Screening 2 and Enrolment Algorithm (should be conducted within 28 days [4 weeks] of screening unless otherwise stated within the protocol)**



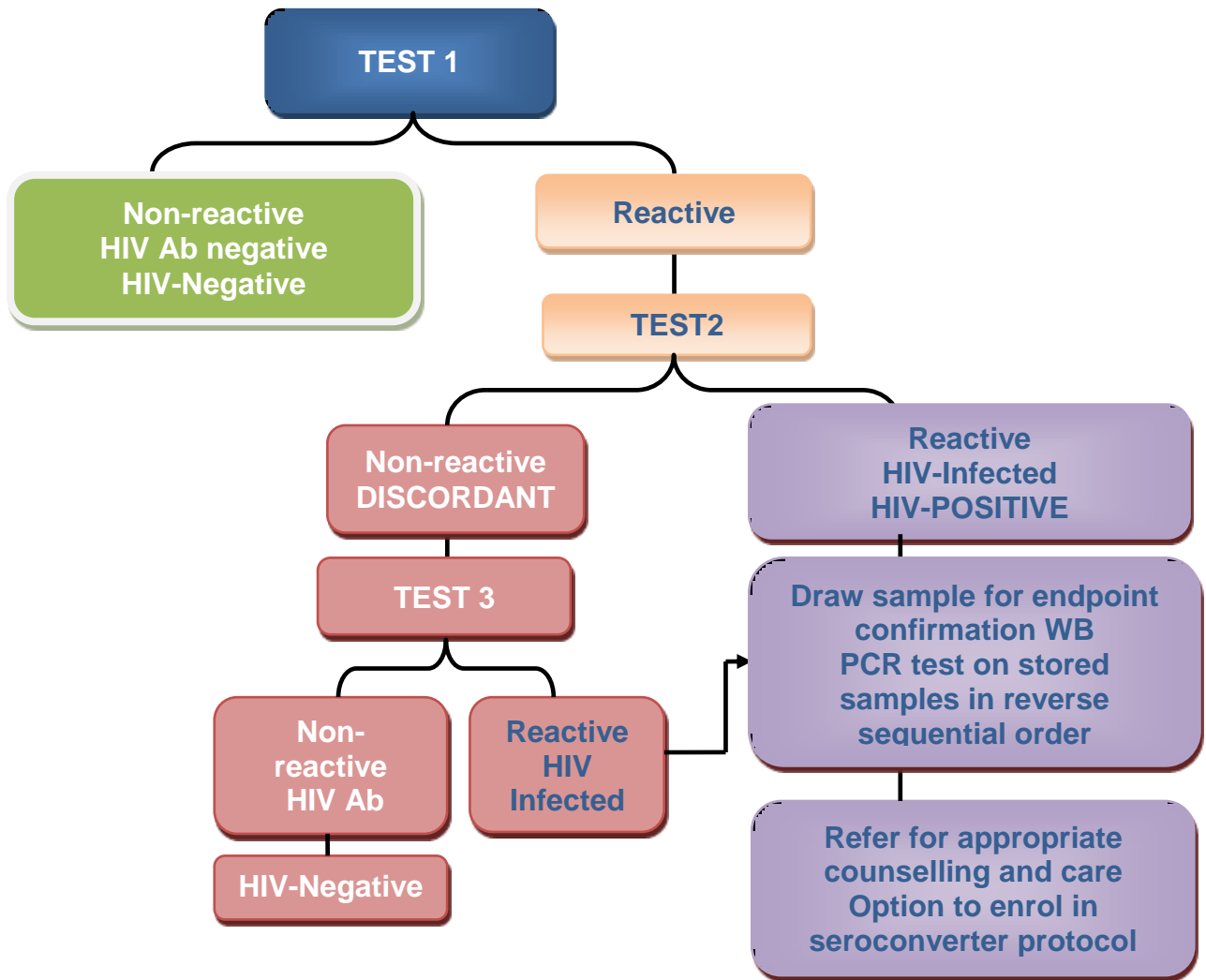
**Figure 3: Trial Visits Algorithm**



**Figure 4: Last Product Use Visit Algorithm**



**Figure 5: Exit Visit Algorithm: 6 weeks after product use**



### APPENDIX D: VISIT SCHEDULE AND 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
<b>Screening 1</b>	HIV rapid* 5 mL	Haematology 5 mL	Chemistry 5 mL	RPR 5 mL		15 - 20 mL
<b>Screening 2 &amp; Enrolment</b>	HIV rapid* 5 mL		Viral genotyping# 10 mL	HSV-2# 5 mL	HIV PCR# 5 mL	20 – 25 mL
<b>Monthly (4-weekly)</b>	HIV rapid 5 mL	Dapivirine levels# 6 mL	Viral genotyping# 10 mL	HSV-2# 5 mL	HIV PCR# 5 mL	31 mL
<b>Quarterly (12-weekly)</b>	HIV rapid 5 mL	Haematology 5 mL ----- Dapivirine levels# 6 mL	Chemistry 5 mL ----- Viral genotyping# 10 mL	HSV-2# 5 mL	HIV PCR# 5 mL	41 mL
<b>Last Product Use Visit</b>	HIV rapid 5 mL	Haematology 5 mL ----- Dapivirine levels# 6 mL	Chemistry 5 mL ----- Viral genotyping# 10 mL	RPR 5 mL ----- HSV-2# 5 mL	HIV PCR# 5 mL	46 mL
<b>Exit Visit</b>	HIV rapid^ 5 mL		Viral genotyping## 10 mL			5 mL or 10 mL##
<b>Sero-converter tests+</b>	Western blot 5 mL	Dapivirine levels 6 mL	Viral genotyping 10 mL	HSV-2 5 mL		26 mL

- \* Depending on the research centre SOP on HIV testing, sampling may be performed by finger prick or venipuncture.
- # Stored plasma samples; tested retrospectively to evaluate different parameters at the time of seroconversion.
- ## Blood samples for viral genotyping will only be collected at the scheduled exit visit following seroconversion.
- ^ HIV rapid test will not be performed 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.

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>TRIAL TITLE (page 1)</p> <p>A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II LONG-TERM SAFETY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-NEGATIVE WOMEN</p>	<p>TRIAL TITLE (page 1)</p> <p>A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED <del>PHASE II LONG-TERM SAFETY</del> <b>AND EFFICACY</b> TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-NEGATIVE WOMEN</p>	<p>Recommendation by Parallel Scientific Advice (PSA) Procedure to also evaluate efficacy of dapivirine vaginal ring.</p>
<p>TRIAL TITLE ON SIGNATURE PAGE (page 2)</p> <p>A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II LONG-TERM SAFETY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-NEGATIVE WOMEN</p>	<p>TRIAL TITLE ON SIGNATURE PAGE (page 2)</p> <p>A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED <del>PHASE II LONG-TERM SAFETY</del> <b>AND EFFICACY</b> TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-NEGATIVE WOMEN</p>	<p>Recommendation by PSA Procedure to also evaluate efficacy of dapivirine vaginal ring.</p>
<p>PROTOCOL SYNOPSIS</p> <p>BACKGROUND</p> <p>HIV/AIDS is the leading cause of death globally in women ages 15 – 44, and exerts an especially high toll in sub-Saharan Africa, where 60% of people living with HIV are women and girls. Developing new HIV prevention options that women can use remains a public health priority. The current generation of vaginal microbicide candidates, containing highly-specific antiretroviral (ARV) drugs, are currently undergoing extensive safety and efficacy trials. ARV-based microbicides specifically target HIV and can be designed in various forms (e.g. vaginal gels, rings, films, tablets) for more flexible dosing, including products for use around the time of sex, or daily or monthly products that could be used independent of sexual activity. Other recently completed and ongoing clinical trials are exploring whether oral daily ARVs taken as pre-exposure prophylaxis (PrEP) are safe and effective for HIV prevention.</p> <p>Recent research confirms the potential of ARV-based HIV prevention. In July 2010, in an important milestone for HIV prevention, the CAPRISA 004 Phase IIB microbicide trial found a 39% lower HIV infection rate in women using 1% <i>tenofovir gel</i> as compared to the women using a placebo gel. 1% <i>Tenofovir gel</i> is the first ARV-based microbicide to be tested in an efficacy trial. It is now being tested as a once-daily product in the MTN-003 (VOICE) Phase IIB trial, with another confirmatory Phase III trial, FACTS 001, planned to start in 2011 (using the CAPRISA 004 BAT24 dosing regimen).</p> <p>Successes with <i>oral</i> ARVs for prevention have also been observed. In November 2010, the iPrEx Phase III trial showed that oral Truvada® was 42% effective in reducing the risk of HIV infection among men who have sex with men. And in May 2011, results of the HPTN 052 “treatment for prevention” trial showed that immediate use of ARV therapy by HIV-positive individuals can reduce the risk of</p>	<p>PROTOCOL SYNOPSIS</p> <p>BACKGROUND</p> <p>HIV/AIDS is the leading cause of death globally in women <u>aged 15 to 44</u>, and exerts an especially high toll in sub-Saharan Africa, where 60% of people living with HIV are women and girls. Developing new HIV prevention options that women can use remains a public health priority. The current generation of vaginal microbicide candidates, containing highly-specific antiretroviral (ARV) drugs, are currently undergoing extensive safety and efficacy trials. ARV-based microbicides specifically target HIV and can be designed in various forms (e.g. vaginal gels, rings, films, tablets) for more flexible dosing, including products for use around the time of sex, or daily or monthly products that could be used independent of sexual activity. Other recently completed and ongoing clinical trials are exploring whether oral daily ARVs taken as pre-exposure prophylaxis (PrEP) are safe and effective for HIV prevention.</p> <p>Recent research confirms the potential of ARV-based HIV prevention. In July 2010, in an important milestone for HIV prevention, the CAPRISA 004 Phase IIB microbicide trial found a 39% lower HIV infection rate in women using 1% tenofovir gel as compared to the women using a placebo gel. 1% Tenofovir gel is the first ARV-based microbicide to be tested in an efficacy trial. <b><u>It has been tested as a once-daily product in the MTN-003 (VOICE) Phase IIB trial, but the tenofovir gel arm was discontinued due to futility. A further confirmatory Phase III trial, FACTS 001, using the CAPRISA 004 BAT24 dosing regimen, started in 2011.</u></b></p> <p>Successes with oral ARVs for prevention have also been observed. In November 2010, the iPrEx Phase III trial showed that oral Truvada® was 42% effective in reducing the risk of HIV infection among men who have sex with men. And in May 2011, results of the HPTN 052 “treatment for prevention” trial showed that</p>	<p>Section revised with updated information on VOICE and FACTS 001 trials, and efficacy evaluation is included in the description of the design of IPM 027.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>transmitting the virus to their uninfected partner by 96%. However, another recent Phase III trial, FEM-PrEP, which tested the effectiveness of daily oral Truvada® in 1,951 high-risk women in Africa, was stopped after an Independent Data Monitoring Committee determined that it was highly unlikely that the trial would be able to show that this strategy was effective.</p> <p>With a successful proof of concept for ARV-based gels and pills, it is evident that ARV approaches to prevention have the potential to transform the response to the HIV/AIDS pandemic. For women, in addition to confirmatory trials on tenofovir gel, 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 and improve upon the level of effectiveness seen in CAPRISA 004.</p> <p>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. In addition, a product used independently of sex could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse. As seen in the CAPRISA 004 and iPrEx trials, higher adherence to the test product was associated with increased effectiveness of the product. It is likely that products that can be applied less frequently will be more acceptable and will achieve better adherence. Vaginal rings that need only be replaced monthly may therefore have benefits over dosage forms that need to be used more frequently. The dapivirine (25 mg) silicone elastomer vaginal matrix ring is IPM's lead candidate for advancement to Phase II long-term safety and Phase III safety and efficacy testing.</p> <p>Multiple Phase I and I/II clinical trials have evaluated the safety of dapivirine in vaginal rings and gels and in an oral formulation. These clinical trials support the favourable safety profile and tolerability of dapivirine in general, and specifically in vaginal delivery formulations. IPM 027 is a Phase II clinical trial that has been designed to assess the long-term safety of dapivirine administered in a silicone elastomer vaginal matrix ring containing 25mg of dapivirine (Ring-004), inserted once every 4 weeks; in healthy, HIV-negative, sexually active women – as compared with a placebo vaginal ring.</p>	<p>immediate use of ARV therapy by HIV-positive individuals can reduce the risk of transmitting the virus to their uninfected partner by 96%. However, another recent Phase III trial, FEM-PrEP, which tested the effectiveness of daily oral Truvada® in 1,951 high-risk women in Africa, was stopped after an Independent Data Monitoring Committee determined that it was highly unlikely that the trial would be able to show that this strategy was effective. <b><u>The efficacy of oral tenofovir tablets has also been tested in the MTN-003 (VOICE) Phase IIB trial, but the oral tenofovir arm was discontinued due to futility.</u></b></p> <p><b><u>It appears</u></b> that ARV approaches to prevention have the potential to transform the response to the HIV/AIDS pandemic. For women, in addition to confirmatory trials on tenofovir gel, 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 and improve upon the level of effectiveness seen in CAPRISA 004.</p> <p>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. In addition, a product used independently of sex could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse. As seen in the CAPRISA 004 and iPrEx trials, higher adherence to the test product was associated with increased effectiveness of the product. It is likely that products that can be applied less frequently will be more acceptable and will achieve better adherence. Vaginal rings that need only be replaced monthly may therefore have benefits over dosage forms that need to be used more frequently. The dapivirine (25 mg) silicone elastomer vaginal matrix ring is IPM's lead candidate for advancement to <del>Phase II long-term safety and Phase III</del> <b><u>clinical</u></b> safety and efficacy testing.</p> <p>Multiple Phase I and I/II clinical trials have evaluated the safety of dapivirine in vaginal rings and gels and in an oral formulation. These clinical trials support the favourable safety profile and tolerability of dapivirine in general, and specifically in vaginal delivery formulations. IPM 027 <del>is a Phase II clinical trial that has been designed to assess the long-term</del> <b><u>evaluate the safety and to determine the efficacy</u></b> of dapivirine administered in a silicone elastomer vaginal matrix ring containing 25mg of dapivirine (Ring-004), inserted once every 4 weeks; in healthy, HIV-negative, sexually active women – as compared with a placebo vaginal ring.</p>	
<p>PROTOCOL SYNOPSIS</p> <p>OBJECTIVES</p> <p><b>The Primary Objective is:</b></p>	<p>PROTOCOL SYNOPSIS</p> <p>OBJECTIVES</p> <p><b>The Primary Objectives are:</b></p>	<p>Efficacy assessment (HIV-1 seroconversion rate) is included as primary endpoint, as per recommendation</p>



OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>1. To assess and compare the safety of dapivirine administered in a silicone elastomer vaginal matrix ring to the placebo vaginal ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks).</p> <p><b>The Secondary Objectives are:</b></p> <ol style="list-style-type: none"> <li>To assess and compare the incidence of HIV-1 and HIV-2 (for safety) in the dapivirine and placebo vaginal ring groups.</li> <li>To assess and compare the incidence of curable sexually-transmitted infections (STIs), and changes in vaginal flora in the dapivirine and placebo vaginal ring groups.</li> <li>To determine the incidence of pregnancy in both trial arms.</li> <li>To assess reported adherence to the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.</li> <li>To assess reported acceptability of the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.</li> <li>To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection while using the investigational product.</li> </ol> <p><b>The Exploratory Objectives are:</b></p> <ol style="list-style-type: none"> <li>To evaluate the association between HSV-2 and HIV-1 infection in both trial arms.</li> <li>To explore the potential relationship between method of contraception, pregnancy incidence and HIV seroconversion in both trial arms.</li> <li>To explore the relationship between drug concentrations and trial outcomes (HIV-1 seroconversion and viral resistance).</li> <li>To explore the correlation of drug concentrations and self-reported adherence measures.</li> </ol>	<p>1. <u>To determine the efficacy of dapivirine administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks), in preventing HIV-1 infection among healthy, sexually active HIV-negative women.</u></p> <p>2. To assess <del>and compare</del> the safety of dapivirine administered in a silicone elastomer vaginal matrix ring <del>to the placebo vaginal ring</del>, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks).</p> <p><b>The Secondary Objectives are:</b></p> <ol style="list-style-type: none"> <li>To <u>determine</u> the incidence of <del>HIV-1 and HIV-2 (for safety)</del> in the dapivirine and placebo vaginal ring groups.</li> <li>To assess and compare the incidence of curable sexually-transmitted infections (STIs), and changes in vaginal flora in the dapivirine and placebo vaginal ring groups.</li> <li>To determine the incidence of pregnancy in both trial arms.</li> <li>To assess reported adherence to the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.</li> <li>To assess reported acceptability of the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.</li> <li>To assess the frequency <u>and type</u> of HIV-1 drug resistance in women who acquire HIV-1 infection while using the investigational product.</li> </ol> <p><b>The Exploratory Objectives are:</b></p> <ol style="list-style-type: none"> <li>To evaluate the association between HSV-2 and HIV-1 infection in both trial arms.</li> <li>To explore the potential relationship between method of contraception, pregnancy incidence and HIV seroconversion in both trial arms.</li> <li>To explore the relationship between drug concentrations and trial outcomes (HIV-1 seroconversion and viral resistance).</li> <li>To explore the correlation of drug concentrations and self-reported adherence measures.</li> </ol>	<p>by PSA Procedure.</p> <p>It is indicated more clearly that the type of HIV-1 drug resistance will be assessed together with the frequency.</p>
<p>PROTOCOL SYNOPSIS</p> <p>ENDPOINTS AND ASSESSMENTS</p> <p><b>The primary endpoints are:</b></p> <ul style="list-style-type: none"> <li>Grade 2 adverse events (AEs) judged to be related to the investigational product;</li> </ul>	<p>PROTOCOL SYNOPSIS</p> <p>ENDPOINTS AND ASSESSMENTS</p> <p><b>The primary endpoints are:</b></p> <ul style="list-style-type: none"> <li><u>The incidence rate of HIV-1 seroconversion;</u></li> <li><u>All adverse events (AEs) (full descriptive evaluation).</u></li> </ul>	<p>Efficacy assessment (HIV-1 seroconversion rate) is included as primary endpoint, as well as <u>all</u> adverse events, as per recommendation by</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<ul style="list-style-type: none"> <li>Grade 3 and 4 AEs.</li> </ul> <p><b>The primary endpoints will be assessed through:</b></p> <ul style="list-style-type: none"> <li>Self-reports, physical examination, gynaecological assessments, including pelvic/speculum examination, laboratory tests and other indicated investigations. All AEs will be reported regardless of grade or relatedness.</li> </ul> <p><b>The secondary endpoints are:</b></p> <ul style="list-style-type: none"> <li>Seroconversion rates of HIV-1 and HIV-2 per woman years of product use at the end of the investigational product (IP) use period;</li> <li>The incidence of curable STIs (i.e. <i>N.gonorrhoea</i>, <i>C.trachomatis</i> and <i>T.vaginalis</i>), and changes in vaginal flora in each trial arm over the IP use period;</li> <li>The incidence of pregnancy in each trial arm over the IP use period;</li> <li>The proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period;</li> <li>The proportion of women who report the use of the vaginal ring as acceptable;</li> <li>HIV-1 drug resistance mutations among participants who acquire HIV-1.</li> </ul> <p><b>The secondary endpoints will be assessed through:</b></p> <ul style="list-style-type: none"> <li>Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C;</li> <li>STI testing, vaginal flora and vaginal pH testing;</li> <li>Pregnancy testing;</li> <li>Questionnaires and qualitative data regarding sexual behaviour and adherence to the use of a vaginal ring inserted once every 4 weeks over the trial period;</li> <li>Questionnaires and qualitative data regarding the acceptability of the use of a vaginal ring inserted once every 4 weeks over the trial period;</li> <li>Viral genotyping methods.</li> </ul> <p><b>The exploratory endpoints are:</b></p> <ul style="list-style-type: none"> <li>The proportion of HSV-2 among analysed samples;</li> <li>Incidence of pregnancy in correlation with HIV seroconversion rates and method(s) of contraception used by participants;</li> <li>Steady-state drug concentrations in blood and vaginal fluid;</li> <li>Steady-state drug concentrations in correlation with self-reported adherence</li> </ul>	<p><b>The primary endpoints will be assessed through:</b></p> <ul style="list-style-type: none"> <li><u>Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C;</u></li> <li>Self-reports, physical examination, gynaecological assessments, including pelvic/speculum examination, laboratory tests and other indicated investigations. All AEs will be reported regardless of grade or relatedness.</li> </ul> <p><b>The secondary endpoints are:</b></p> <ul style="list-style-type: none"> <li><u>The incidence rate of HIV-2 seroconversion;</u></li> <li>The incidence of curable STIs (i.e. <i>N.gonorrhoea</i>, <i>C.trachomatis</i> and <i>T.vaginalis</i>), and changes in vaginal flora in each trial arm over the IP use period;</li> <li>The incidence of pregnancy in each trial arm over the IP use period;</li> <li>The proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period;</li> <li>The proportion of women who report the use of the vaginal ring as acceptable;</li> <li><u>The proportion of participants with</u> HIV-1 drug resistance mutations among participants who acquire HIV-1.</li> </ul> <p><b>The secondary endpoints will be assessed through:</b></p> <ul style="list-style-type: none"> <li>Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C;</li> <li>STI testing, vaginal flora and vaginal pH testing;</li> <li>Pregnancy testing;</li> <li>Questionnaires and qualitative data regarding sexual behaviour and adherence to the use of a vaginal ring inserted once every 4 weeks over the trial period;</li> <li>Questionnaires and qualitative data regarding the acceptability of the use of a vaginal ring inserted once every 4 weeks over the trial period;</li> <li>Viral genotyping methods.</li> </ul> <p><b>The exploratory endpoints are:</b></p> <ul style="list-style-type: none"> <li>The proportion of HSV-2 among analysed samples;</li> <li>Incidence of pregnancy in correlation with HIV seroconversion rates and method(s) of contraception used by participants;</li> <li>Steady-state drug concentrations in blood and vaginal fluid;</li> </ul>	<p>PSA Procedure.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>as outlined above for the secondary objective.</p> <p><b>The exploratory endpoints will be assessed through:</b></p> <ul style="list-style-type: none"> <li>- HSV-2 testing;</li> <li>- Pregnancy testing and HIV testing as outlined above for the secondary objective, and documentation of participant contraceptive method/s;</li> <li>- Drug concentrations in blood and vaginal fluid;</li> <li>- Vaginal fluid, plasma and/or ring residual drug concentrations and self-reported behavioural measures as outlined above for the secondary objective.</li> </ul>	<ul style="list-style-type: none"> <li>• Steady-state drug concentrations in correlation with self-reported adherence as outlined above for the secondary objective.</li> </ul> <p><b>The exploratory endpoints will be assessed through:</b></p> <ul style="list-style-type: none"> <li>- HSV-2 testing;</li> <li>- Pregnancy testing and HIV testing as outlined above for the secondary objective, and documentation of participant contraceptive method(s);</li> <li>- Drug concentrations in blood and vaginal fluid;</li> <li>- Vaginal fluid, plasma and/or ring residual drug concentrations and self-reported behavioural measures as outlined above for the secondary objective.</li> </ul>	
<p>PROTOCOL SYNOPSIS</p> <p>TRIAL DESIGN</p> <p>IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled Phase II trial to evaluate the long-term safety of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks; in healthy, sexually active HIV-negative women, when compared to a placebo vaginal ring. Approximately 1,650 participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.</p>	<p>PROTOCOL SYNOPSIS</p> <p>TRIAL DESIGN</p> <p>IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled <del>Phase II</del> trial to <del>evaluate the long-term</del> <b>assess the safety and efficacy</b> of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks, in healthy, sexually active HIV-negative women, when compared to a placebo vaginal ring. Approximately 1,650 participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.</p>	<p>Recommendation by PSA Procedure to also evaluate efficacy of dapivirine vaginal ring.</p>
<p>PROTOCOL SYNOPSIS</p> <p>POPULATION</p> <p>Approximately 1,650 sexually active HIV-negative women, 18 – 60 years of age, who understand the trial and can provide informed consent, will be enrolled and randomised in a 2:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a placebo vaginal ring.</p> <p>Approximately 300 participants over 40 years of age will be enrolled in the trial.</p>	<p>PROTOCOL SYNOPSIS</p> <p>POPULATION</p> <p>Approximately 1,650 sexually active HIV-negative women, 18 – <b>45</b> years of age, who understand the trial and can provide informed consent, will be enrolled and randomised in a 2:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a placebo vaginal ring.</p> <p><del>Approximately 300 participants over 40 years of age will be enrolled in the trial.</del></p>	<p>Harmonisation of participant selection criteria with another safety and efficacy trial that will be conducted with the dapivirine vaginal ring (MTN-020), as recommended by PSA Procedure.</p>
<p>PROTOCOL SYNOPSIS</p> <p>INCLUSION CRITERIA</p> <p>Women must meet all of the following criteria to be eligible for trial enrolment:</p> <ol style="list-style-type: none"> <li>1. Women ≥ 18 and ≤ 60 years of age, at screening, who can provide informed consent;</li> <li>2. Available for all visits and consent to follow all procedures scheduled for the trial;</li> <li>3. Self-reported sexually active (defined as an average of at least one</li> </ol>	<p>PROTOCOL SYNOPSIS</p> <p>INCLUSION CRITERIA</p> <p>Women must meet all of the following criteria to be eligible for trial enrolment:</p> <ol style="list-style-type: none"> <li>1. Women ≥ 18 and ≤ <b>45</b> years of age, at screening, who can provide informed consent;</li> <li>2. Available for all visits and consent to follow all procedures scheduled for the trial;</li> <li>3. Self-reported sexually active (defined as an average of at least one</li> </ol>	<p>Harmonisation of participant selection criteria with another safety and efficacy trial that will be conducted with the dapivirine vaginal ring (MTN-020), as recommended by PSA Procedure.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>penetrative penile vaginal coital act per month for the last 3 months prior to screening);</p> <ol style="list-style-type: none"> <li>4. HIV-negative as determined by the HIV algorithm applied at screening and enrolment;</li> <li>5. On a stable form of contraception as defined within section 5.4 and willing to continue on stable contraception for the duration of the clinical trial; unless post-menopausal or surgically sterilised;</li> <li>6. Asymptomatic for genital infections at the time of enrolment (if a woman is diagnosed with any clinically significant curable STI, she must have initiated treatment at least 1 week prior to enrolment and have completed the full course of treatment);</li> <li>7. Willing to answer questions about adherence, sexual behaviour, and ring acceptability;</li> <li>8. 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;</li> <li>9. Willing to refrain from participation in another research trial using drugs, vaccines, medical devices, microbicides or oral pre-exposure prophylaxis investigational drugs for the duration of the IPM 027 trial;</li> <li>10. Willing to refrain from use of vaginal products or objects including spermicides, lubricants, intravaginal medication, other vaginal rings, female condoms, cotton wool, rags, diaphragms, cervical caps (or any other vaginal barrier method), douches, drying agents and herbs within 14 days from enrolment and for the duration of the trial. Tampons are not included in this list and may be used for the duration of the trial.</li> </ol>	<p>penetrative penile-vaginal coital act per month for the last 3 months prior to screening);</p> <ol style="list-style-type: none"> <li>4. HIV-negative as determined by the HIV algorithm applied at screening and enrolment;</li> <li>5. On a stable form of contraception as defined within section 5.4 and willing to continue on stable contraception for the duration of the clinical trial, unless post-menopausal or surgically sterilised;</li> <li>6. Asymptomatic for genital infections at the time of enrolment (if a woman is diagnosed with any clinically significant curable STI, she must have initiated treatment at least 1 week prior to enrolment and have completed the full course of treatment);</li> <li><del>7. Willing to answer questions about adherence, sexual behaviour, and ring acceptability;</del></li> <li>7. 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;</li> <li>8. Willing to refrain from participation in another research trial using drugs, vaccines, medical devices, microbicides or oral pre-exposure prophylaxis investigational drugs for the duration of the IPM 027 trial;</li> <li><del>9. Willing to refrain from use of vaginal products or objects including spermicides, lubricants, intravaginal medication, other vaginal rings, female condoms, cotton wool, rags, diaphragms, cervical caps (or any other vaginal barrier method), douches, drying agents and herbs within 14 days from enrolment and for the duration of the trial. Tampons are not included in this list and may be used for the duration of the trial.</del></li> </ol>	
<p>PROTOCOL SYNOPSIS</p> <p>EXCLUSION CRITERIA</p> <p>Women who have any of the exclusion criteria below are not eligible:</p> <ol style="list-style-type: none"> <li>1. Currently pregnant or last pregnancy within 3 months prior to screening;</li> <li>2. Currently breast-feeding;</li> <li>3. Women who have had a hysterectomy;</li> <li>4. Participated in another research trial using drugs, medical devices, microbicides or oral pre-exposure prophylaxis agents within 60 days prior to screening;</li> <li>5. Previously participated or currently participating in any HIV vaccine trial;</li> <li>6. Untreated, clinically significant urogenital infections , e.g., urinary tract, or other sexually transmitted infections, or other gynaecological symptoms within</li> </ol>	<p>PROTOCOL SYNOPSIS</p> <p>EXCLUSION CRITERIA</p> <p>Women who have any of the exclusion criteria below are not eligible:</p> <ol style="list-style-type: none"> <li>1. Currently pregnant or last pregnancy within 3 months prior to screening <u>or intends to become pregnant during trial participation</u>;</li> <li>2. Currently breast-feeding;</li> <li>3. <del>Women who have had a hysterectomy;</del></li> <li>3. <u>Non-therapeutic injection drug use in the 12 months prior to screening</u>;</li> <li>4. Participated in another research trial using drugs, medical devices, microbicides or oral pre-exposure prophylaxis agents within 60 days prior to screening;</li> <li>5. Previously participated or currently participating in any HIV vaccine trial;</li> </ol>	<p>Harmonisation of participant selection criteria with another safety and efficacy trial that will be conducted with the dapivirine vaginal ring (MTN-020), as recommended by PSA Procedure.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>1 week prior to enrolment;</p> <p>7. Has a Grade 2 or higher pelvic examination finding, according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; Addendum 1 Female Genital Grading Table for Use in Microbicide Studies;</p> <p>8. History of significant urogenital or uterine prolapse, undiagnosed vaginal bleeding, diagnosed chronic and/or recurrent vulvovaginal candidiasis, urethral obstruction, incontinence or urge incontinence;</p> <p>9. Any gynaecological surgery within 90 days prior to screening;</p> <p>10. Any Grade 2, 3 or 4 baseline haematology, chemistry or urinalysis laboratory value according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events;</p> <p>11. Any history of anaphylaxis or severe allergy resulting in angioedema; or a history of sensitivity/allergy to latex or a silicone elastomer;</p> <p>12. Any history of diabetes mellitus and chronic use of oral corticosteroid therapy; and any uncontrolled serious chronic or progressive disease;</p> <p>13. Cervical cytology at screening that requires cryotherapy, biopsy or treatment (other than for infection). Women with Grade 1 cervical cytology findings can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology);</p> <p>14. Any condition(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.</p>	<p>6. Untreated, clinically significant urogenital infections , e.g., urinary tract, or other sexually transmitted infections, or other gynaecological symptoms within 1 week prior to enrolment;</p> <p>7. Has a Grade 2 or higher pelvic examination finding, according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; Addendum 1 Female Genital Grading Table for Use in Microbicide Studies;</p> <p>8. History of significant urogenital or uterine prolapse, undiagnosed vaginal bleeding, diagnosed chronic and/or recurrent vulvovaginal candidiasis, urethral obstruction, incontinence or urge incontinence;</p> <p>9. Any gynaecological surgery within 90 days prior to screening;</p> <p>10. Any <b><u>Grade 1 or higher baseline aspartate aminotransferase (AST), alanine transaminase (ALT), or platelet count, and any</u></b> Grade 2, <del>3 or 4</del> <b><u>or higher</u></b> baseline haematology, chemistry or urinalysis laboratory value according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events;</p> <p>11. Any history of anaphylaxis or severe allergy resulting in angioedema; or a history of sensitivity/allergy to latex or a silicone elastomer;</p> <p>12. Any history of diabetes mellitus and chronic use of oral corticosteroid therapy; and any uncontrolled serious chronic or progressive disease;</p> <p>13. Cervical cytology at screening that requires cryotherapy, biopsy or treatment (other than for infection). Women with Grade 1 cervical cytology findings can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology);</p> <p>14. Any condition(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.</p>	
<p>PROTOCOL SYNOPSIS</p> <p>METHODS</p> <p><u>Screening and enrolment:</u> Potential participants who consent will be invited to screen for the trial. At screening 1, these potential participants will provide information on inclusion and exclusion criteria, including locator and menses information, demographic information, 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 condoms), contraceptive counselling and HIV pre- and post-test counselling, and tested for pregnancy, HIV, STIs and cervical cytology, as well as safety laboratory assessments. At screening 2, further information will be collected on medical history, concomitant medication, locator and menses information. Those women who meet specified inclusion</p>	<p>PROTOCOL SYNOPSIS</p> <p>METHODS</p> <p><u>Screening and enrolment:</u> Potential participants who consent will be invited to screen for the trial. At screening 1, these potential participants will provide information on inclusion and exclusion criteria, including locator and menses information, demographic information, 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 condoms), contraceptive counselling and HIV pre- and post-test counselling, and tested for pregnancy, HIV, STIs and cervical cytology, as well as safety laboratory assessments. At screening 2, further information will be collected on medical history, concomitant medication, locator and menses information. Those women who meet specified inclusion</p>	<p>Viral genotyping will only be performed on blood samples, and not vaginal fluid samples, to harmonise IPM 027 with another safety and efficacy trial that will be conducted with the dapivirine vaginal ring (MTN-020), as recommended by PSA Procedure.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>criteria and no exclusion criteria, have a normal pelvic examination, negative pregnancy and HIV rapid tests, and consent to participate in the trial, will be invited to enrol in the trial. Eligible women will be randomly assigned in a 2:1 ratio to one of the two trial arms. At enrolment, each participant will receive a baseline behavioural questionnaire and a diary card to record sexual activity and ring experiences over the upcoming 4-week period. Blood samples will be collected for storage, and will be tested retrospectively for HIV-RNA PCR, HIV viral genotyping and HSV-2 serology subsequent to HIV-1 seroconversion. In addition, vaginal specimens will be taken prior to ring insertion to determine vaginal pH and assess vaginal flora.</p> <p>At enrolment, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled visit.</p> <p><u>Trial visits:</u> Dapivirine or placebo vaginal rings will be inserted at 4-weekly intervals for the duration of the IP use trial period. Similar to the enrolment visit, at each regularly scheduled trial visit while on the IP, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled visit. All participants will receive pre- and post-test HIV counselling; HIV/STI risk reduction counselling, condom and vaginal ring adherence counselling, HIV and pregnancy testing; and collection of locator, menses, and concomitant medication information. Male condoms will be provided at all visits as part of HIV/STI risk reduction counselling. Contraceptive counselling will be provided at all visits.</p> <p>Blood and vaginal fluid samples will be collected for storage at all visits; including the last product use visit. These stored blood samples will be tested for HIV-RNA PCR and viral genotyping only in HIV-1 seroconverters, while HSV-2 serology, blood and vaginal fluid dapivirine concentrations measurement will be conducted in confirmed HIV-1 seroconverters and a randomly selected control group of HIV-negative participants.</p> <p>The rapid and confirmatory laboratory tests used in the HIV testing algorithm will be able to detect both subtypes, HIV-1 and HIV-2. At the point of HIV seroconversion, the IP will be discontinued, and additional samples will be collected and tested for viral genotyping (blood and vaginal fluid), dapivirine concentrations (blood and vaginal fluid) and HSV-2 serology (blood). In addition, blood and vaginal fluid samples for viral genotyping will also be collected at the scheduled exit visit, approximately 6 weeks following seroconversion. No further storage samples will be collected in these participants.</p>	<p>criteria and no exclusion criteria, have a normal pelvic examination, negative pregnancy and HIV rapid tests, and consent to participate in the trial, will be invited to enrol in the trial. Eligible women will be randomly assigned in a 2:1 ratio to one of the two trial arms. At enrolment, each participant will receive a baseline behavioural questionnaire and a diary card to record sexual activity and ring experiences over the upcoming 4-week period. Blood samples will be collected for storage, and will be tested retrospectively for HIV-RNA PCR, HIV viral genotyping and HSV-2 serology subsequent to HIV-1 seroconversion. In addition, vaginal specimens will be taken prior to ring insertion to determine vaginal pH and assess vaginal flora.</p> <p>At enrolment, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled visit.</p> <p><u>Trial visits:</u> Dapivirine or placebo vaginal rings will be inserted at 4-weekly intervals for the duration of the IP use trial period. Similar to the enrolment visit, at each regularly scheduled trial visit while on the IP, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled visit. All participants will receive pre- and post-test HIV counselling, HIV/STI risk reduction counselling, condom and vaginal ring adherence counselling, HIV and pregnancy testing, and collection of locator, menses, and concomitant medication information. Male condoms will be provided at all visits as part of HIV/STI risk reduction counselling. Contraceptive counselling will be provided at all visits.</p> <p>Blood and vaginal fluid samples will be collected for storage at all visits, including the last product use visit. These stored blood samples will be tested for HIV-RNA PCR and viral genotyping only in HIV-1 seroconverters, while HSV-2 serology, blood and vaginal fluid dapivirine concentrations measurement will be conducted in confirmed HIV-1 seroconverters and a randomly selected control group of HIV-negative participants.</p> <p>The rapid and confirmatory laboratory tests used in the HIV testing algorithm will be able to detect both subtypes, HIV-1 and HIV-2. At the point of HIV seroconversion, the IP will be discontinued, and additional samples will be collected and tested for viral genotyping (blood and vaginal fluid), dapivirine concentrations (blood and vaginal fluid) and HSV-2 serology (blood). In addition, blood and vaginal fluid samples for viral genotyping will also be collected at the scheduled exit visit, approximately 6 weeks following seroconversion. No further storage samples will be collected in these participants.</p>	<p>Reference to cervical cytology, which will also be performed at Last Product Use Visit, was inadvertently omitted from previous version.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>Adherence assessments will be conducted through an interviewer-administered questionnaire at all 4-weekly trial visits, except the exit visit. Participants will be provided with diary cards at all 4-weekly visits except the last product use and exit visits. The participant may consult the diary card during the adherence assessments and the adherence counselling sessions at each 4-weekly visit. The cards will be collected at each visit. Acceptability questionnaires will be administered at the second trial visit (week 4), and at 24-weekly intervals thereafter, until the last product use visit.</p> <p>Twenty-four (24) to 36 weeks after trial initiation, each research centre will conduct 6 – 10 qualitative individual interviews with participants, and 6 – 10 qualitative individual interviews with male partners. These interviews will provide data on acceptability, sexual behaviour and adherence issues. The recruitment and sampling strategy will be specified in the Statistical Analysis Plan (SAP).</p> <p>AEs will be assessed at all visits post-randomisation. In addition, safety laboratory assessments, pelvic examination, vaginal pH and vaginal flora as well as STI tests will be performed at 12-weekly intervals. Cervical cytology will be repeated at the end of the first and second year of IP use. Residual dapivirine levels in returned rings will be measured for a selected group of participants at predetermined time-points.</p> <p><u>Last product use visit:</u> At the last product use visit, participants will return the last used rings; report any medical problems and/or concomitant medications since the last visit; provide locator and menses information; receive pre- and post-test HIV counselling, contraceptive counselling and HIV/STI risk-reduction counselling (including provision of male condoms); complete vaginal ring use, adherence and acceptability questionnaires; undergo a physical examination as well as a pelvic examination for evaluation of STIs and changes in vaginal flora; and provide blood and vaginal fluid specimens for storage, and specimens for pregnancy and HIV testing, and safety laboratory assessments.</p> <p>Each research centre will conduct 2 – 3 focus groups with participants who have been recruited for these groups at the last product use visit. Additionally, 6 – 10 qualitative individual interviews with male partners will be conducted at each research centre. These interviews will provide data on acceptability and adherence issues. The recruitment and sampling strategy will be specified in the SAP.</p> <p><u>Exit visit - 6 weeks after ring discontinuation:</u> Participants may be notified of any abnormal findings and asked to return to the research centre prior to the exit visit;</p>	<p>Adherence assessments will be conducted through an interviewer-administered questionnaire at all 4-weekly trial visits, except the exit visit. Participants will be provided with diary cards at all 4-weekly visits except the last product use and exit visits. The participant may consult the diary card during the adherence assessments and the adherence counselling sessions at each 4-weekly visit. The cards will be collected at each visit. Acceptability questionnaires will be administered at the second trial visit (week 4), and at 24-weekly intervals thereafter, until the last product use visit.</p> <p>Twenty-four (24) to 36 weeks after trial initiation, each research centre will conduct 6 – 10 qualitative individual interviews with participants, and 6 – 10 qualitative individual interviews with male partners. These interviews will provide data on acceptability, sexual behaviour and adherence issues. The recruitment and sampling strategy will be specified in the Statistical Analysis Plan (SAP).</p> <p>AEs will be assessed at all visits post-randomisation. In addition, safety laboratory assessments, pelvic examination, vaginal pH and vaginal flora as well as STI tests will be performed at 12-weekly intervals. Cervical cytology will be repeated at the end of the first and second year of IP use. Residual dapivirine levels in returned rings will be measured for a selected group of participants at predetermined time-points.</p> <p><u>Last product use visit:</u> At the last product use visit, participants will return the last used rings; report any medical problems and/or concomitant medications since the last visit; provide locator and menses information; receive pre- and post-test HIV counselling, contraceptive counselling and HIV/STI risk-reduction counselling (including provision of male condoms); complete vaginal ring use, adherence and acceptability questionnaires; undergo a physical examination as well as a pelvic examination for evaluation of STIs and changes in vaginal flora; <b><u>have a specimen collected for cervical cytology;</u></b> and provide blood and vaginal fluid specimens for storage, and specimens for pregnancy and HIV testing, and safety laboratory assessments.</p> <p>Each research centre will conduct 2 – 3 focus groups with participants who have been recruited for these groups at the last product use visit. Additionally, 6 – 10 qualitative individual interviews with male partners will be conducted at each research centre. These interviews will provide data on acceptability and adherence issues. The recruitment and sampling strategy will be specified in the SAP.</p> <p><u>Exit visit - 6 weeks after ring discontinuation:</u> Participants may be notified of any</p>	

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>as needed for treatment and/or referral. On the day of the scheduled exit visit, participants will return to the research centre to receive results from their pelvic examination/STI testing and safety laboratory assessments done at the last product use visit, and treatment or referral as needed. AEs and concomitant medications will also be recorded at this visit.</p> <p>Participants will receive pre- and post-test counselling for HIV and undergo final HIV testing. HIV/STI risk reduction counselling (including provision of male condoms) and contraceptive counselling will also be provided at the exit visit. If a clinically significant gynaecological or other related AE remains unresolved at the time of trial completion, a clinical assessment will be made by the research centre's investigator or designated qualified physician and the IPM Clinical Physician or designee to determine whether continued follow-up of the AE is warranted.</p> <p>Participants will then be considered to have completed trial participation, and informed that they may be re-contacted at a future date to be provided information about trial results including individual unblinding.</p>	<p>abnormal findings and asked to return to the research centre prior to the exit visit, as needed for treatment and/or referral. On the day of the scheduled exit visit, participants will return to the research centre to receive results from their pelvic examination/STI testing and safety laboratory assessments done at the last product use visit, and treatment or referral as needed. AEs and concomitant medications will also be recorded at this visit.</p> <p>Participants will receive pre- and post-test counselling for HIV and undergo final HIV testing. HIV/STI risk reduction counselling (including provision of male condoms) and contraceptive counselling will also be provided at the exit visit. If a clinically significant gynaecological or other related AE remains unresolved at the time of trial completion, a clinical assessment will be made by the research centre's investigator or designated qualified physician and the IPM Clinical Physician or designee to determine whether continued follow-up of the AE is warranted.</p> <p>Participants will then be considered to have completed trial participation, and informed that they may be re-contacted at a future date to be provided information about trial results including individual unblinding.</p>	
<p>PROTOCOL SYNOPSIS</p> <p>STATISTICAL CONSIDERATIONS</p> <p><u>General:</u> IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled Phase II trial to assess the long-term safety of dapivirine in a silicone elastomer vaginal matrix ring; to be conducted at approximately 7 clinical research centres. Individuals meeting all inclusion criteria and no exclusion criteria will be randomised in a 2:1 (dapivirine: placebo) ratio to either the investigational product or placebo. Randomisation will be stratified by research centre and age at the time of enrolment (<math>\leq 40</math> years of age, <math>&gt; 40</math> years of age; N = 1,350 and N = 300 respectively) using a pre-specified block size and will be determined via the use of an automated randomisation system to ensure balance of the treatment assignments.</p> <p><u>Sample Size and Power Calculations:</u> IPM 027 will be conducted in a sample of approximately 1,650 HIV-negative women in a 2:1 ratio such that 1,100 participants will be assigned to the investigational product and 550 participants will be assigned to the placebo ring. The sample size is determined based on the probability of detecting rare AEs in the active arm and the ability of the trial to detect differences in the proportion of primary endpoints between the two trial arms assuming an AE rate of 1% in the placebo arm. In a trial with 1,000 participants assigned to the investigational product, there is a 95% probability of</p>	<p>PROTOCOL SYNOPSIS</p> <p>STATISTICAL CONSIDERATIONS</p> <p><u>General:</u> IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled <del>Phase II</del> trial to assess the <del>long-term</del> safety <b>and efficacy</b> of dapivirine in a silicone elastomer vaginal matrix ring; to be conducted at approximately 7 clinical research centres. Individuals meeting all inclusion criteria and no exclusion criteria will be randomised in a 2:1 (dapivirine: placebo) ratio to either the investigational product or placebo. Randomisation will be stratified by research centre <del>and age</del> at the time of enrolment (<del><math>\leq 40</math> years of age, <math>&gt; 40</math> years of age; N = 1,350 and N = 300 respectively</del>), using a pre-specified block size and will be determined via the use of an automated randomisation system to ensure balance of the treatment assignments.</p> <p><u>Sample Size and Power Calculations:</u> IPM 027 will <b>randomise</b> approximately 1,650 HIV-negative women in a 2:1 ratio such that 1,100 participants will be assigned to the investigational product and 550 participants will be assigned to the placebo ring. <b><u>Under this design, a total of 80 HIV-1 seroconversions are expected and will provide approximately 83% power to detect a 50% reduction in the rate of HIV-1 seroconversions in the active arm, assuming an annual HIV-1 seroconversion rate of 4% in the placebo arm.</u></b></p>	<p>The addition of efficacy assessment as a primary endpoint, and limiting the enrolment age to <math>\leq 45</math> years, necessitated amendment of the Statistical Considerations section to include a revised sample size motivation, revised statistical analysis methods, omission of a subgroup analysis of women over 40 years, and the addition of an interim efficacy analysis when 50% of the endpoints have been observed.</p>



OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>detecting an AE occurring at a rate of 0.3% or higher.</p> <p>Using a Fisher's Exact Test under 0.05 type I error, a trial with 1,000 participants assigned to the active arm and 500 participants assigned to the placebo arm would provide approximately 91% power to detect a difference of 4% or larger if the AE rate in the placebo arm were 1%. To adjust for loss-to-follow-up the sample size of N=1,500 is inflated by 10% for a final sample size of 1,650.</p> <p><u>Statistical Analyses:</u> The analysis of the primary safety assessments will be descriptive in nature; all estimated treatment effects will be provided with 95% confidence intervals (CIs) and will be evaluated under a significance level of 0.05. Descriptive analyses of participant characteristics will be provided. The safety population will include all participants who were randomised to the investigational product and received at least one dose of the investigational product. A per-protocol analysis will also be performed and will exclude participants who did not adhere to the trial protocol.</p> <p>The safety parameters will be compared between participants assigned to the dapivirine-containing vaginal ring and participants assigned to the placebo vaginal ring, using Chi-square and a Fisher's Exact Test, when appropriate. Poisson and/or logistic regression models may be used to estimate the crude and adjusted effect of the dapivirine ring on the safety of the trial participants. Time to event outcomes will be assessed using Kaplan-Meier survival curves, and may utilise the log-rank test statistic and Cox proportional hazards model.</p> <p>The analysis of the social and behavioural secondary endpoints will focus on the assessment of acceptability of the vaginal ring, adherence to the use of the vaginal ring, as well as investigation of possible factors influencing adherence of women participating in the trial. Data for vaginal ring acceptability, sexual behaviour, condom use and vaginal ring use will be collected by self-report through interviewer-administered questionnaires, focus groups and individual interviews. Comparison between the two treatment arms will be conducted and will take into account the repeated measures by using a general estimating equation (GEE) framework.</p> <p>Appropriate statistical analyses of the exploratory endpoints will be performed.</p> <p>Subgroup Analyses: To assess the long-term safety of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks in healthy, HIV-negative women over 40 years of age, when compared to a placebo vaginal ring, an analysis of the primary, secondary and exploratory endpoints will be performed</p>	<p><b><u>Statistical Analyses: The analysis of the primary efficacy endpoint (HIV-1 seroconversion rate) will be performed on the modified Intent-to-Treat (m-ITT) population, which will include all participants who were HIV-1 negative at the time of enrolment, analysed according to the treatment arm to which they were randomised, regardless of adherence to the product. A per-protocol analysis may also be performed on a subset of participants who did not experience a major protocol violation.</u></b></p> <p><b><u>The primary efficacy analysis will provide an estimate of the HIV-1 seroconversion rates for the treatment and placebo arms, with 95% confidence intervals (CIs). The log-rank test, stratified by research centre, will formally evaluate at a 5% significance level the null hypothesis that the probability of an HIV-1 seroconversion occurring at any time point is the same for the active and placebo arms. Kaplan-Meier curves will also be presented, stratified by research centre.</u></b></p> <p><b><u>For the safety analysis, a descriptive analysis of all AEs will be presented in tables and listings. Fisher's Exact test will be performed to compare the proportion of participants in the active and placebo arms, with regard to all Grade 3 and 4 AEs, all SAEs, and AEs leading to IP discontinuation, at a 0.05 significance level.</u></b></p> <p>The analysis of the social and behavioural secondary endpoints will focus on the assessment of acceptability of the vaginal ring, adherence to the use of the vaginal ring, as well as investigation of possible factors influencing adherence of women participating in the trial. Data for vaginal ring acceptability, sexual behaviour, condom use and vaginal ring use will be collected by self-report through interviewer-administered questionnaires, focus groups and individual interviews. Comparison between the two treatment arms will be conducted and will take into account the repeated measures by using a general estimating equation (GEE) framework.</p> <p>Appropriate statistical analyses of the exploratory endpoints will be performed.</p> <p><del>Subgroup Analyses: To assess the long-term safety of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks in healthy, HIV-negative women over 40 years of age, when compared to a placebo vaginal ring, an analysis of the primary, secondary and exploratory endpoints will be performed on a subgroup of women over 40 years of age.</del></p> <p><del>A subgroup with approximately 200 participants over 40 years of age in the active</del></p>	

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>on a subgroup of women over 40 years of age.</p> <p>A subgroup with approximately 200 participants over 40 years of age in the active arm, or approximately 300 participants in both arms, would be sufficient to detect at least one AE with a rate of 2% and at least three events if the AE rate was 5%. The subgroup analysis will not be powered to detect small differences in the safety profile between the active and placebo arms. However, with 300 participants in the subgroup, the trial has 94% power to detect a difference when the AE rate in the active arm is 20% and the AE rate in the placebo arm is 5%. The qualitative individual interviews will include a sample of women over 40 years of age, to provide further descriptive information on acceptability, sexual behaviour and adherence issues for this population.</p> <p>The Data and Safety Monitoring Board (DSMB) will perform thorough reviews of the data at pre-specified time points during the trial duration. They may recommend the early termination of the trial or modification due to evidence of safety concerns among participants.</p>	<p><del>arm, or approximately 300 participants in both arms, would be sufficient to detect at least one AE with a rate of 2% and at least three events if the AE rate was 5%. The subgroup analysis will not be powered to detect small differences in the safety profile between the active and placebo arms. However, with 300 participants in the subgroup, the trial has 94% power to detect a difference when the AE rate in the active arm is 20% and the AE rate in the placebo arm is 5%. The qualitative individual interviews will include a sample of women over 40 years of age, to provide further descriptive information on acceptability, sexual behaviour and adherence issues for this population.</del></p> <p>The Data and Safety Monitoring Board (DSMB) will perform thorough reviews of the data at pre-specified time points during the trial duration. They may recommend the early termination of the trial or modification due to evidence of safety concerns among participants. <b><u>An interim analysis will be conducted when 50% of the endpoints have been observed and will be based on futility and efficacy.</u></b></p>	
<p>SECTION 1.1 Background</p> <p>According to UNAIDS, the estimated number of people living with HIV worldwide in 2010 (30 years after the HIV/AIDS epidemic first started) was 34 million<sup>1</sup>. In 2009, 2.6 million people became newly infected with HIV and 1.8 million lost their lives to AIDS<sup>2</sup>. Over 95 percent of new infections are occurring in developing countries, specifically sub-Saharan Africa, where new infections threaten the sustainability of expanded access to HIV/AIDS treatment. According to UNAIDS, for every 3 people placed on antiretroviral treatment in 2010, 5 others become newly infected worldwide<sup>1</sup>. The ongoing development of safe and effective HIV prevention technologies that can be made easily accessible to developing countries remains a public health priority.</p> <p>“AIDS at 30: Nations at the Crossroads”, the report published by UNAIDS in 2011, shows that women and girls continue to be affected disproportionately by HIV in sub-Saharan Africa, where they account for 60% of people living with HIV<sup>1</sup>. Unprotected heterosexual intercourse is currently the leading mode of HIV transmission among women. Correct and consistent use of latex condoms is one proven method of preventing HIV transmission; however, condoms are widely regarded as inadequate prevention options for women, because many women are unable to negotiate condom use with their partners. Most current HIV prevention methods require the consent (as well as some action or behaviour change) of the male partner<sup>3</sup>.</p>	<p>SECTION 1.1 Background</p> <p>According to UNAIDS, the estimated number of people living with HIV worldwide in 2010 (30 years after the HIV/AIDS epidemic first started) was 34 million<sup>1</sup>. In 2009, 2.6 million people became newly infected with HIV and 1.8 million lost their lives to AIDS<sup>2</sup>. Over 95 percent of new infections are occurring in developing countries, specifically sub-Saharan Africa, where new infections threaten the sustainability of expanded access to HIV/AIDS treatment. According to UNAIDS, for every 3 people placed on antiretroviral treatment in 2010, 5 others become newly infected worldwide<sup>1</sup>. The ongoing development of safe and effective HIV prevention technologies that can be made easily accessible to developing countries remains a public health priority.</p> <p>“AIDS at 30: Nations at the Crossroads”, the report published by UNAIDS in 2011, shows that women and girls continue to be affected disproportionately by HIV in sub-Saharan Africa, where they account for 60% of people living with HIV<sup>1</sup>. Unprotected heterosexual intercourse is currently the leading mode of HIV transmission among women. Correct and consistent use of latex condoms is one proven method of preventing HIV transmission; however, condoms are widely regarded as inadequate prevention options for women, because many women are unable to negotiate condom use with their partners. Most current HIV prevention methods require the consent (as well as some action or behaviour change) of the male partner<sup>3</sup>.</p>	<p>Section revised with updated information on VOICE and FACTS 001 trials, and efficacy evaluation is included in the description of the design of IPM 027.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>Developing HIV prevention options that women can use remains a global concern, given the high rates of HIV infection among women. Vaginal microbicides, which are self-initiated, would offer women a critically needed new tool to prevent HIV. Microbicide candidates, based on antiretroviral (ARV) drugs that specifically target HIV, are planned to undergo extensive safety and efficacy trials. 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.</p> <p>In July 2010, in an important milestone for HIV prevention came from the CAPRISA 004 Phase IIB microbicide trial, which found a 39% lower HIV infection rate in women using 1% <i>tenofovir gel</i> within 12 hours before and after sex (i.e. two applications per sex act), as compared to the women using a placebo gel. In women who reported using the gel with more than 80% of sex acts, the protection level was even higher, at 54%<sup>4</sup>. <i>Tenofovir gel</i> is the first ARV-based microbicide to be tested in an efficacy trial. It is also being tested as a once-daily product in the MTN-003 (VOICE) Phase IIB trial in Africa, and an additional confirmatory Phase III trial, FACTS 001, is planned to start in 2011 using the same BAT24 dose regimen as in the CAPRISA 004 trial.</p> <p>Successes with <i>oral ARVs</i> for prevention have also been observed. In November 2010, the iPrEx Phase III trial showed that oral Truvada® was 42% effective in reducing the risk of HIV infection among men who have sex with men<sup>5</sup>. And in May 2011, results of the HPTN 052 “treatment for prevention” trial showed that immediate use of ARV therapy by HIV-positive individuals can reduce the risk of transmitting the virus to their uninfected partner by 96%<sup>6</sup>.</p> <p>However, another recent Phase III trial, FEM-PrEP, which tested the effectiveness of daily oral Truvada® in preventing HIV transmission in 1,951 high-risk women in Africa, was stopped after an Independent Data Monitoring Committee (IDMC) determined that it was highly unlikely that the trial would be able to show that this strategy was effective. In this trial, 56 new HIV infections were equally distributed among women who received Truvada® and those who received placebo<sup>7</sup>. The reasons for this failure are still being investigated.</p> <p>With a successful ‘proof of concept’ that an ARV-based microbicide can reduce the risk of HIV acquisition in women (coupled with similar research findings from the iPrEx oral PrEP trial for men who have sex with men, and from the HPTN 052 treatment for prevention trial in serodiscordant partners), it is evident that ARV approaches to prevention have the potential to transform the response to the HIV/AIDS epidemic. For women, in addition to confirmatory work on tenofovir gel, further research is needed on microbicides that contain different ARV compounds</p>	<p>Developing HIV prevention options that women can use remains a global concern, given the high rates of HIV infection among women. Vaginal microbicides, which are self-initiated, would offer women a critically needed new tool to prevent HIV. Microbicide candidates, based on antiretroviral (ARV) drugs that specifically target HIV, are planned to undergo extensive safety and efficacy trials. 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.</p> <p>In July 2010, in an important milestone for HIV prevention came from the CAPRISA 004 Phase IIB microbicide trial, which found a 39% lower HIV infection rate in women using 1% tenofovir gel within 12 hours before and after sex (i.e. two applications per sex act), as compared to the women using a placebo gel. In women who reported using the gel with more than 80% of sex acts, the protection level was even higher, at 54%<sup>4</sup>. Tenofovir gel is the first ARV-based microbicide to be tested in an efficacy trial. <b><u>It has been tested as a once-daily product in the MTN-003 (VOICE) Phase IIB trial in Africa, but the tenofovir gel arm was discontinued due to futility. A further confirmatory Phase III trial, FACTS 001, using the same BAT24 dose regimen as in the CAPRISA 004 trial, started in 2011.</u></b></p> <p>Successes with oral ARVs for prevention have also been observed. In November 2010, the iPrEx Phase III trial showed that oral Truvada® was 42% effective in reducing the risk of HIV infection among men who have sex with men<sup>5</sup>. And in May 2011, results of the HPTN 052 “treatment for prevention” trial showed that immediate use of ARV therapy by HIV-positive individuals can reduce the risk of transmitting the virus to their uninfected partner by 96%<sup>6</sup>.</p> <p>However, another recent Phase III trial, FEM-PrEP, which tested the effectiveness of daily oral Truvada® in preventing HIV transmission in 1,951 high-risk women in Africa, was stopped after an Independent Data Monitoring Committee (IDMC) determined that it was highly unlikely that the trial would be able to show that this strategy was effective. In this trial, 56 new HIV infections were equally distributed among women who received Truvada® and those who received placebo<sup>7</sup>. The reasons for this failure are still being investigated. <b><u>Similarly, the efficacy of oral tenofovir tablets was evaluated in the MTN-003 (VOICE) Phase IIB trial, but after an independent interim review of the data it was concluded that the trial will not be able to demonstrate that tenofovir tablets are effective in preventing HIV infection, and the oral tenofovir arm was consequently discontinued.</u></b></p> <p><b><u>It appears</u></b> that ARV approaches to prevention have the potential to transform the</p>	

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>in different formulations and using different dosing strategies, to provide options and improve upon the level of effectiveness seen in CAPRISA 004.</p> <p>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. In addition, a product used independently of sex could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse. As seen in the CAPRISA 004 trial, higher adherence to product may translate into higher effectiveness of the product. It is likely that products that can be applied less frequently will be more acceptable and will achieve better adherence. Vaginal rings that need only be replaced monthly may therefore have benefits over dosage forms that need to be used more frequently. The dapivirine (25 mg) silicone elastomer vaginal ring is IPM's lead candidate for advancement to Phase II long-term safety and Phase III safety and efficacy testing.</p> <p>Multiple Phase I and I/II clinical trials have evaluated the safety of dapivirine in vaginal rings, gels and in an oral formulation. These clinical trials support the favourable safety profile and tolerability of dapivirine in general and specifically in vaginal delivery formulations.</p>	<p>response to the HIV/AIDS epidemic. For women, in addition to confirmatory work on tenofovir gel, further research is needed on microbicides that contain different ARV compounds in different formulations and using different dosing strategies, to provide options and improve upon the level of effectiveness seen in CAPRISA 004.</p> <p>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. In addition, a product used independently of sex could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse. As seen in the CAPRISA 004 trial, higher adherence to product may translate into higher effectiveness of the product. It is likely that products that can be applied less frequently will be more acceptable and will achieve better adherence. Vaginal rings that need only be replaced monthly may therefore have benefits over dosage forms that need to be used more frequently. The dapivirine (25 mg) silicone elastomer vaginal ring is IPM's lead candidate for advancement to <del>Phase II long-term safety and Phase III</del> <u>clinical</u> safety and efficacy testing.</p> <p>Multiple Phase I and I/II clinical trials have evaluated the safety of dapivirine in vaginal rings, gels and in an oral formulation. These clinical trials support the favourable safety profile and tolerability of dapivirine in general and specifically in vaginal delivery formulations.</p>	
<p>SECTION 1.3 Rationale for Protocol IPM 027</p> <p>Based on <i>in vitro</i>, <i>in vivo</i>, and <i>ex vivo</i> studies described in the Dapivirine Vaginal Ring IB, dapivirine shows great promise as a topical microbicide to prevent HIV-1 infection.</p> <p>In order for a microbicide to be most effective, it is essential that it is used correctly and consistently. It is likely that products that can be applied less frequently, and have a minimal effect on the vaginal environment during sex will be more acceptable to women and their male partners and will achieve better user-adherence. Vaginal rings that need only be replaced every month may have benefits over dosage forms that need to be used more frequently.</p> <p>Silicone elastomer vaginal rings have already been developed and approved as delivery methods for medications. For example, Pfizer (formerly Pharmacia and Upjohn Company) has marketed Estring<sup>®</sup> (estradiol vaginal ring), a vaginal ring that is also made from silicone elastomer and contains estradiol used to treat local symptoms of urogenital atrophy, since 1993. Prior to the launch of Estring<sup>®</sup>, the biological safety of the silicone elastomer was studied in various <i>in vitro</i> and <i>in vivo</i> test models. The results show that the silicone elastomer is non-toxic, non-</p>	<p>SECTION 1.3 Rationale for Protocol IPM 027</p> <p>Based on <i>in vitro</i>, <i>in vivo</i>, and <i>ex vivo</i> studies described in the Dapivirine Vaginal Ring IB, dapivirine shows great promise as a topical microbicide to prevent HIV-1 infection.</p> <p>In order for a microbicide to be most effective, it is essential that it is used correctly and consistently. It is likely that products that can be applied less frequently, and have a minimal effect on the vaginal environment during sex will be more acceptable to women and their male partners and will achieve better user-adherence. Vaginal rings that need only be replaced every month may have benefits over dosage forms that need to be used more frequently.</p> <p>Silicone elastomer vaginal rings have already been developed and approved as delivery methods for medications. For example, Pfizer (formerly Pharmacia and Upjohn Company) has marketed Estring<sup>®</sup> (estradiol vaginal ring), a vaginal ring that is also made from silicone elastomer and contains estradiol used to treat local symptoms of urogenital atrophy, since 1993. Prior to the launch of Estring<sup>®</sup>, the biological safety of the silicone elastomer was studied in various <i>in vitro</i> and <i>in vivo</i> test models. The results show that the silicone elastomer is non-toxic, non-</p>	<p>Efficacy evaluation of dapivirine vaginal ring included in description of design of IPM 027, as per recommendation by PSA Procedure.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>pyrogenic, non-irritating, and non-sensitising<sup>9</sup>. Femring<sup>®</sup> (estradiol acetate vaginal ring), a hormone replacement product approved in June 2003 by the United States (U.S.) Food and Drug Administration (FDA), is another silicone ring that treats menopause-induced vasomotor symptoms (e.g., hot flushes) and symptoms of vulvar and vaginal atrophy (e.g., dryness)<sup>10</sup>. Although these rings are not exactly the same as the IPM ring, the extensive clinical trial and post-marketing experience gained from these products provides further assurance of the safety of silicone elastomer rings as vaginal drug delivery devices. An acceptability trial of the silicone elastomer ring used in Femring<sup>®</sup> (but containing no drug) among postmenopausal women in the U.S. demonstrated very high acceptability and ease of use<sup>11</sup>. IPM recently evaluated the acceptability and safety of a similar placebo vaginal ring in the IPM 011 study (n=170). This study confirmed that the placebo ring was safe and acceptable to users and their male partners<sup>12</sup>.</p> <p>IPM 027 has been designed to compare the safety of dapivirine (25 mg) in a silicone elastomer vaginal matrix ring (Ring-004), inserted once every 4 weeks in healthy, HIV-negative sexually active women, with a placebo vaginal ring.</p>	<p>pyrogenic, non-irritating, and non-sensitising<sup>9</sup>. Femring<sup>®</sup> (estradiol acetate vaginal ring), a hormone replacement product approved in June 2003 by the United States (U.S.) Food and Drug Administration (FDA), is another silicone ring that treats menopause-induced vasomotor symptoms (e.g., hot flushes) and symptoms of vulvar and vaginal atrophy (e.g., dryness)<sup>10</sup>. Although these rings are not exactly the same as the IPM ring, the extensive clinical trial and post-marketing experience gained from these products provides further assurance of the safety of silicone elastomer rings as vaginal drug delivery devices. An acceptability trial of the silicone elastomer ring used in Femring<sup>®</sup> (but containing no drug) among postmenopausal women in the U.S. demonstrated very high acceptability and ease of use<sup>11</sup>. IPM recently evaluated the acceptability and safety of a similar placebo vaginal ring in the IPM 011 study (n=170). This study confirmed that the placebo ring was safe and acceptable to users and their male partners<sup>12</sup>.</p> <p>IPM 027 has been designed to <u>evaluate</u> the safety <u>and determine the efficacy</u> of dapivirine (25 mg) in a silicone elastomer vaginal matrix ring (Ring-004), inserted once every 4 weeks in healthy, HIV-negative sexually active women, <u>as compared</u> with a placebo vaginal ring.</p>	
<p>SECTION 2.1 Trial Objectives</p> <p><u>Primary Objective</u></p> <ol style="list-style-type: none"> <li>To assess and compare the safety of dapivirine administered in a silicone elastomer vaginal matrix ring to the placebo vaginal ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks).</li> </ol> <p><u>Secondary Objectives</u></p> <ol style="list-style-type: none"> <li>To assess and compare the incidence of HIV-1 and HIV-2 (for safety) in the dapivirine and placebo vaginal ring groups.</li> <li>To assess and compare the incidence of curable sexually-transmitted infections (STIs), and changes in vaginal flora in the dapivirine and placebo vaginal ring groups.</li> <li>To determine the incidence of pregnancy in both trial arms.</li> <li>To assess reported adherence to the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.</li> <li>To assess reported acceptability of the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.</li> <li>To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection while using the investigational product.</li> </ol>	<p>SECTION 2.1 Trial Objectives</p> <p><u>Primary Objectives</u></p> <ol style="list-style-type: none"> <li><u>To determine the efficacy of dapivirine administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks), in preventing HIV-1 infection among healthy, sexually active HIV-negative women.</u></li> <li>To assess <del>and compare</del> the safety of dapivirine administered in a silicone elastomer vaginal matrix ring <del>to the placebo vaginal ring</del>, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks).</li> </ol> <p><u>Secondary Objectives</u></p> <ol style="list-style-type: none"> <li>To <u>determine</u> the incidence of <del>HIV-1 and HIV-2 (for safety)</del> in the dapivirine and placebo vaginal ring groups.</li> <li>To assess and compare the incidence of curable sexually-transmitted infections (STIs), and changes in vaginal flora in the dapivirine and placebo vaginal ring groups.</li> <li>To determine the incidence of pregnancy in both trial arms.</li> <li>To assess reported adherence to the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period.</li> <li>To assess reported acceptability of the use of either a dapivirine or a placebo</li> </ol>	<p>Efficacy assessment (HIV-1 seroconversion rate) included as primary endpoint, as per recommendation by PSA Procedure.</p> <p>It is indicated more clearly that the type of HIV-1 drug resistance will be assessed together with the frequency</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p><u>Exploratory Objectives</u></p> <ol style="list-style-type: none"> <li>To evaluate the association between HSV-2 and HIV-1 infection in both trial arms.</li> <li>To explore the potential relationship between method of contraception, pregnancy incidence and HIV seroconversion in both trial arms.</li> <li>To explore the relationship between drug concentrations and trial outcomes (HIV-1 seroconversion and viral resistance).</li> <li>To explore the correlation of drug concentrations and self-reported adherence measures.</li> </ol>	<p>vaginal ring inserted once every 4 weeks over the investigational product use period.</p> <ol style="list-style-type: none"> <li>To assess the frequency <b>and type</b> of HIV-1 drug resistance in women who acquire HIV-1 infection while using the investigational product.</li> </ol> <p><u>Exploratory Objectives</u></p> <ol style="list-style-type: none"> <li>To evaluate the association between HSV-2 and HIV-1 infection in both trial arms.</li> <li>To explore the potential relationship between method of contraception, pregnancy incidence and HIV seroconversion in both trial arms.</li> <li>To explore the relationship between drug concentrations and trial outcomes (HIV-1 seroconversion and viral resistance).</li> <li>To explore the correlation of drug concentrations and self-reported adherence measures.</li> </ol>	
<p>SECTION 2.2 Trial Endpoints and Assessments</p> <p><b>The primary endpoints are:</b></p> <ul style="list-style-type: none"> <li>Grade 2 adverse events (AEs) judged to be related to the investigational product;</li> <li>Grade 3 and 4 AEs.</li> </ul> <p>The primary endpoints will be assessed through:</p> <ul style="list-style-type: none"> <li>Self-reports, physical examination, gynaecological assessments, including pelvic/speculum examination, laboratory tests and other indicated investigations. All AEs will be reported regardless of grade or relatedness.</li> </ul> <p><b>The secondary endpoints are:</b></p> <ul style="list-style-type: none"> <li>Seroconversion rates of HIV-1 and HIV-2 per woman years of product use at the end of the investigational product (IP) use period;</li> <li>The incidence of curable STIs (i.e. <i>N.gonorrhoea</i>, <i>C.trachomatis</i> and <i>T.vaginalis</i>), and changes in vaginal flora in each trial arm over the IP use period;</li> <li>The incidence of pregnancy in each trial arm over the IP use period;</li> <li>The proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period;</li> <li>The proportion of women who report the use of the vaginal ring as acceptable;</li> <li>HIV-1 drug resistance mutations among participants who acquire HIV-1.</li> </ul>	<p>SECTION 2.2 Trial Endpoints and Assessments</p> <p><b>The primary endpoints are:</b></p> <ul style="list-style-type: none"> <li><b><u>The incidence rate of HIV-1 seroconversion;</u></b></li> <li><b><u>All adverse events (AEs) (full descriptive evaluation).</u></b></li> </ul> <p>The primary endpoints will be assessed through:</p> <ul style="list-style-type: none"> <li><b><u>Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C;</u></b></li> <li>Self-reports, physical examination, gynaecological assessments, including pelvic/speculum examination, laboratory tests and other indicated investigations. All AEs will be reported regardless of grade or relatedness.</li> </ul> <p><b>The secondary endpoints are:</b></p> <ul style="list-style-type: none"> <li><b><u>The incidence rate of HIV-2 seroconversion;</u></b></li> <li>The incidence of curable STIs (i.e. <i>N.gonorrhoea</i>, <i>C.trachomatis</i> and <i>T.vaginalis</i>), and changes in vaginal flora in each trial arm over the IP use period;</li> <li>The incidence of pregnancy in each trial arm over the IP use period;</li> <li>The proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period;</li> <li>The proportion of women who report the use of the vaginal ring as acceptable;</li> <li><b><u>The proportion of participants with</u></b> HIV-1 drug resistance mutations among</li> </ul>	<p>Efficacy assessment (HIV-1 seroconversion rate) included as primary endpoint, as well as <u>all</u> adverse events, as per recommendation by PSA Procedure.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>The secondary endpoints will be assessed through:</p> <ul style="list-style-type: none"> <li>- Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C;</li> <li>- STI testing, vaginal flora and vaginal pH testing;</li> <li>- Pregnancy testing;</li> <li>- Questionnaires and qualitative data regarding sexual behaviour and adherence to the use of a vaginal ring inserted once every 4 weeks over the trial period;</li> <li>- Questionnaires and qualitative data regarding the acceptability of the use of a vaginal ring inserted once every 4 weeks over the trial period;</li> <li>- Viral genotyping methods.</li> </ul> <p><b>The exploratory endpoints are:</b></p> <ul style="list-style-type: none"> <li>• The proportion of HSV-2 among analysed samples;</li> <li>• Incidence of pregnancy in correlation with HIV seroconversion rates and method(s) of contraception used by participants;</li> <li>• Steady-state drug concentrations in blood and vaginal fluid;</li> <li>• Steady-state drug concentrations in correlation with self-reported adherence as outlined above for the secondary objective.</li> </ul> <p>The exploratory endpoints will be assessed through:</p> <ul style="list-style-type: none"> <li>- HSV-2 testing;</li> <li>- Pregnancy testing and HIV testing as outlined above for the secondary objective, and documentation of participant contraceptive method/s;</li> <li>- Drug concentrations in blood and vaginal fluid;</li> <li>- Vaginal fluid, plasma and/or ring residual drug concentrations and self-reported behavioural measures as outlined above for the secondary objective.</li> </ul>	<p>participants who acquire HIV-1.</p> <p>The secondary endpoints will be assessed through:</p> <ul style="list-style-type: none"> <li>- Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C;</li> <li>- STI testing, vaginal flora and vaginal pH testing;</li> <li>- Pregnancy testing;</li> <li>- Questionnaires and qualitative data regarding sexual behaviour and adherence to the use of a vaginal ring inserted once every 4 weeks over the trial period;</li> <li>- Questionnaires and qualitative data regarding the acceptability of the use of a vaginal ring inserted once every 4 weeks over the trial period;</li> <li>- Viral genotyping methods.</li> </ul> <p><b>The exploratory endpoints are:</b></p> <ul style="list-style-type: none"> <li>• The proportion of HSV-2 among analysed samples;</li> <li>• Incidence of pregnancy in correlation with HIV seroconversion rates and method(s) of contraception used by participants;</li> <li>• Steady-state drug concentrations in blood and vaginal fluid;</li> <li>• Steady-state drug concentrations in correlation with self-reported adherence as outlined above for the secondary objective.</li> </ul> <p>The exploratory endpoints will be assessed through:</p> <ul style="list-style-type: none"> <li>- HSV-2 testing;</li> <li>- Pregnancy testing and HIV testing as outlined above for the secondary objective, and documentation of participant contraceptive method(s);</li> <li>- Drug concentrations in blood and vaginal fluid;</li> <li>- Vaginal fluid, plasma and/or ring residual drug concentrations and self-reported behavioural measures as outlined above for the secondary objective.</li> </ul>	
<p>SECTION 3.1 Trial Design</p> <p>IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled Phase II trial to evaluate the long-term safety of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks in healthy, sexually active HIV-negative women, when compared to a placebo vaginal ring. The trial will be conducted at approximately 7 clinical research centres in sub-Saharan Africa. Approximately 1,650 participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.</p>	<p>SECTION 3.1 Trial Design</p> <p>IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled <del>Phase II</del> trial to <u>assess</u> the long-term safety <u>and efficacy</u> of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks in healthy, sexually active HIV-negative women, when compared to a placebo vaginal ring. The trial will be conducted at approximately 7 clinical research centres in sub-Saharan Africa. Approximately 1,650 participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.</p>	<p>Efficacy evaluation of dapivirine vaginal ring included in description of trial design, as per recommendation by PSA Procedure.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>Each participant will engage in the screening period of up to 4 weeks (28 days) prior to enrolment, and will use the IP for an estimated period of 24 months. Each participant will have an additional 6 weeks of follow-up after ring discontinuation to assess for safety and identify HIV seroconversions after product discontinuation.</p>	<p>Each participant will engage in the screening period of up to 4 weeks (28 days) prior to enrolment, and will use the IP for an estimated period of 24 months <b><u>(104 weeks)</u></b>. Each participant will have an additional 6 weeks of follow-up after ring discontinuation to assess for safety and identify HIV seroconversions after product discontinuation.</p>	
<p>SECTION 3.1 Trial Design</p> <p><b><u>Trial visits (during investigational product use)</u></b></p> <p>Dapivirine or placebo vaginal rings, according to the allocated randomisation group, will be inserted at 4-weekly intervals for the duration of the IP use period. Similar to enrolment, at each regularly scheduled trial visit while on the IP, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled trial visit. All participants will receive pre- and post-test HIV counselling; HIV/STI risk reduction counselling, condom and vaginal ring adherence counselling, HIV and pregnancy testing; and collection of locator, menses, and concomitant medication information. Male condoms will be provided at all visits as part of HIV/STI risk reduction counselling. Contraceptive counselling will be provided at all visits. Blood samples and vaginal fluid samples will be collected for storage at all visits. These stored blood samples will be tested for HIV-RNA PCR and viral genotyping only in HIV-1 seroconverters, while HSV-2 serology, blood and vaginal fluid dapivirine concentrations measurement will be conducted in these seroconverters and a randomly selected control group of HIV-negative participants.</p> <p>The rapid and confirmatory laboratory tests used in the HIV testing algorithm will detect both subtypes, HIV-1 and HIV-2. At the point of HIV seroconversion, the IP will be discontinued, and additional samples will be collected and tested for viral genotyping (blood and vaginal fluid), dapivirine concentrations (blood and vaginal fluid) and HSV-2 serology (blood). In addition, blood and vaginal fluid samples for viral genotyping will also be collected at the scheduled exit visit approximately 6 weeks following seroconversion. No further storage samples will be taken in these participants.</p> <p>Adherence assessments will be conducted through an interviewer-administered questionnaire at all 4-weekly trial visits, except the exit visit. Participants will be provided with a diary card at each 4-weekly visit except the last product use and exit visits. The diary card will be self-administered, and record the participant's sexual activity and ring use during the 4-week period. The diary card is meant to be completed daily by the participant, and returned to the research centre at each 4-weekly visit, to serve as a memory aid for participants to review during adherence counselling, and the adherence questionnaires. Acceptability questionnaires will be administered at the second trial visit (week 4), and 24-</p>	<p>SECTION 3.1 Trial Design</p> <p><b><u>Trial visits (during investigational product use)</u></b></p> <p>Dapivirine or placebo vaginal rings, according to the allocated randomisation group, will be inserted at 4-weekly intervals for the duration of the IP use period. Similar to enrolment, at each regularly scheduled trial visit while on the IP, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled trial visit. All participants will receive pre- and post-test HIV counselling, HIV/STI risk reduction counselling, condom and vaginal ring adherence counselling, HIV and pregnancy testing, and collection of locator, menses, and concomitant medication information. Male condoms will be provided at all visits as part of HIV/STI risk reduction counselling. Contraceptive counselling will be provided at all visits. Blood samples and vaginal fluid samples will be collected for storage at all visits. These stored blood samples will be tested for HIV-RNA PCR and viral genotyping only in HIV-1 seroconverters, while HSV-2 serology, blood and vaginal fluid dapivirine concentrations measurement will be conducted in these seroconverters and a randomly selected control group of HIV-negative participants.</p> <p>The rapid and confirmatory laboratory tests used in the HIV testing algorithm will detect both subtypes, HIV-1 and HIV-2. At the point of HIV seroconversion, the IP will be discontinued, and additional samples will be collected and tested for viral genotyping (blood <del>and vaginal fluid</del>), dapivirine concentrations (blood and vaginal fluid) and HSV-2 serology (blood). In addition, blood <del>and vaginal fluid</del> samples for viral genotyping will also be collected at the scheduled exit visit approximately 6 weeks following seroconversion. No further storage samples will be taken in these participants.</p> <p>Adherence assessments will be conducted through an interviewer-administered questionnaire at all 4-weekly trial visits, except the exit visit. Participants will be provided with a diary card at each 4-weekly visit except the last product use and exit visits. The diary card will be self-administered, and record the participant's sexual activity and ring use during the 4-week period. The diary card is meant to be completed daily by the participant, and returned to the research centre at each 4-weekly visit, to serve as a memory aid for participants to review during adherence counselling, and the adherence questionnaires. Acceptability questionnaires will be administered at the second trial visit (week 4), and 24-</p>	<p>Viral genotyping will only be performed on blood samples, and not vaginal fluid samples, to harmonise IPM 027 with another safety and efficacy trial that will be conducted with the dapivirine vaginal ring (MTN-020), as recommended by PSA Procedure.</p>



OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>weekly intervals from week 24 thereafter, until the last product use visit.</p> <p>Twenty-four (24) to 36 weeks after trial initiation, each research centre will conduct 6 – 10 qualitative individual interviews with participants, and 6 – 10 qualitative individual interviews with male partners. These interviews will provide data on acceptability, sexual behaviour and adherence issues. The recruitment and sampling strategy will be specified in the Statistical Analysis Plan (SAP).</p> <p>AEs will be assessed at all visits post-randomisation. In addition, safety laboratory assessments, pelvic examination, vaginal pH and vaginal flora as well as STI tests will be performed at 12-weekly intervals. Cervical cytology will be repeated at the end of the first and second year of IP use. Residual dapivirine levels in returned rings will be measured for a selected group of participants at pre-determined time-points.</p>	<p>weekly intervals from week 24 thereafter, until the last product use visit.</p> <p>Twenty-four (24) to 36 weeks after trial initiation, each research centre will conduct 6 – 10 qualitative individual interviews with participants, and 6 – 10 qualitative individual interviews with male partners. These interviews will provide data on acceptability, sexual behaviour and adherence issues. The recruitment and sampling strategy will be specified in the Statistical Analysis Plan (SAP).</p> <p>AEs will be assessed at all visits post-randomisation. In addition, safety laboratory assessments, pelvic examination, vaginal pH and vaginal flora as well as STI tests will be performed at 12-weekly intervals. Cervical cytology will be repeated at the end of the first and second year of IP use. Residual dapivirine levels in returned rings will be measured for a selected group of participants at pre-determined time-points.</p>	
<p>SECTION 3.3 Trial Population</p> <p>Approximately 1,650 sexually active HIV-negative women, 18 – 60 years of age, who understand the trial and can provide informed consent, will be enrolled and randomised in a 2:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a placebo vaginal ring.</p> <p>Approximately 300 participants over 40 years of age will be enrolled in the trial.</p>	<p>SECTION 3.3 Trial Population</p> <p>Approximately 1,650 sexually active HIV-negative women, 18 – <u>45</u> years of age, who understand the trial and can provide informed consent, will be enrolled and randomised in a 2:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a placebo vaginal ring.</p> <p><del>Approximately 300 participants over 40 years of age will be enrolled in the trial.</del></p>	<p>The enrolment age will be limited to ≤ 45 years, to harmonise participant selection criteria with another safety and efficacy trial that will be conducted with the dapivirine vaginal ring (MTN-020), as recommended by PSA Procedure.</p>
<p>SECTION 3.3.1 Inclusion Criteria</p> <p>Women must meet all of the following criteria to be eligible for trial enrolment:</p> <ol style="list-style-type: none"> <li>1. Women ≥ 18 and ≤ 60 years of age, at screening, who can provide informed consent;</li> <li>2. Available for all visits and consent to follow all procedures scheduled for the trial;</li> <li>3. Self-reported sexually active (defined as an average of at least one penetrative penile vaginal coital act per month for the last 3 months prior to screening);</li> <li>4. HIV-negative as determined by the HIV algorithm applied at screening and enrolment;</li> <li>5. On a stable form of contraception as defined within section 5.4 and willing to</li> </ol>	<p>SECTION 3.3.1 Inclusion Criteria</p> <p>Women must meet all of the following criteria to be eligible for trial enrolment:</p> <ol style="list-style-type: none"> <li>1. Women ≥ 18 and ≤ <u>45</u> years of age, at screening, who can provide informed consent;</li> <li>2. Available for all visits and consent to follow all procedures scheduled for the trial;</li> <li>3. Self-reported sexually active (defined as an average of at least one penetrative penile-vaginal coital act per month for the last 3 months prior to screening);</li> <li>4. HIV-negative as determined by the HIV algorithm applied at screening and enrolment;</li> <li>5. On a stable form of contraception as defined within section 5.4 and willing to</li> </ol>	<p>Harmonisation of participant selection criteria with another safety and efficacy trial that will be conducted with the dapivirine vaginal ring (MTN-020), as recommended by PSA Procedure.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>continue on stable contraception for the duration of the clinical trial; unless post-menopausal or surgically sterilised;</p> <p>6. Asymptomatic for genital infections at the time of enrolment (if a woman is diagnosed with any clinically significant curable STI, she must have initiated treatment at least 1 week prior to enrolment and have completed the full course of treatment);</p> <p>7. Willing to answer questions about adherence, sexual behaviour, and ring acceptability;</p> <p>8. 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;</p> <p>9. Willing to refrain from participation in another research trial using drugs, vaccines, medical devices, microbicides or oral pre-exposure prophylaxis investigational drugs for the duration of the IPM 027 trial;</p> <p>10. Willing to refrain from use of vaginal products or objects including spermicides, lubricants, intravaginal medication, other vaginal rings, female condoms, cotton wool, rags, diaphragms, cervical caps (or any other vaginal barrier method), douches, drying agents and herbs within 14 days from enrolment and for the duration of the trial. Tampons are not included in this list and may be used for the duration of the trial.</p>	<p>continue on stable contraception for the duration of the clinical trial, unless post-menopausal or surgically sterilised;</p> <p>6. Asymptomatic for genital infections at the time of enrolment (if a woman is diagnosed with any clinically significant curable STI, she must have initiated treatment at least 1 week prior to enrolment and have completed the full course of treatment);</p> <p><del>7. Willing to answer questions about adherence, sexual behaviour, and ring acceptability;</del></p> <p>7. 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;</p> <p>8. Willing to refrain from participation in another research trial using drugs, vaccines, medical devices, microbicides or oral pre-exposure prophylaxis investigational drugs for the duration of the IPM 027 trial;</p> <p><del>9. Willing to refrain from use of vaginal products or objects including spermicides, lubricants, intravaginal medication, other vaginal rings, female condoms, cotton wool, rags, diaphragms, cervical caps (or any other vaginal barrier method), douches, drying agents and herbs within 14 days from enrolment and for the duration of the trial. Tampons are not included in this list and may be used for the duration of the trial.</del></p>	
<p>SECTION 3.3.2 Exclusion Criteria</p> <p>Women who have any of the exclusion criteria below are not eligible:</p> <ol style="list-style-type: none"> <li>1. Currently pregnant or last pregnancy within 3 months prior to screening;</li> <li>2. Currently breast-feeding;</li> <li>3. Women who have had a hysterectomy;</li> <li>4. Participated in another research trial using drugs, medical devices, microbicides or oral pre-exposure prophylaxis agents within 60 days prior to screening;</li> <li>5. Previously participated or currently participating in any HIV vaccine trial;</li> <li>6. Untreated, clinically significant urogenital infections , e.g., urinary tract, or other sexually transmitted infections, or other gynaecological symptoms within 1 week prior to enrolment;</li> <li>7. Has a Grade 2 or higher pelvic examination finding, according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; Addendum 1 Female Genital Grading Table for Use in Microbicide Studies;</li> <li>8. History of significant urogenital or uterine prolapse, undiagnosed vaginal bleeding, diagnosed chronic and/or recurrent vulvovaginal candidiasis, urethral obstruction, incontinence or urge incontinence;</li> </ol>	<p>SECTION 3.3.2 Exclusion Criteria</p> <p>Women who have any of the exclusion criteria below are not eligible:</p> <ol style="list-style-type: none"> <li>1. Currently pregnant or last pregnancy within 3 months prior to screening <b><u>or intends to become pregnant during trial participation</u></b>;</li> <li>2. Currently breast-feeding;</li> <li>3. <del>Women who have had a hysterectomy;</del></li> <li>3. <b><u>Non-therapeutic injection drug use in the 12 months prior to screening</u></b>;</li> <li>4. Participated in another research trial using drugs, medical devices, microbicides or oral pre-exposure prophylaxis agents within 60 days prior to screening;</li> <li>5. Previously participated or currently participating in any HIV vaccine trial;</li> <li>6. Untreated, clinically significant urogenital infections , e.g., urinary tract, or other sexually transmitted infections, or other gynaecological symptoms within 1 week prior to enrolment;</li> <li>7. Has a Grade 2 or higher pelvic examination finding, according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; Addendum 1 Female Genital Grading Table for Use in Microbicide Studies;</li> <li>8. History of significant urogenital or uterine prolapse, undiagnosed vaginal</li> </ol>	<p>Harmonisation of participant selection criteria with another safety and efficacy trial that will be conducted with the dapivirine vaginal ring (MTN-020), as recommended by PSA Procedure.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>9. Any gynaecological surgery within 90 days prior to screening;</p> <p>10. Any Grade 2, 3 or 4 baseline haematology, chemistry or urinalysis laboratory value according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events;</p> <p>11. Any history of anaphylaxis or severe allergy resulting in angioedema; or a history of sensitivity/allergy to latex or a silicone elastomer;</p> <p>12. Any history of diabetes mellitus and chronic use of oral corticosteroid therapy; and any uncontrolled serious chronic or progressive disease;</p> <p>13. Cervical cytology at screening that requires cryotherapy, biopsy or treatment (other than for infection). Women with Grade 1 cervical cytology findings can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology);</p> <p>14. Any condition(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.</p>	<p>bleeding, diagnosed chronic and/or recurrent vulvovaginal candidiasis, urethral obstruction, incontinence or urge incontinence;</p> <p>9. Any gynaecological surgery within 90 days prior to screening;</p> <p>10. Any <b>Grade 1 or higher baseline aspartate aminotransferase (AST), alanine transaminase (ALT), or platelet count, and any</b> Grade 2, <del>3 or 4</del> <b>or higher</b> baseline haematology, chemistry or urinalysis laboratory value according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events;</p> <p>11. Any history of anaphylaxis or severe allergy resulting in angioedema; or a history of sensitivity/allergy to latex or a silicone elastomer;</p> <p>12. Any history of diabetes mellitus and chronic use of oral corticosteroid therapy; and any uncontrolled serious chronic or progressive disease;</p> <p>13. Cervical cytology at screening that requires cryotherapy, biopsy or treatment (other than for infection). Women with Grade 1 cervical cytology findings can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology);</p> <p>14. Any condition(s) that, in the opinion of the investigator, might put the participant at risk, or interfere with the trial objectives or <b>the participant's</b> adherence to trial requirements.</p>	
<p>SECTION 4.1.1 Screening 1</p> <p><b>NOTE:</b> For potential participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility has been determined.</p> <p>a. Explain screening and trial procedures to the potential participant.</p> <p>b. If the potential participant agrees to be screened, obtain written informed consent (screening consent). Illiterate participants may provide a thumbprint or mark witnessed and signed by a person independent from trial staff. A comprehension assessment will be performed as part of the screening consent process.</p> <p>c. Assign a unique Participant Identification number to the potential participant. A confidential master log of screening participants, with demographic and locator information will be maintained.</p> <p>d. Conduct a preliminary review of inclusion/exclusion criteria with the potential participant.</p> <p>e. Collect demographic information from the potential participant.</p> <p>f. Obtain and record locator information.</p> <p>g. Record menses information, relevant medical history, and concomitant medication taken within the last 30 days (Refer to Section 5.6 for more details)</p>	<p>SECTION 4.1.1 Screening 1</p> <p><b>NOTE:</b> For potential participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility has been determined. <b><u>Women who fail screening may be re-screened a maximum of once and may be enrolled if they are found to meet ALL inclusion and NO exclusion criteria at the second screening visit.</u></b></p> <p>a. Explain screening and trial procedures to the potential participant.</p> <p>b. If the potential participant agrees to be screened, obtain written informed consent (screening consent). Illiterate participants may provide a thumbprint or mark witnessed and signed by a person independent from trial staff. <del>A comprehension assessment will be performed as part of the screening consent process.</del></p> <p>c. Assign a unique Participant Identification number to the potential participant. A confidential master log of screening participants, with demographic and locator information will be maintained.</p> <p>d. Conduct a preliminary review of inclusion/exclusion criteria with the potential participant.</p> <p>e. Collect demographic information from the potential participant.</p>	<p>Provision made for potential participants who fail screening to be re-screened a maximum of once, and then be enrolled if found to be eligible.</p> <p>The phrase "A comprehension assessment will be performed as part of the screening consent process" was removed, as a standardised comprehension assessment checklist will be used as part of the enrolment consent process.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>about relevant medical history).</p> <p>h. Perform urine pregnancy and urinalysis dipstick testing (microscopy only if indicated). Refer pregnant women to local prenatal clinic for support services (Refer to Sections 5.5 and 5.9).</p> <p>i. Provide HIV/STI risk-reduction counselling (including provision of male condoms) and contraceptive counselling. (Refer to Sections 5.2.2 and 5.4)</p> <p>j. Provide HIV pre- and post-test counselling. (Refer to Section 5.2.1)</p> <p>k. Perform HIV rapid testing as detailed in Section 5.3.</p> <p>l. Perform general physical examination (Refer to Section 5.7 for a description of the elements required in the general physical examination).</p> <p>m. Perform pelvic examination (Refer to Section 5.8). If pelvic examination indicates abnormal findings, e.g., any symptoms or evidence of genital infections, abrasions, ulcerations, etc., provide or refer for appropriate treatment. <b>NOTE:</b> <i>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.</i></p> <p>n. Collect cervicovaginal swabs for STI testing and a specimen for cervical cytology (Refer to Sections 5.10 and 5.11).</p> <p>o. Collect blood samples by venipuncture for syphilis testing (RPR), and the following safety laboratory tests (Blood volumes specified in Appendix D):</p> <ul style="list-style-type: none"> <li>○ haematology (FBC with differential and platelet count),</li> <li>○ chemistry (sodium, potassium, phosphate, chloride, calcium, urea, creatinine, total bilirubin, ALT, AST and ALP). (Refer to Section 5.9).</li> </ul> <p>p. Invite potential participant to return to the research centre within no more than 4 weeks for the screening 2 and enrolment visit.</p>	<p>f. Obtain and record locator information.</p> <p>g. Record menses information, relevant medical history, and concomitant medication taken within the last 30 days (Refer to Section 5.6 for more details about relevant medical history).</p> <p>h. Perform urine pregnancy and urinalysis dipstick testing (microscopy only if indicated). Refer pregnant women to local prenatal clinic for support services (Refer to Sections 5.5 and 5.9).</p> <p>i. Provide HIV/STI risk-reduction counselling (including provision of male condoms) and contraceptive counselling. (Refer to Sections 5.2.2 and 5.4).</p> <p>j. Provide HIV pre- and post-test counselling. (Refer to Section 5.2.1).</p> <p>k. Perform HIV rapid testing as detailed in Section 5.3.</p> <p>l. Perform general physical examination (Refer to Section 5.7 for a description of the elements required in the general physical examination).</p> <p>m. Perform pelvic examination (Refer to Section 5.8). If pelvic examination indicates abnormal findings, e.g., any symptoms or evidence of genital infections, abrasions, ulcerations, etc., provide or refer for appropriate treatment. <b>NOTE:</b> <i>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.</i></p> <p>n. Collect cervicovaginal swabs for STI testing and a specimen for cervical cytology (Refer to Sections 5.10 and 5.11).</p> <p>o. Collect blood samples by venipuncture for syphilis testing (RPR), and the following safety laboratory tests (Blood volumes specified in Appendix D):</p> <ul style="list-style-type: none"> <li>○ haematology (FBC with differential and platelet count),</li> <li>○ chemistry (sodium, potassium, phosphate, chloride, calcium, urea, creatinine, total bilirubin, ALT, AST and ALP). (Refer to Section 5.9).</li> </ul> <p>p. Invite potential participant to return to the research centre within no more than 4 weeks for the screening 2 and enrolment visit.</p>	
<p>SECTION 4.2 Enrolment Visit</p> <p><b>NOTE:</b> <i>If the potential participant is menstruating at this visit, the entire visit should be rescheduled for two days after completion of menses, but must be completed within 4 weeks of screening 1. The enrolment visit may occur on the same day as screening 2 or subsequently; provided it is still within 4 weeks of screening 1.</i></p> <p>a. If a potential participant agrees to enrol in the trial, obtain written informed consent (enrolment consent). Illiterate participants may provide a thumbprint</p>	<p>SECTION 4.2 Enrolment Visit</p> <p><b>NOTE:</b> <i>If the potential participant is menstruating at this visit, the entire visit should be rescheduled for two days after completion of menses, but must be completed within 4 weeks of screening 1. The enrolment visit may occur on the same day as screening 2 or subsequently; provided it is still within 4 weeks of screening 1.</i></p> <p>a. If a potential participant agrees to enrol in the trial, obtain written informed consent (enrolment consent). Illiterate participants may provide a thumbprint or mark witnessed and signed by a person independent from trial staff. A</p>	<p>The collection of a specimen for vaginal flora and pH assessment at the time the screening 2 pelvic examination is performed will be allowed, to avoid that participants undergo two speculum examinations in one</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>or mark witnessed and signed by a person independent from trial staff. A comprehension assessment checklist will be used to support the enrolment consent process.</p> <ul style="list-style-type: none"> <li>b. Administer the baseline behavioural questionnaire.</li> <li>c. Provide and explain the use of the diary card to the participant.</li> <li>d. Dispense one vaginal ring to the participant according to the unique participant identification number assigned at screening 1.</li> <li>e. Collect specimen for assessment of vaginal flora and vaginal pH.</li> <li>f. Instruct the participant to insert the vaginal ring (Refer to Section 5.12). Perform brief digital examination to verify the vaginal ring has been properly placed.</li> <li>g. After ring insertion, the participant will remain in the research centre under observation for 30 minutes to be observed for immediate reactions (immediate reactions will be recorded as AEs).</li> <li>h. Provide adherence counselling, including contraceptive adherence, adherence to trial visit schedule and requirements and vaginal ring adherence. (Refer to Sections 5.4 and 5.13). Participants will be instructed to keep the ring inserted for a period of 28 consecutive days (4 weeks). 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. Adherence counselling will include information on actions that should be taken in the event of expulsion or removal.</li> <li>i. Collect a blood specimen by venipuncture for HSV-2 serology, HIV viral genotyping and HIV-RNA PCR sample storage (Blood volume specified in Appendix D). <b>NOTE:</b> <i>Research centres using venipuncture for HIV testing at screening 2 may have opted to collect these storage samples at the same time as the screening 2 HIV test sample.</i></li> <li>j. Schedule the next visit.</li> </ul>	<p>comprehension assessment checklist will be used to support the enrolment consent process.</p> <ul style="list-style-type: none"> <li>b. Administer the baseline behavioural questionnaire.</li> <li>c. Provide and explain the use of the diary card to the participant.</li> <li>d. Dispense one vaginal ring to the participant according to the unique participant identification number assigned at screening 1.</li> <li>e. Collect specimen for assessment of vaginal flora and vaginal pH. <b><u>NOTE: At the discretion of the investigator or designee, this specimen may be collected at the same time the screening 2 pelvic examination is performed.</u></b></li> <li>f. Instruct the participant to insert the vaginal ring (Refer to Section 5.12). Perform brief digital examination to verify the vaginal ring has been properly placed.</li> <li>g. After ring insertion, the participant will remain in the research centre under observation for 30 minutes to be observed for immediate reactions (immediate reactions will be recorded as AEs).</li> <li>h. Provide adherence counselling, including contraceptive adherence, adherence to trial visit schedule and requirements and vaginal ring adherence. (Refer to Sections 5.4 and 5.13). Participants will be instructed to keep the ring inserted for a period of 28 consecutive days (4 weeks). 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. Adherence counselling will include information on actions that should be taken in the event of expulsion or removal.</li> <li>i. Collect a blood specimen by venipuncture for HSV-2 serology, HIV viral genotyping and HIV-RNA PCR sample storage (Blood volume specified in Appendix D). <b>NOTE:</b> <i>Research centres using venipuncture for HIV testing at screening 2 may have opted to collect these storage samples at the same time as the screening 2 HIV test sample.</i></li> <li>j. Schedule the next visit.</li> </ul>	<p>day, when the enrolment visit occur on the same day as screening 2.</p>
<p>SECTION 4.3.1 4-Weekly Trial Visits (Weeks 4 to 104)</p> <p><b>(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. Although the visit window is ± 7days, consecutive visits should be no less than 21 days and no more than 35 days apart).</b></p> <p><b>NOTE:</b> <i>Additional procedures for participants who test HIV-positive are described in Section 5.3 of the protocol.</i></p>	<p>SECTION 4.3.1 4-Weekly Trial Visits (Weeks 4 to <u>100</u>)</p> <p><b>(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. Although the visit window is ± 7days, consecutive visits should be no less than 21 days and no more than 35 days apart).</b></p> <p><b>NOTE:</b> <i>Additional procedures for participants who test HIV-positive are described in Section 5.3 of the protocol.</i></p>	<p>The 4-weekly procedures are described up until Week 100, as Week 104 will be the Last Product Use Visit, described in Section 4.3.5.</p> <p>In bullet point “I”, the method of vaginal fluid</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>a. Update locator and menses information as necessary.</p> <p>b. Obtain and record any AEs and concomitant medications since the last visit.</p> <p>c. Collect and review the diary card and provide a new diary card. Administer the adherence questionnaire.</p> <p>d. Provide adherence counselling, including contraceptive adherence, adherence to trial visit schedule and requirements and vaginal ring adherence. (Refer to Sections 5.4 and 5.13). Participants will be instructed to keep the ring inserted for a period of 28 consecutive days (4 weeks). 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. Adherence counselling will include further details on actions that should be taken in the event of expulsion or removal.</p> <p>e. Administer the acceptability questionnaire (<b>NOTE: ONLY at the second trial visit (week 4) after enrolment, and at 24-weekly intervals thereafter, starting at week 24 until the last product use visit).</b></p> <p>f. Provide HIV/STI risk reduction counselling; including provision of male condoms (Refer to Section 5.2.2).</p> <p>g. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).</p> <p>h. Perform HIV rapid testing as detailed in Section 5.3. (Additional procedures for participants who test HIV-positive are also described in Section 5.3 of the protocol).</p> <p>i. Perform urine pregnancy testing.</p> <p>j. Collect blood specimens by venipuncture for storage (Blood volume specified in Appendix D).</p> <p>k. Instruct the participant to remove the vaginal ring. Perform IP accountability.</p> <p>l. Collect vaginal fluid samples through the use of Tear Test Strips for storage (Refer to Section 5.15). <b>NOTE: For dapivirine concentration measurements, blood and vaginal fluid samples must be collected prior to removal of the vaginal ring. Blood and vaginal fluid samples will also be taken for analysis following HIV seroconversion according to the HIV testing algorithm described in Section 5.3</b> (Blood volume specified in Appendix D).</p> <p>m. Dispense a new vaginal ring and instruct participant to self-insert the new ring.</p> <p>n. Perform brief digital examination to ensure the ring is properly placed (Refer to Section 5.12).</p> <p>o. Schedule the next visit.</p>	<p>a. Update locator and menses information as necessary.</p> <p>b. Obtain and record any AEs and concomitant medications since the last visit.</p> <p>c. Collect and review the diary card and provide a new diary card. Administer the adherence questionnaire.</p> <p>d. Provide adherence counselling, including contraceptive adherence, adherence to trial visit schedule and requirements and vaginal ring adherence. (Refer to Sections 5.4 and 5.13). Participants will be instructed to keep the ring inserted for a period of 28 consecutive days (4 weeks). 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. Adherence counselling will include further details on actions that should be taken in the event of expulsion or removal.</p> <p>e. Administer the acceptability questionnaire (<b>NOTE: ONLY at the second trial visit (week 4) after enrolment, and at 24-weekly intervals thereafter, starting at week 24 until the last product use visit).</b></p> <p>f. Provide HIV/STI risk reduction counselling; including provision of male condoms (Refer to Section 5.2.2).</p> <p>g. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).</p> <p>h. Perform HIV rapid testing as detailed in Section 5.3. (Additional procedures for participants who test HIV-positive are also described in Section 5.3 of the protocol).</p> <p>i. Perform urine pregnancy testing.</p> <p>j. Collect blood specimens by venipuncture for storage (Blood volume specified in Appendix D).</p> <p>k. Instruct the participant to remove the vaginal ring. Perform IP accountability.</p> <p>l. Collect vaginal fluid samples <del>through the use of Tear Test Strips</del> for storage (Refer to Section 5.15). <b>NOTE: For dapivirine concentration measurements, blood and vaginal fluid samples must be collected prior to removal of the vaginal ring. <del>Blood and vaginal fluid samples will also be taken for analysis following HIV seroconversion according to the HIV testing algorithm described in Section 5.3</del></b> (Blood volume specified in Appendix D).</p> <p>m. Dispense a new vaginal ring and instruct participant to self-insert the new ring.</p> <p>n. Perform brief digital examination to ensure the ring is properly placed (Refer to Section 5.12).</p> <p>o. Schedule the next visit.</p>	<p>sample collection was removed, as this will be described in greater detail in the Study Operations Manual. The <b>Note</b> was revised to remove redundant information.</p>
<p>SECTION 4.3.3 24-Weekly Trial Visits (Weeks 24, 48, 72 and 96)</p> <p><b>(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of ± 7 days. Although the visit</b></p>	<p>SECTION 4.3.3 24-Weekly Trial Visits (Weeks 24, 48, 72 and 96)</p> <p><b>(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of ± 7 days. Although the visit</b></p>	<p>Bullet point “h” was revised to clarify that for male partner interviews, male</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>window is <math>\pm 7</math> days, consecutive visits should be no less than 21 days and no more than 35 days apart).</p> <p><i>NOTE: Participants will 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.</i></p> <ol style="list-style-type: none"> <li>Complete all 4-weekly and 12-weekly trial visit procedures as detailed above.</li> <li>Administer the acceptability questionnaire.</li> <li>Invite 6 – 10 participants to participate in an individual interview to be held at each research centre during weeks 24 – 36.</li> <li>Request permission from these participants to recruit their male partner for an individual interview, and recruit from this pool of partners until 6 – 10 of these interviews have been conducted at each research centre.</li> </ol>	<p>window is <math>\pm 7</math> days, consecutive visits should be no less than 21 days and no more than 35 days apart).</p> <p><i>NOTE: Participants will 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.</i></p> <ol style="list-style-type: none"> <li>Complete all 4-weekly and 12-weekly trial visit procedures as detailed above.</li> <li>Administer the acceptability questionnaire.</li> <li>Invite 6 – 10 participants to participate in an individual interview to be held at each research centre during weeks 24 – 36.</li> <li>Request permission from <del>these participants</del> <u>that have completed Week 24</u> to recruit their male partner for an individual interview, <del>and recruit from this pool of partners</del> until 6 – 10 <u>male partner</u> interviews have been conducted at each research centre.</li> </ol>	<p>partners will be recruited from the pool of partners of all women who have completed 24 weeks of product use, and not only from those 6 to 10 participants that have participated in the individual interviews themselves.</p>
<p>SECTION 4.3.4 Annual Visits (Weeks 52 and 104)</p> <p><b>(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of <math>\pm 7</math> days. Although the visit window is <math>\pm 7</math> days, consecutive visits should be no less than 21 days and no more than 35 days apart).</b></p> <ol style="list-style-type: none"> <li>Complete all 4-weekly trial visit procedures as detailed above.</li> <li>Collect a specimen for cervical cytology.</li> </ol>	<p>SECTION 4.3.4 Annual Visits (<u>Week 52</u>)</p> <p><b>(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of <math>\pm 7</math> days. Although the visit window is <math>\pm 7</math> days, consecutive visits should be no less than 21 days and no more than 35 days apart).</b></p> <ol style="list-style-type: none"> <li>Complete all 4-weekly trial visit procedures as detailed above.</li> <li>Collect a specimen for cervical cytology.</li> </ol>	<p>The procedures for annual visits only apply to Week 52, as Week 104 will be the Last Product Use Visit, described in Section 4.3.5.</p>
<p>SECTION 4.3.5 Last Product Use Visit (or Early Discontinuation)</p> <p><b>(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of <math>\pm 7</math> days. Although the visit window is <math>\pm 7</math> days, consecutive visits should be no less than 21 days and no more than 35 days apart).</b></p> <p><i>NOTE: These trial procedures will also apply at the point of HIV seroconversion, and the visit will be considered the last product use visit for the participant.</i></p> <ol style="list-style-type: none"> <li>Update locator and menses information as necessary.</li> <li>Obtain and record any AEs and concomitant medications since the last visit.</li> <li>Collect the diary card.</li> <li>Administer the adherence questionnaire.</li> </ol>	<p>SECTION 4.3.5 Last Product Use Visit (<u>Week 104</u> or Early Discontinuation)</p> <p><b>(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of <math>\pm 7</math> days. Although the visit window is <math>\pm 7</math> days, consecutive visits should be no less than 21 days and no more than 35 days apart).</b></p> <p><i>NOTE: These trial procedures will also apply at the point of HIV seroconversion, and the visit will be considered the last product use visit for the participant.</i></p> <ol style="list-style-type: none"> <li>Update locator and menses information as necessary.</li> <li>Obtain and record any AEs and concomitant medications since the last visit.</li> <li>Collect the diary card.</li> <li>Administer the adherence questionnaire.</li> </ol>	<p>Cervical cytology will be performed at the Last Product Use Visit; this was inadvertently omitted before.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>e. Administer the acceptability questionnaire.</p> <p>f. Provide HIV/STI risk-reduction counselling (including dispensing of condoms) and contraceptive counselling (Refer to Sections 5.2.2 and 5.4).</p> <p>g. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).</p> <p>h. Perform HIV rapid testing as detailed in section 5.3. (Additional procedures for participants who test HIV-positive are also described in Section 5.3 of the protocol)</p> <p>i. Perform pregnancy testing and urinalysis dipstick testing (microscopy only if indicated).</p> <p>j. Collect blood specimen by venipuncture for syphilis testing (RPR) and safety laboratory tests (haematology and chemistry). Blood volume is specified in Appendix D.</p> <p>k. Collect blood specimen by venipuncture for sample storage (Blood volume specified in Appendix D).</p> <p>l. Perform physical examination.</p> <p>m. Collect vaginal fluid sample for storage. <b>NOTE:</b> For dapivirine concentration measurements, blood and vaginal fluid samples must be collected prior to removal of the vaginal ring.</p> <p>n. Instruct the participant to remove the last vaginal ring. Perform IP accountability.</p> <p>o. Perform pelvic examination (Refer to Section 5.8) and collect specimen for assessment of vaginal flora and vaginal pH, and cervicovaginal swabs for STI testing (Refer to Section 5.10). If pelvic examination indicates abnormal findings, e.g., any symptoms or evidence of genital infections, abrasions, ulcerations, etc., provide or refer for appropriate treatment.</p> <p>p. Schedule the exit visit.</p> <p>q. Each research centre will conduct 2 – 3 focus groups with participants who have been recruited for these groups at the last product use visit. Additionally, 6 – 10 individual interviews with male partners will be conducted at each research centre.</p>	<p>e. Administer the acceptability questionnaire.</p> <p>f. Provide HIV/STI risk-reduction counselling (including dispensing of condoms) and contraceptive counselling (Refer to Sections 5.2.2 and 5.4).</p> <p>g. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).</p> <p>h. Perform HIV rapid testing as detailed in section 5.3. (Additional procedures for participants who test HIV-positive are also described in Section 5.3 of the protocol).</p> <p>i. Perform pregnancy testing and urinalysis dipstick testing (microscopy only if indicated).</p> <p>j. Collect blood specimen by venipuncture for syphilis testing (RPR) and safety laboratory tests (haematology and chemistry). Blood volume is specified in Appendix D.</p> <p>k. Collect blood specimen by venipuncture for sample storage (Blood volume specified in Appendix D).</p> <p>l. Perform physical examination.</p> <p>m. Collect vaginal fluid sample for storage. <b>NOTE:</b> For dapivirine concentration measurements, blood and vaginal fluid samples must be collected prior to removal of the vaginal ring.</p> <p>n. Instruct the participant to remove the last vaginal ring. Perform IP accountability.</p> <p>o. Perform pelvic examination (Refer to Section 5.8) and collect specimen for assessment of vaginal flora and vaginal pH, and cervicovaginal swabs for STI testing (Refer to Section 5.10). If pelvic examination indicates abnormal findings, e.g., any symptoms or evidence of genital infections, abrasions, ulcerations, etc., provide or refer for appropriate treatment.</p> <p>p. <u>Collect a specimen for cervical cytology.</u></p> <p>q. Schedule the exit visit.</p> <p>r. Each research centre will conduct 2 – 3 focus groups with participants who have been recruited for these groups at the last product use visit. Additionally, 6 – 10 individual interviews with male partners will be conducted at each research centre.</p>	
<p>SECTION 4.4 Exit Visit (6 weeks after the Last Product Use Visit)</p> <p><b>(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of ± 7 days. Although the visit window is ± 7 days, consecutive visits should be no less than 21 days and no more than 35 days apart).</b></p> <p><b>NOTE:</b> 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.</p>	<p>SECTION 4.4 Exit Visit (6 weeks after the Last Product Use Visit)</p> <p><del>(All visit dates will be calculated from the enrolment visit as baseline date. The scheduled visit has a window period of ± 7 days. Although the visit window is ± 7 days, consecutive visits should be no less than 21 days and no more than 35 days apart).</del></p> <p><u>The scheduled visit has a window period of ± 7 days. Although the visit window is ± 7 days, consecutive visits should be no less than 21 days and no more than 35 days apart).</u></p> <p><b>NOTE:</b> 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.</p>	<p>Instructions on the calculation of the Exit Visit date were revised, as this visit date is determined relative to the Last Product Use Visit, and not enrolment.</p>



OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p><i>Additional trial procedures for exit visits scheduled following HIV seroconversion are described in Section 5.3 (No further HIV counselling and testing will be done unless indicated for additional confirmatory testing).</i></p> <ul style="list-style-type: none"> <li>a. Update locator information as necessary.</li> <li>b. Obtain and record any AEs and concomitant medications since the last visit.</li> <li>c. Provide final safety and STI laboratory results to participant.</li> <li>d. Provide HIV/STI risk-reduction counselling; including provision of male condoms (Refer to Section 5.2.2).</li> <li>e. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).</li> <li>f. Perform HIV rapid testing as detailed in Section 5.3.</li> <li>g. Exit the participant from the trial.</li> </ul>	<p><i>Additional trial procedures for exit visits scheduled following HIV seroconversion are described in Section 5.3 (No further HIV counselling and testing will be done unless indicated for additional confirmatory testing).</i></p> <ul style="list-style-type: none"> <li>h. Update locator information as necessary.</li> <li>i. Obtain and record any AEs and concomitant medications since the last visit.</li> <li>j. Provide final safety and STI laboratory results to participant.</li> <li>k. Provide HIV/STI risk-reduction counselling; including provision of male condoms (Refer to Section 5.2.2).</li> <li>l. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).</li> <li>m. Perform HIV rapid testing as detailed in Section 5.3.</li> <li>n. Exit the participant from the trial.</li> </ul>	
<p>SECTION 4.7 Missed &amp; Late Visits</p> <p>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 clinic for a scheduled visit during the trial window, e.g., within <math>\pm</math> 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 and applicable CRFs.</p> <p>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 3 by the time the trial window has begun for Visit 4, i.e., within 7 days from Visit 4, Visit 3 will be considered missed. Trial procedures will be performed as scheduled for the current visit (e.g. Visit 4 in this instance) or as deemed necessary by the investigator or IPM Clinical Physician or designee. Missed visits will be documented as protocol deviations.</p> <p>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 be put back on her original visit schedule.</p>	<p>SECTION 4.7 Missed <u>and</u> Late Visits</p> <p>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 clinic for a scheduled visit during the trial window, e.g., within <math>\pm</math> 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 and applicable CRFs.</p> <p>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 3 by the time the trial window has begun for Visit 4, i.e., within 7 days from Visit 4, Visit 3 will be considered missed. Trial procedures will be performed as scheduled for the current visit (e.g. Visit 4 in this instance) or as deemed necessary by the investigator or IPM Clinical Physician or designee. Missed visits will be documented as protocol deviations. <b><u>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.</u></b></p> <p>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 be put back on her original visit schedule.</p>	<p>Instructions on the retrieval of used and unused vaginal rings were included in order to ensure adequate and accurate accountability of investigational product at trial end.</p>
<p>SECTION 4.8 Early Discontinuation Visit</p> <p>Participants may be discontinued early from the trial prior to completion of the last</p>	<p>SECTION 4.8 Early Discontinuation Visit</p> <p>Participants may be discontinued early from the trial prior to completion of the last</p>	<p>Recording of the date and reason for permanent trial discontinuation is</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>trial visit for any of the following reasons:</p> <ul style="list-style-type: none"> <li>• Participant withdraws her consent.</li> <li>• Participant fails to follow protocol requirements which are deemed to be serious enough by the investigator to warrant a discontinuation, e.g., in the absence of an AE or discomfort, participant refuses to keep vaginal ring inserted for duration of the trial.</li> <li>• Participant is lost to follow-up, i.e., research centre is unsuccessful (following reasonable attempts as defined in the local SOP) in contacting participant or bringing the participant back to the research centre and she misses 3 consecutive visits.</li> <li>• Participant is confirmed to be pregnant.</li> <li>• Participant tests HIV-positive according to the HIV-testing algorithm in Appendix C.</li> <li>• If for safety reasons the investigator considers it in the best interest of the participant to discontinue her from the trial. Genital AEs that may warrant permanent IP discontinuation are described in the Clinical Management of Genital Diagnoses section of the Study Operations Manual. For laboratory investigations, any of the following abnormal parameters may apply: <ul style="list-style-type: none"> <li>- Haemoglobin &lt; 9.0 g/dL <b>or</b> &lt; 1.40 mmol/L</li> <li>- Absolute Neutrophil Count (ANC): &lt; 1000/mm<sup>3</sup> <b>or</b> &lt; 1.0 x 10<sup>9</sup>/L</li> <li>- Absolute Lymphocyte Count (ALC): ≤ 500/mm<sup>3</sup> <b>or</b> ≤ 0.5 x 10<sup>9</sup>/L</li> <li>- Platelets: ≤ 90,000 ≥ 550,000/mm<sup>3</sup> <b>or</b> ≤ 90 x 10<sup>9</sup> ≥ 550 x 10<sup>9</sup>/L</li> <li>- Creatinine: &gt; 1.4 x ULN</li> <li>- AST: &gt; 3.0 x ULN</li> <li>- ALT: &gt; 3.0 x ULN</li> </ul> </li> <li>• At the discretion of the investigator, Sponsor, IRB/IEC or the government health agency.</li> </ul> <p><b>NOTE:</b> The DSMB may provide recommendations to the Sponsor or to the investigators regarding participants who should be discontinued, or allowed to continue in the trial.</p> <p>The date, time, and reason for permanent trial discontinuation will be noted in the source documents and applicable CRFs. All participants who prematurely discontinue 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 6 weeks after product discontinuation can be completed.</p> <p>Participants who miss three (3) consecutive trial visits and cannot be contacted</p>	<p>trial visit for any of the following reasons:</p> <ul style="list-style-type: none"> <li>• Participant withdraws her consent.</li> <li>• Participant fails to follow protocol requirements which are deemed to be serious enough by the investigator to warrant a discontinuation, e.g., in the absence of an AE or discomfort, participant refuses to keep vaginal ring inserted for duration of the trial.</li> <li>• Participant is lost to follow-up, i.e., research centre is unsuccessful (following reasonable attempts as defined in the local SOP) in contacting participant or bringing the participant back to the research centre and she misses 3 consecutive visits.</li> <li>• Participant is confirmed to be pregnant.</li> <li>• Participant tests HIV-positive according to the HIV-testing algorithm in Appendix C.</li> <li>• If for safety reasons the investigator considers it in the best interest of the participant to discontinue her from the trial. Genital AEs that may warrant permanent IP discontinuation are described in the Clinical Management of Genital Diagnoses section of the Study Operations Manual. For laboratory investigations, any of the following abnormal parameters may apply: <ul style="list-style-type: none"> <li>- Haemoglobin &lt; 9.0 g/dL <b>or</b> &lt; 1.40 mmol/L</li> <li>- Absolute Neutrophil Count (ANC): &lt; 1000/mm<sup>3</sup> <b>or</b> &lt; 1.0 x 10<sup>9</sup>/L</li> <li>- Absolute Lymphocyte Count (ALC): ≤ 500/mm<sup>3</sup> <b>or</b> ≤ 0.5 x 10<sup>9</sup>/L</li> <li>- Platelets: ≤ 90,000 ≥ 550,000/mm<sup>3</sup> <b>or</b> ≤ 90 x 10<sup>9</sup> ≥ 550 x 10<sup>9</sup>/L</li> <li>- Creatinine: &gt; 1.4 x ULN</li> <li>- AST: &gt; 3.0 x ULN</li> <li>- ALT: &gt; 3.0 x ULN</li> </ul> </li> <li>• At the discretion of the investigator, Sponsor, IRB/IEC or the government health agency.</li> </ul> <p><b>NOTE:</b> The DSMB may provide recommendations to the Sponsor or to the investigators regarding participants who should be discontinued, or allowed to continue in the trial.</p> <p>The date, <del>time</del>, and reason for permanent trial discontinuation will be noted in the source documents and applicable CRFs. All participants who prematurely discontinue 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 6 weeks after product discontinuation can be completed.</p> <p>Participants who miss three (3) consecutive trial visits and cannot be contacted</p>	<p>considered sufficient, i.e. recording of the time would not add value.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>during this time will be considered lost to follow-up and will be permanently discontinued from the trial. Reasonable contact attempts will be made according to the locator information provided by the participant and local SOPs, and final 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 clinic chart (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 communication with the IPM Clinical Project Manager, depending on the reason for the missed visits. Participants who discontinue early from the trial will not be replaced.</p>	<p>during this time will be considered lost to follow-up and will be permanently discontinued from the trial. Reasonable contact attempts will be made according to the locator information provided by the participant and local SOPs, and final 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 clinic chart (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 communication with the IPM Clinical Project Manager, depending on the reason for the missed visits. Participants who discontinue early from the trial will not be replaced.</p>	
<p>SECTION 4.9 Premature Discontinuation of the Trial</p> <p>The Sponsor has the right to discontinue this trial at any time for any reason. If the clinical trial is prematurely discontinued, the investigator must promptly inform the participants and IRB/IECs, and ensure medical follow-up of participants in consultation with the Sponsor. If the trial is prematurely discontinued, all procedures and requirements pertaining to the archiving of documents will be observed. The Sponsor will provide the research centres with instructions on the proper disposition of any clinical supplies and IP remaining at the research centre.</p>	<p>SECTION 4.9 Premature Discontinuation of the Trial</p> <p>The Sponsor has the right to discontinue this trial at any time for any reason. If the clinical trial is prematurely discontinued, the investigator must promptly inform the participants and IRB/IECs, and ensure medical follow-up of participants in consultation with the Sponsor. If the trial is prematurely discontinued, all procedures and requirements pertaining to the archiving of documents will be observed. The Sponsor will provide the research centres with instructions on the proper <u>retrieval and</u> disposition of any clinical supplies and IP remaining at the research centre.</p>	<p>Instructions on the retrieval of used and unused vaginal rings will be provided to the research centres to ensure adequate and accurate accountability of investigational product at trial end.</p>
<p>SECTION 5.1.2 Comprehension Checklist</p> <p>Trial staff will assess the candidate participant's understanding of informed consent information prior to obtaining a signature on the informed consent form at Screening 1 and Enrollment. At enrolment, this assessment will be done using a standardised comprehension checklist. All comprehension problems that are discovered during the assessment will be discussed until staff are satisfied that the participant can verbalise her understanding of the issue. This process will be documented on the comprehension checklist. The comprehension 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.</p>	<p>SECTION 5.1.2 Comprehension <u>Assessment</u> Checklist</p> <p>Trial staff will assess the candidate participant's understanding of informed consent information prior to obtaining a signature on the informed consent form at Screening 1 and Enrollment. At enrolment, this assessment will be done using a standardised comprehension <u>assessment</u> checklist. All comprehension problems that are discovered during the assessment will be discussed until staff are satisfied that the participant can verbalise her understanding of the issue. This process will be documented on the comprehension <u>assessment</u> checklist. <u>This</u> 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.</p>	<p>For consistency, there is now referred to "Comprehension Assessment Checklist" throughout the protocol.</p>
<p>SECTION 5.2.2 HIV/STI Risk Reduction Counselling</p> <p>HIV/STI risk reduction guidelines will be developed in conjunction with local voluntary counselling and testing (VCT) guidelines. Counselling will be provided at both screening visits, and all trial visits including the exit visit. Efforts will be made to ensure standardisation of risk reduction counselling at the trial clinics.</p> <p><b>NOTE:</b> Risk reduction counselling will include recommendation of male condom</p>	<p>SECTION 5.2.2 HIV/STI Risk Reduction Counselling</p> <p>HIV/STI risk reduction guidelines will be developed in conjunction with local voluntary counselling and testing (VCT) guidelines. Counselling will be provided at both screening visits, and all trial visits including the exit visit. Efforts will be made to ensure standardisation of risk reduction counselling at the trial clinics.</p> <p><b>NOTE:</b> Risk reduction counselling will include recommendation of male condom</p>	<p>In order to harmonise protocol IPM 027 with another safety and efficacy trial of dapivirine vaginal rings (MTN-020), as recommended by the PSA Procedure, the</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p><i>use. Participants will be provided with a supply of male non-spermicidal condoms during each trial visit. The use of female condoms is not permitted in this trial, in order to protect the integrity of the lower genital tract and reduce the possibility of AEs due to agents other than the investigational product.</i></p>	<p><i>use. Participants will be provided with a supply of male non-spermicidal condoms during each trial visit. The use of female condoms is not <b>encouraged</b> in this trial, in order to protect the integrity of the lower genital tract and reduce the possibility of AEs due to agents other than the investigational product.</i></p>	<p>use of vaginal products (including female condoms) will be allowed, but discouraged.</p>
<p>SECTION 5.3.2 Screening 2 and Enrolment</p> <p>On the scheduled day of possible enrolment, as part of the screening 2 procedure, the participant will be tested for HIV and will only be enrolled if the result is considered to be HIV-negative and the participant is otherwise eligible. Test 1 will be performed. If the test is 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-negative and eligible for enrolment. After enrolment, a blood sample will be obtained by venipuncture to be sent for sample storage at a central laboratory, for potential HIV-RNA PCR testing if the participant seroconverts (blood volume specified in Appendix D). Research centres using venipuncture for HIV testing at screening 2 may opt to collect the storage samples at the same time the screening 2 HIV test sample is drawn. If this option is taken, storage samples for participants who do not enrol will be destroyed according to local SOPs.</p> <p>If HIV Test 1 is reactive, the potential participant will be retested using Test 2, which must be done with a venous sample. If Test 2 is reactive, the woman will be considered HIV-infected 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. If Test 2 is non-reactive the result is discordant. Rapid Test 3 will be performed for all discordant rapid tests. If Test 3 is reactive then the potential participant is considered to be HIV-infected and not eligible for enrolment. If Test 3 is non-reactive, the person is considered to be probably HIV-negative BUT the participant is NOT eligible for enrolment. She will be counselled and referred to the local health facilities for appropriate follow-up. The participant can return to the research centre for rescreening after 8 weeks for one more cycle of HIV testing. Refer to Appendix C: HIV Testing Algorithms.</p>	<p>SECTION 5.3.2 Screening 2 and Enrolment</p> <p>On the scheduled day of possible enrolment, as part of the screening 2 procedure, the participant will be tested for HIV and will only be enrolled if the result is considered to be HIV-negative and the participant is otherwise eligible. Test 1 will be performed. If the test is 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-negative and eligible for enrolment. After enrolment, a blood sample will be obtained by venipuncture to be sent for sample storage <b>locally or</b> at a central laboratory, for potential HIV-RNA PCR testing if the participant seroconverts (blood volume specified in Appendix D). Research centres using venipuncture for HIV testing at screening 2 may opt to collect the storage samples at the same time the screening 2 HIV test sample is drawn. If this option is taken, storage samples for participants who do not enrol will be destroyed according to local SOPs.</p> <p>If HIV Test 1 is reactive, the potential participant will be retested using Test 2, which must be done with a venous sample. If Test 2 is reactive, the woman will be considered HIV-infected 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. If Test 2 is non-reactive the result is discordant. Rapid Test 3 will be performed for all discordant rapid tests. If Test 3 is reactive then the potential participant is considered to be HIV-infected and not eligible for enrolment. If Test 3 is non-reactive, the person is considered to be probably HIV-negative BUT the participant is NOT eligible for enrolment. She will be counselled and referred to the local health facilities for appropriate follow-up. The participant can return to the research centre for rescreening after 8 weeks for one more cycle of HIV testing. Refer to Appendix C: HIV Testing Algorithms.</p>	<p>Sample storage might also take place at the research centres.</p>
<p>SECTION 5.3.3 Trial Visits</p> <p>Both the 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 C) will be applied for all 4-weekly trial visits, including the last product use visit. HIV-testing while the participant is enrolled in the trial will be performed on blood samples obtained by venipuncture (blood volumes specified in Appendix</p>	<p>SECTION 5.3.3 Trial Visits</p> <p>Both the 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 C) will be applied for all 4-weekly trial visits, including the last product use visit. HIV-testing while the participant is enrolled in the trial will be performed on blood samples obtained by venipuncture (blood volumes specified in Appendix</p>	<p>Sample storage might also take place at the research centres.</p> <p>It was also clarified that the blood and vaginal fluid samples</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>D).</p> <p>If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative and continue using the IP. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2 (done on the same blood sample). If Test 2 is reactive, the participant is considered to have been infected while on the trial, and will be permanently discontinued from the IP. Additional confirmatory testing will be performed by Western Blot or another confirmatory test where appropriate. Additional testing will be performed on stored samples of seroconverters as described in Section 5.15. Nucleic acid-amplification testing (NAAT) by an HIV-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.</p> <p>If Test 2 is non-reactive, the result is discordant and 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 then the participant is considered to be HIV-infected. The IP is stopped immediately and a sample drawn for endpoint confirmation (by Western Blot). Nucleic acid-amplification testing (NAAT) by an HIV-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.</p> <p>If Test 3 is non-reactive, the participant is considered to be probably HIV-negative. The participant will continue on the IP and be requested to return for repeat testing after two weeks. In such cases the research centre will notify the IPM Clinical Physician or designee. If a similar result is obtained on testing after two weeks, the process of repeat testing after 2 weeks may continue for a third cycle.</p> <p>All enrolled participants will, in addition, have blood taken at each trial visit to be stored at a central laboratory, for possible HIV-RNA PCR 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 the PCR test result is negative. This will be done to approximate the period of HIV infection. If the enrolment HIV-RNA PCR test result is positive, the participant is not considered to have been infected while using the IP.</p> <p>Additional blood (blood volume as specified in Appendix D) and vaginal fluid samples will also be obtained for analysis at the point of HIV seroconversion according to the HIV testing algorithm described above. Stored samples (blood and vaginal fluids) will also be analysed retrospectively as described in section</p>	<p>D).</p> <p>If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative and continue using the IP. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2 (done on the same blood sample). If Test 2 is reactive, the participant is considered to have been infected while on the trial, and will be permanently discontinued from the IP. Additional confirmatory testing will be performed by Western Blot or another confirmatory test where appropriate. Additional testing will be performed on stored samples of seroconverters as described in Section 5.15. Nucleic acid-amplification testing (NAAT) by an HIV-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.</p> <p>If Test 2 is non-reactive, the result is discordant and 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 then the participant is considered to be HIV-infected. The IP is stopped immediately and a sample drawn for endpoint confirmation (by Western Blot). Nucleic acid-amplification testing (NAAT) by an HIV-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.</p> <p>If Test 3 is non-reactive, the participant is considered to be probably HIV-negative. The participant will continue on the IP and be requested to return for repeat testing after two weeks. In such cases the research centre will notify the IPM Clinical Physician or designee. If a similar result is obtained on testing after two weeks, the process of repeat testing after 2 weeks may continue for a third cycle.</p> <p>All enrolled participants will, in addition, have blood taken at each trial visit to be stored <b>locally or</b> at a central laboratory, for possible HIV-RNA PCR 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 the PCR test result is negative. This will be done to approximate the period of HIV infection. If the enrolment HIV-RNA PCR test result is positive, the participant is not considered to have been infected while using the IP.</p> <p>Additional blood (blood volume as specified in Appendix D) and vaginal fluid samples will also be obtained for <b>dapivirine measurement</b> at the point of HIV seroconversion according to the HIV testing algorithm described above. Stored samples (blood and vaginal fluids) will <del>also</del> be analysed retrospectively as</p>	<p>to be taken at the point of seroconversion, will be analysed for dapivirine concentrations.</p> <p>Reference to a protocol number for IPM's planned seroconverter protocol has been removed, as this protocol still needs to be finalised and approved.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>5.15.</p> <p>Any participant who is confirmed HIV-positive while on the trial and will be discontinued from the IP. Trial procedures relevant to the last product use visit as detailed in Section 4.3.5 will be performed, and an exit visit will be scheduled approximately 6 weeks 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 (IPM 007A).</p>	<p>described in section 5.15.</p> <p>Any participant who is confirmed HIV-positive while on the trial <del>and</del> will be discontinued from the IP. Trial procedures relevant to the last product use visit as detailed in Section 4.3.5 will be performed, and an exit visit will be scheduled approximately 6 weeks 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 (<del>IPM 007A</del>).</p>	
<p>SECTION 5.3.4 Exit Visit</p> <p>At the exit visit, the participants will be tested using the same testing algorithm. If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2. If Test 2 is reactive, this will be considered an HIV seroconversion after product discontinuation. This 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 an HIV-RNA PCR test will be performed on stored samples in reverse sequential order to estimate the time point of HIV infection.</p> <p>Initial counselling services will be provided at the research centre and women will be referred for additional counselling, support services and treatment.</p> <p>If Test 2 is non-reactive, the result is discordant. HIV Rapid Test 3 will be performed for discordant rapid test results. If Test 3 is reactive then the participant will be considered to be HIV-infected. 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- negative and will be counselled appropriately. Refer to Appendix C: HIV Testing Algorithms.</p> <p>As stated in Section 5.3.3 above, an exit visit will be scheduled approximately 6 weeks following HIV-seroconversion and IP discontinuation. Blood and vaginal fluid samples for viral genotyping will be collected from these participants. Additional trial procedures for exit visits scheduled following HIV seroconversion are described in Section 4.4 (No further HIV counselling and testing will be done unless indicated for additional confirmatory testing).</p> <p><b>NOTE:</b> <i>Up to 15% of all HIV rapid test samples will be retested at a central laboratory, for quality control purposes. Details of this testing will be provided in</i></p>	<p>SECTION 5.3.4 Exit Visit</p> <p>At the exit visit, the participants will be tested using the same testing algorithm. If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2. If Test 2 is reactive, this will be considered an HIV seroconversion after product discontinuation. This 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 an HIV-RNA PCR test will be performed on stored samples in reverse sequential order to estimate the time point of HIV infection.</p> <p>Initial counselling services will be provided at the research centre and women will be referred for additional counselling, support services and treatment.</p> <p>If Test 2 is non-reactive, the result is discordant. HIV Rapid Test 3 will be performed for discordant rapid test results. If Test 3 is reactive then the participant will be considered to be HIV-infected. 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- negative and will be counselled appropriately. Refer to Appendix C: HIV Testing Algorithms.</p> <p>As stated in Section 5.3.3 above, an exit visit will be scheduled approximately 6 weeks following HIV-seroconversion and IP discontinuation. Blood <del>and vaginal fluid</del> samples for viral genotyping will be collected from these participants. Additional trial procedures for exit visits scheduled following HIV seroconversion are described in Section 4.4 (No further HIV counselling and testing will be done unless indicated for additional confirmatory testing).</p> <p><b>NOTE:</b> <i>Up to 15% of all HIV rapid test samples will be retested at a central laboratory, for quality control purposes. Details of this testing will be provided in</i></p>	<p>Viral genotyping will only be performed on blood samples, and not vaginal fluid samples, to harmonise IPM 027 with another safety and efficacy trial of dapivirine vaginal rings (MTN-020), as recommended by the PSA Procedure.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p><i>the Laboratory Manual. The Laboratory Manual will also provide details of the IPM specified Test 1; Test 2 and Test 3.</i></p> <p>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 (PMTCT) services.</p> <p>The research centres will inform IPM Medical Safety of any new HIV infections within 24 hours of diagnosis. The applicable regulatory authorities and ethics committees who require expedited notification of HIV seroconversions 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.</p>	<p><i>the Laboratory Manual. The Laboratory Manual will also provide details of the IPM specified Test 1; Test 2 and Test 3.</i></p> <p>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 (PMTCT) services.</p> <p>The research centres will inform IPM Medical Safety of any new HIV infections within 24 hours of diagnosis. The applicable regulatory authorities and ethics committees who require expedited notification of HIV seroconversions 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.</p>	
<p><b>SECTION 5.4 Management of Contraception</b></p> <p>To meet eligibility criteria, unless postmenopausal; with no history of menses for one year prior to screening, participants must be on stable contraception prior to screening and enrolment, have demonstrated adherence to her chosen method of contraception and have no significant resultant problems.</p> <p>Stable contraception is defined, for the purposes of the trial, as surgical sterilisation at least 3 months prior to enrolment OR one of the following:</p> <p>Participants who have used contraceptives for at least the preceding year should be on the same:</p> <ul style="list-style-type: none"> <li>• Oral contraceptive regimen for at least 2 months prior to enrolment, OR</li> <li>• Transdermal contraceptive patch for at least 2 months prior to enrolment, OR,</li> <li>• Long-acting injectable progestins for at least 2 consecutive injections, OR,</li> <li>• Subcutaneous implant inserted at least 3 months prior to enrolment, OR</li> <li>• An IUCD inserted at least 3 months prior to enrolment.</li> </ul> <p>Participants who have newly commenced contraceptive use or have recommenced contraceptive use after a period of greater than 6 months should be on the same:</p> <ul style="list-style-type: none"> <li>• Oral contraceptive regimen for at least 3 months prior to enrolment, OR</li> <li>• Transdermal contraceptive patch for at least 3 months prior to enrolment, OR,</li> <li>• Long-acting injectable progestins for at least 6 months, OR,</li> <li>• Subcutaneous implant inserted at least 3 months prior to enrolment, OR</li> </ul>	<p><b>SECTION 5.4 Management of Contraception</b></p> <p>To meet eligibility criteria, unless postmenopausal with no history of menses for one year prior to screening, participants must be on stable contraception prior to screening and enrolment, have demonstrated adherence to her chosen method of contraception and have no significant resultant problems.</p> <p>Stable contraception is defined, for the purposes of the trial, as surgical sterilisation at least 3 months prior to enrolment OR one of the following:</p> <p>Participants who have used contraceptives for at least the preceding year should be on the same:</p> <ul style="list-style-type: none"> <li>• Oral contraceptive regimen for at least 2 months prior to enrolment, OR</li> <li>• Transdermal contraceptive patch for at least 2 months prior to enrolment, OR,</li> <li>• Long-acting injectable progestins for at least 2 consecutive injections, OR,</li> <li>• Subcutaneous implant inserted at least 3 months prior to enrolment, OR</li> <li>• An IUCD inserted at least 3 months prior to enrolment.</li> </ul> <p>Participants who have newly commenced contraceptive use or have recommenced contraceptive use after a period of greater than 6 months should be on the same:</p> <ul style="list-style-type: none"> <li>• Oral contraceptive regimen for at least 3 months prior to enrolment, OR</li> <li>• Transdermal contraceptive patch for at least 3 months prior to enrolment, OR,</li> <li>• Long-acting injectable progestins for at least 6 months, OR,</li> <li>• Subcutaneous implant inserted at least 3 months prior to enrolment, OR</li> </ul>	<p>In order to harmonise protocol IPM 027 with another safety and efficacy trial of dapivirine vaginal rings (MTN-020), as recommended by the PSA Procedure, the use of vaginal products (including contraceptive rings) will be allowed, but discouraged.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<ul style="list-style-type: none"> <li>An IUCD inserted at least 3 months prior to enrolment.</li> </ul> <p>As referred in the inclusion criteria in Section 3.3.1, the use of contraceptive rings will not be allowed.</p> <p>In order to address challenges that participants may experience in consistently obtaining reliable contraception, research centres will provide participants with contraceptives from enrolment for the duration of the trial. The contraceptives provided will be consistent with what is available locally and what the participant had been using prior to enrolment. Alternatively, participants will be referred to the local family planning clinic if a referral system has been implemented. Under supervision of the investigator or designated qualified personnel, the participant may switch from one contraceptive method to another, provided that stable contraception is maintained.</p> <p>Contraceptive counselling will be provided at screening and all trial visits; including the last product use and exit 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.</p> <p>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 <i>Pregnancy Testing and Management</i> below in Section 5.5.</p>	<ul style="list-style-type: none"> <li>An IUCD inserted at least 3 months prior to enrolment.</li> </ul> <p><del>As referred in the inclusion criteria in Section 3.3.1, the use of contraceptive rings will not be allowed.</del></p> <p>In order to address challenges that participants may experience in consistently obtaining reliable contraception, research centres will provide participants with contraceptives from enrolment for the duration of the trial. The contraceptives provided will be consistent with what is available locally and what the participant had been using prior to enrolment. Alternatively, participants will be referred to the local family planning clinic if a referral system has been implemented. Under supervision of the investigator or designated qualified personnel, the participant may switch from one contraceptive method to another, provided that stable contraception is maintained.</p> <p>Contraceptive counselling will be provided at screening and all trial visits; including the last product use and exit 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.</p> <p>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 <i>Pregnancy Testing and Management</i> below in Section 5.5.</p>	
<p>SECTION 5.7 Vital Signs and Physical Examination</p> <p>A general physical examination will also be conducted at screening 1 and the last product use visit; which includes weight, vital signs, 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 screening 1. A symptom-directed physical examination will be conducted at screening 2 and as needed throughout the trial.</p>	<p>SECTION 5.7 Vital Signs and Physical Examination</p> <p>A general physical examination will <del>also</del> be conducted at screening 1 and the last product use visit, <u>and will include</u> weight, vital signs, 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 screening 1. A symptom-directed physical examination will be conducted at screening 2 and as needed throughout the trial.</p>	<p>Syntax error corrected.</p>
<p>SECTION 5.11 Cervical Cytology</p> <p>A cervical cytology sample will be collected at screening 1, week 52 and week 104. Women with Grade 1 abnormal cervical cytology findings at screening can be enrolled upon completion of the initial phase of evaluation if no current treatment</p>	<p>SECTION 5.11 Cervical Cytology</p> <p>A cervical cytology sample will be collected at screening 1, week 52 and <u>at the last product use visit</u>. Women with Grade 1 abnormal cervical cytology findings at screening can be enrolled upon completion of the initial phase of evaluation if</p>	<p>As cervical cytology will be performed at the Last Product Use Visit (which would be Week 104 for participants who</p>



OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>is indicated (based on local standard of care for management of abnormal cervical cytology). Cervical cytology will be repeated according to the local standard of care, or after 6 months; whichever is more conservative.</p> <p>Women with Grade 1 cervical cytology findings at week 52 will continue using the IP, and cervical cytology will be repeated according to the local standard of care, or after 6 months; whichever is more conservative.</p> <p>Women with Grade 2 or 3 cervical cytology findings at week 52 will discontinue IP use and will be referred for appropriate medical services. These referral systems 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.</p>	<p>no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology). Cervical cytology will be repeated according to the local standard of care, or after 6 months; whichever is more conservative.</p> <p>Women with Grade 1 cervical cytology findings at week 52 will continue using the IP, and cervical cytology will be repeated according to the local standard of care, or after 6 months; whichever is more conservative.</p> <p>Women with Grade 2 or 3 cervical cytology findings at week 52 will discontinue IP use and will be referred for appropriate medical services. These referral systems 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.</p>	<p>complete the trial), the sentence was rephrased to state this more clearly.</p>
<p>SECTION 5.12 Vaginal Ring Insertion and Placement Check and Ring Removal</p> <p>At the enrolment and 4-weekly trial visits, participants will insert their vaginal rings under clinic supervision. The participant will be instructed to wash her hands thoroughly, 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 wash her hands thoroughly again. A brief digital examination will be performed immediately after by an appropriately qualified and trained trial staff member as designated by the investigator, to verify proper placement of the ring. If upon digital examination the ring is not inserted correctly, the investigator or nurse will allow the participant a maximum of 2 additional attempts to re-insert the ring properly or provide assistance as required to put the ring in place. At all trial visits when a pelvic examination is performed, the participant will remove the ring prior to the examination.</p> <p>If the participant requests help with either removal or re-insertion of the vaginal ring, or after she has made a maximum of 3 attempts to remove/re-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 Study Operations Manual.</p>	<p>SECTION 5.12 Vaginal Ring Insertion and Placement Check and Ring Removal</p> <p>At the enrolment and 4-weekly trial visits, participants will insert their vaginal rings under clinic supervision. The participant will be instructed to wash her hands thoroughly, 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 wash her hands thoroughly again. A brief digital examination will be performed immediately after by an appropriately qualified and trained trial staff member as designated by the investigator, to verify proper placement of the ring. <b><u>The verification of the placement of the ring at subsequent visits will be done at the discretion of the designated trial staff.</u></b> If upon digital examination the ring is not inserted correctly, the investigator or nurse will allow the participant a maximum of 2 additional attempts to re-insert the ring properly or provide assistance as required to put the ring in place. At all trial visits when a pelvic examination is performed, the participant will remove the ring prior to the examination.</p> <p>If the participant requests help with either removal or re-insertion of the vaginal ring, or after she has made a maximum of 3 attempts to remove/re-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 Study Operations Manual.</p>	<p>Text was added to indicate that if a participant can place the ring correctly there might be no need to perform further digital examinations every month for 24 months.</p>
<p>SECTION 5.13 Vaginal Ring Adherence Counselling</p> <p>At all 4-weekly trial visits except the last product use and exit visits, participants</p>	<p>SECTION 5.13 Vaginal Ring Adherence Counselling</p> <p>At all 4-weekly trial visits except the last product use and exit visits, participants</p>	<p>Vaginal ring adherence counselling will take place at the</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>will receive vaginal ring adherence counselling at the time of ring insertion. Research centre staff will counsel participants to refrain from removing the ring (except as directed during clinic visits) and from using concomitant vaginal products or other objects. However, tampon use is permitted. Research centre staff will also provide instructions for re-insertion 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.</p> <p>If, for any reason, the participant is non-adherent in her 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 in the source documents and applicable CRFs. The behavioural questionnaires will document the reason for non-adherence and additional adherence counselling will be provided.</p>	<p>will receive vaginal ring adherence counselling <del>at the time of ring insertion.</del> Research centre staff will counsel participants to refrain from removing the ring (except as directed during clinic visits) and <u>to avoid</u> using concomitant vaginal products or other objects. However, tampon use is permitted. Research centre staff will also provide instructions for re-insertion 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.</p> <p>If, for any reason, the participant is non-adherent in her 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 in the source documents and applicable CRFs. The behavioural questionnaires will document the reason for non-adherence and additional adherence counselling will be provided.</p>	<p>4-weekly visits, but not necessarily at the time of ring insertion.</p> <p>In order to harmonise protocol IPM 027 with protocol MTN-020, as recommended by the PSA Procedure, the use of vaginal products will be allowed, but discouraged.</p>
<p>SECTION 5.15 Sample Storage and Analysis</p> <p>Blood and vaginal fluid samples will be collected for storage at a central laboratory at all trial visits, to be tested subsequent to confirmed HIV-1 seroconversion. Blood samples for HSV-2 serology, HIV viral genotyping and HIV-RNA PCR will be stored from enrolment (or screening 2 for research centres that use this option). Testing will be conducted on stored samples from confirmed HIV-1 seroconverters and specifically for dapivirine concentration measurements and HSV-2 serology from both HIV-1 seroconverters and a random sample of HIV-negative participants. Blood samples will be collected by venipuncture and vaginal fluids will be collected through the use of Tear Test Strips. For dapivirine concentration measurements, blood and vaginal fluid samples must be collected prior to removal of the vaginal ring. Further details regarding these procedures will be provided in the Laboratory Manual (which forms part of the Study Operations Manual).</p> <p>As described in Section 5.3.3 above, additional blood (blood volume as specified in Appendix D) and vaginal fluid samples will also be obtained for analysis at the point of HIV seroconversion according to the HIV testing algorithm described in Section 5.3.</p> <p>The blood samples will be tested retrospectively for HIV-RNA PCR and HSV-2 serology, while both blood and vaginal fluid will be tested for dapivirine concentrations and viral genotyping. Plasma and vaginal fluid drug concentrations will be used to evaluate the relationship between drug concentrations and HIV seroconversion. HSV-2 serology and dapivirine concentration analyses will be conducted in HIV-1 seroconverters and a randomly selected control group of HIV-negative participants.</p>	<p>SECTION 5.15 Sample Storage and Analysis</p> <p>Blood and vaginal fluid samples will be collected for storage <u>locally or</u> at a central laboratory at all trial visits, to be tested subsequent to confirmed HIV-1 seroconversion. Blood samples for HSV-2 serology, HIV viral genotyping and HIV-RNA PCR will be stored from enrolment (or screening 2 for research centres that use this option). Testing will be conducted on stored samples from confirmed HIV-1 seroconverters and specifically for dapivirine concentration measurements and HSV-2 serology from both HIV-1 seroconverters and a random sample of HIV-negative participants. <del>Blood samples will be collected by venipuncture and vaginal fluids will be collected through the use of Tear Test Strips.</del> For dapivirine concentration measurements, blood and vaginal fluid samples must be collected prior to removal of the vaginal ring. Further details regarding these procedures will be provided in the Laboratory Manual (which forms part of the Study Operations Manual).</p> <p>As described in Section 5.3.3 above, additional blood (blood volume as specified in Appendix D) and vaginal fluid samples will also be obtained for analysis at the point of HIV seroconversion according to the HIV testing algorithm described in Section 5.3.</p> <p>The blood samples will be tested retrospectively for HIV-RNA PCR, <u>and</u> HSV-2 serology <u>and viral genotyping</u>, while both blood and vaginal fluid will be tested for dapivirine concentrations <del>and viral genotyping</del>. Plasma and vaginal fluid drug concentrations will be used to evaluate the relationship between drug concentrations and HIV seroconversion. HSV-2 serology and dapivirine concentration analyses will be conducted in HIV-1 seroconverters and a randomly selected control group of HIV-negative participants.</p>	<p>Sample storage might also take place at the research centres.</p> <p>The methods of blood and vaginal fluid sample collection will be described in detail in the Study Operations Manual.</p> <p>Viral genotyping will only be performed on blood samples, and not vaginal fluid samples, to harmonise IPM 027 with MTN-020, as recommended by the PSA Procedure.</p> <p>Typographical error (“quality assurance”) corrected to “quality control”.</p>

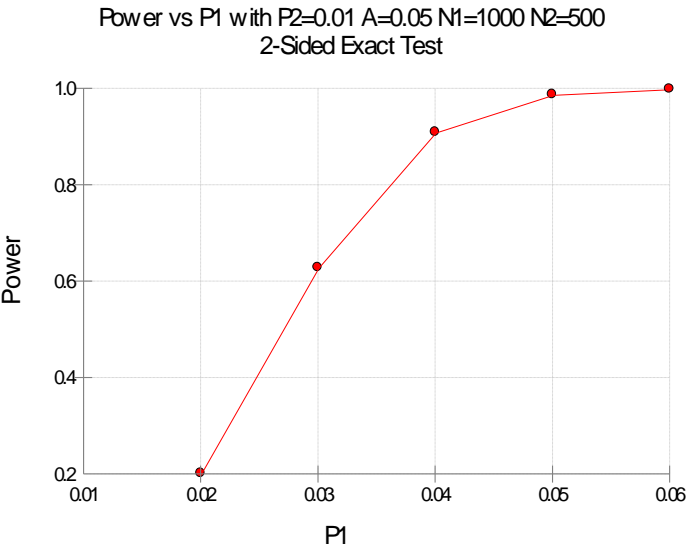
OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>All specimens will be collected and analysed according to methods described in the Laboratory Manual and standard operating procedures (SOPs) for proper collection, processing, labelling, and transport of specimens to the laboratories conducting the assays. Where possible and appropriate, stored specimens will be re-tested to assess validity of unusual or unexpected assay results.</p> <p>Any residual specimens will be destroyed at the end of the trial after all protocol-required and quality assurance testing has been completed.</p>	<p>All specimens will be collected and analysed according to methods described in the Laboratory Manual and standard operating procedures (SOPs) for proper collection, processing, labelling, and transport of specimens to the laboratories conducting the assays. Where possible and appropriate, stored specimens will be re-tested to assess validity of unusual or unexpected assay results.</p> <p>Any residual specimens will be destroyed at the end of the trial after all protocol-required and quality <u>control</u> testing has been completed.</p>	
<p>SECTION 5.16 Method of Treatment Assignment</p> <p>Participants who meet all of the trial inclusion criteria and no exclusion criterion at baseline will be randomly assigned in a 2:1 ratio to one of two groups receiving either the vaginal ring containing dapivirine or the placebo vaginal ring respectively. Randomisation will be stratified by research centre and age at the time of enrolment (<math>\leq 40</math> years of age, <math>&gt; 40</math> years of age) using a pre-specified block size and will be determined via the use of an automated randomisation system to ensure balance of the treatment assignments. Both groups will use a 4-weekly administered ring continuously for the duration of trial participation and have a follow-up visit 6 weeks after ring removal.</p> <p>A master randomisation list for the trial will be generated which links each participant identification number to a trial treatment assignment (dapivirine ring or placebo ring). At each research centre, as each new participant enters the trial, a unique participant identification number will be assigned to that participant using an automated response system.</p>	<p>SECTION 5.16 Method of Treatment Assignment</p> <p>Participants who meet all of the trial inclusion criteria and no exclusion criterion at baseline will be randomly assigned in a 2:1 ratio to one of two groups receiving either the vaginal ring containing dapivirine or the placebo vaginal ring respectively. Randomisation will be stratified by research centre <del>and age</del> at the time of enrolment (<del><math>\leq 40</math> years of age, <math>&gt; 40</math> years of age</del>), using a pre-specified block size and will be determined via the use of an automated randomisation system to ensure balance of the treatment assignments. Both groups will use a 4-weekly administered ring continuously for the duration of trial participation and have a follow-up visit 6 weeks after ring removal.</p> <p>A master randomisation list for the trial will be generated which links each participant identification number to a trial treatment assignment (dapivirine ring or placebo ring). At each research centre, as each new participant enters the trial, a unique participant identification number will be assigned to that participant using an automated response system.</p>	<p>As the enrolment age will be limited to <math>\leq 45</math> years, no subgroup analysis of women over 40 years will be conducted, and the randomisation thus does not need to be stratified by age.</p>
<p>SECTION 6.5 Investigational Product Storage</p> <p>The recommended storage condition for the dapivirine and placebo rings is 15°C to 30°C. 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.</p> <p>The investigator (or pharmacist) will maintain an inventory and acknowledge receipt of all shipments of IP. The automated response system will also be used to confirm receipt of and activate dispensed kits.</p>	<p>SECTION 6.5 Investigational Product Storage</p> <p>The recommended storage condition for the dapivirine and placebo rings is 15°C to 30°C. 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.</p> <p>The investigator (or pharmacist) will maintain an inventory and acknowledge receipt of all shipments of IP. The automated response system will also be used to confirm receipt of and activate <del>dispensed</del> <u>for use</u> kits.</p>	<p>Sentence on the automated response system was rephrased for clarity.</p>
<p>SECTION 6.6 Investigational Product Administration</p> <p>Participants will self-insert a new vaginal ring at enrolment and each 4-weekly visit</p>	<p>SECTION 6.6 Investigational Product Administration</p> <p>Participants will self-insert a new vaginal ring at enrolment and each 4-weekly visit</p>	<p>Due to the duration of the trial, participants may not be able to</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>through the period of trial participation. A brief digital examination will be performed by an appropriately delegated trial staff member at each 4-weekly trial visit to ensure the ring is properly placed. Participants should continue ring use through menses.</p>	<p>through the period of trial participation. A brief digital examination will be performed by an appropriately delegated trial staff member at each 4-weekly trial visit to ensure the ring is properly placed. Participants should continue ring use through menses.</p> <p><b><u>In the event that a participant will be away and unable to attend one of the 4-weekly visits where a new vaginal ring would be inserted, the research centre could dispense an additional ring, which the participant should then self-insert on the day that her 4-weekly visit was due to take place. Management thereof will be on a case by case basis following discussion by the investigator with the IPM Clinical Physician or designee.</u></b></p>	<p>attend all 4-weekly visits for new ring insertion. In such instances the research centre will be allowed to dispense an additional ring for self-insertion by the participant, on a case by case basis, and as appropriate.</p>
<p>SECTION 6.7 Investigational Product Expulsion or Loss</p> <p>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 it. If the vaginal ring is expelled and cannot be successfully reinserted, the ring should be appropriately rinsed and stored in a clean place, until the earliest possible opportunity the participant can return for reinsertion of a new ring at the clinic. After second expulsion the IPM Clinical Physician should be consulted with regards to appropriate follow up action.</p> <p>The participant 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 return to the clinic. Also in cases where a ring is removed due to a genital AE, a new ring will be dispensed and inserted. Visits associated with expulsion or loss of rings will be regarded as unscheduled visits and management thereof will be on a case by case basis following discussion by the investigator with the IPM Clinical Physician or designee, unless the visit is within the <math>\pm 7</math> days window period of the next scheduled visit.</p>	<p>SECTION 6.7 Investigational Product Expulsion or Loss</p> <p>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 it. If the vaginal ring is expelled and cannot be successfully reinserted, the ring should be appropriately rinsed and stored in <b><u>the bag provided for this purpose</u></b>, until the earliest possible opportunity the participant can return for reinsertion of a new ring at the clinic. After <b><u>the</u></b> second expulsion the IPM Clinical Physician should be consulted with regards to appropriate follow-up action.</p> <p>The participant 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 return to the clinic. Also in cases where a ring is removed due to a genital AE, a new ring will be dispensed and inserted. Visits associated with expulsion or loss of rings will be regarded as unscheduled visits and management thereof will be on a case by case basis following discussion by the investigator with the IPM Clinical Physician or designee, unless the visit is within the <b><u>7-day</u></b> window period of the next scheduled visit.</p> <p><b><u>6.8 Retrieval of Investigational Product</u></b></p> <p><b><u>All participants who prematurely discontinue 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.</u></b></p>	<p>Some of the sentences in Section 6.7 was revised for clarity.</p> <p>Section 6.8 was included in order to ensure adequate and accurate accountability of investigational product at trial end.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
	<p><b><u>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.</u></b></p>	
<p>SECTION 6.9 Concomitant Medications &amp; Products</p> <p>All prescription and non-prescription medications, including any treatment for STIs and other reproductive tract infections, will be collected and recorded on the source documents and applicable CRFs.</p> <p>All cases of symptomatic candidiasis will be treated with oral fluconazole. Concomitant use of vaginal products or other objects including spermicides, lubricants, intravaginal medication, other vaginal rings, female condoms, cotton wool, rags, diaphragms, cervical caps (or any other vaginal barrier method), douches, drying agents and herbs are prohibited for the duration of the trial. <i>NOTE: If any of these products are used, this will be considered a protocol deviation and will be documented on the source document and applicable CRFs. Tampons are not included in this list and may be used for the duration of the trial.</i></p>	<p>SECTION 6.10 Concomitant Medications <b>and</b> Products</p> <p>All prescription and non-prescription medications, including any treatment for STIs and other reproductive tract infections, will be collected and recorded on the source documents and applicable CRFs.</p> <p>All cases of symptomatic candidiasis will be treated with oral fluconazole. <b><u>Oral therapy will also be prescribed for the treatment of STIs and other reproductive tract infections. Concomitant use of non-trial vaginal products, practices or use of other devices including but not limited to spermicides, diaphragms, contraceptive vaginal rings, female condoms, vaginally applied medication, menstrual cups, cervical caps, douches, lubricants, etc., will be discouraged. Participants will be instructed to avoid these medications and practices in order to protect the integrity of the lower genital tract and reduce the possibility of AEs due to agents other than the investigational product.</u></b> <i>NOTE: If any of these products are used, this will be considered a protocol deviation and will be documented on the source document and applicable CRFs. Tampons are not included in this list and may be used for the duration of the trial.</i></p>	<p>In order to harmonise protocol IPM 027 with MTN-020, as recommended by the PSA Procedure, the use of vaginal products will be allowed, but discouraged.</p>
<p>SECTION 9.1 General Design</p> <p>IPM 027 is a Phase II clinical trial that has been designed to assess the long-term safety of dapivirine administered in a silicone elastomer vaginal ring (Ring-004) containing 25mg of dapivirine and inserted once every 4 weeks; among approximately 1,650 healthy, HIV-negative, sexually active women aged 18 – 60 years – as compared with a placebo vaginal ring.</p> <p>Individuals meeting all inclusion criteria and no exclusion criteria will be randomised in a 2:1 ratio to either the investigational product or a placebo vaginal ring. To maintain the treatment ratio within each research centre and to ensure that a similar balance is preserved within the subgroup of participants over 40 years of age, randomisation, via an automated randomisation system, will be stratified by research centre and age group (<math>\leq 40</math> years of age, <math>&gt; 40</math> years of age; N = 1,350 and N = 300 respectively), using a pre-specified block size.</p> <p>All enrolled participants will self-insert a vaginal ring (either placebo or containing</p>	<p>SECTION 9.1 General Design</p> <p>IPM 027 <del>is a Phase II clinical trial that</del> has been designed to assess the long-term safety <b>and efficacy</b> of dapivirine administered in a silicone elastomer vaginal ring (Ring-004) containing 25mg of dapivirine and inserted once every 4 weeks, among approximately 1,650 healthy, HIV-negative, sexually active women aged 18 – <b>45</b> years – as compared with a placebo vaginal ring.</p> <p>Individuals meeting all inclusion criteria and no exclusion criteria will be randomised in a 2:1 ratio to either the investigational product or a placebo vaginal ring. To maintain the treatment ratio within each research centre <del>and to ensure that a similar balance is preserved within the subgroup of participants over 40 years of age,</del> randomisation, via an automated randomisation system, will be stratified by research centre <del>and age group (<math>\leq 40</math> years of age, <math>&gt; 40</math> years of age; N = 1,350 and N = 300 respectively),</del> using a pre-specified block size.</p> <p><b><u>Participants will be followed on IP over a period of approximately 24 months</u></b></p>	<p>The addition of efficacy assessment as a primary endpoint, and limiting the enrolment age to <math>\leq 45</math> years, necessitated amendment of the Statistical Methods sections.</p> <p>Also, as the enrolment age will be limited to <math>\leq 45</math> years, no subgroup analysis of women over 40 years will be conducted, and the randomisation thus</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>dapivirine) at enrolment to be worn continuously for the duration of the trial participation period, with ring replacements at 4-weekly intervals until the last product use visit. Participants will be asked to return to the research centre at 4-weekly intervals post-enrolment to monitor safety outcomes (AEs and SAEs). A follow-up visit will be conducted 6 weeks after removal of the last ring (last product use visit). In addition, all participants will be tested at 12-weekly visits for curable STIs and changes in vaginal flora and tested for pregnancy at all trial visits. Safety laboratory assessments will be performed at 12-weekly intervals. Blood and vaginal fluid samples will be collected for storage at all visits. These stored samples will be tested for HIV-RNA PCR (blood) and viral genotyping (blood and vaginal fluid) only in HIV-1 seroconverters, while HSV-2 serology (blood), blood and vaginal fluid dapivirine concentrations measurement will be conducted in HIV-1 seroconverters and a randomly selected control group of HIV-negative participants. Adherence, sexual behaviour, vaginal practices and condom use pre-randomisation and during follow-up will also be assessed at all 4-weekly trial visits. Ring acceptability will be assessed at week 4 after enrolment and at 24-weekly intervals thereafter.</p>	<p><b><u>(104 weeks). Each participant will have an additional 6 weeks of follow-up after ring discontinuation.</u></b></p>	<p>does not need to be stratified by age.</p> <p>The comprehensive description of the study schedule was considered redundant, and replaced by a short paragraph on the duration of the trial.</p>
<p>SECTION 9.3 Primary Trial Hypotheses</p> <p>From previous safety trials of dapivirine, there is reason to believe that the investigational product is safe and well tolerated. Thus, it is hypothesised that the dapivirine vaginal ring will be safe and well tolerated in healthy HIV-negative women, aged 18 – 60 years, over a 24-month period of exposure.</p>	<p>SECTION 9.3 Primary Trial Hypotheses</p> <p><b><u>Primary efficacy hypothesis</u></b>  <b><u>IPM 027 is designed to test the efficacy of the investigational product in preventing HIV-1 infection as compared with placebo. The null hypothesis is that the rate of HIV-1 seroconversion is not different among participants assigned the dapivirine vaginal ring compared with participants assigned to the placebo ring.</u></b></p> <p><b><u>Primary safety analysis</u></b>  <b><u>The primary safety analysis is descriptive in nature. Tabular summaries and listings will be provided and will include all participants who have received the IP.</u></b></p>	<p>The addition of efficacy assessment as a primary endpoint necessitated amendment of this section.</p>
<p>SECTION 9.4 Sample Size and Power Calculations</p> <p>IPM 027 will be conducted in a sample of approximately 1,650 HIV-negative women in a 2:1 ratio, such that 1,100 participants will be assigned to the investigational product and 550 participants will be assigned to the placebo ring. The sample size is determined based on the probability of detecting rare AEs in the active arm and the ability for the trial to detect differences in the proportion of primary endpoints between the two trial arms assuming an AE rate of 1% in the placebo arm.</p> <p>In a trial with 1,000 participants assigned to the investigational product, there is a</p>	<p>SECTION 9.4 Sample Size and Power Calculations</p> <p>IPM 027 will be conducted in a sample of approximately 1,650 HIV-negative women in a 2:1 ratio, such that 1,100 participants will be assigned to the investigational product and 550 participants will be assigned to the placebo ring. <b><u>The sample size for this trial was determined based on the primary efficacy endpoint, the incidence rate of HIV-1 seroconversions, in the two treatment arms. The statistical assumptions used in determining this sample size therefore include:</u></b></p>	<p>The addition of efficacy assessment as a primary endpoint necessitated amendment of the Sample Size and Power Calculations section.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE																																			
<p>95% probability of detecting an AE occurring at a rate of 0.3% or higher. The table below presents the probability of detecting at least one and at least two AEs in a sample of 1,000 participants assigned to the investigational product for varying AE rates. A sample of this size has a high probability of detecting at least one AE that occurs at a rate of 0.3%; the probability of detecting at least two AEs is high for events with rates greater than 0.5%. A trial of this size is sufficient to observe at least three or higher events during the trial duration if the event occurs at a rate less than 0.6%.</p> <table border="1" data-bbox="114 432 792 711"> <thead> <tr> <th rowspan="2">AE rate</th> <th colspan="3">Probability* of detecting</th> </tr> <tr> <th>at least 1 event</th> <th>at least 2 events</th> <th>at least 3 events</th> </tr> </thead> <tbody> <tr> <td>0.003</td> <td>95%</td> <td>80%</td> <td>58%</td> </tr> <tr> <td>0.004</td> <td>98%</td> <td>91%</td> <td>76%</td> </tr> <tr> <td>0.005</td> <td>99%</td> <td>96%</td> <td>88%</td> </tr> <tr> <td>0.006</td> <td>100%</td> <td>98%</td> <td>94%</td> </tr> </tbody> </table> <p>*based on binomial distribution, n=1000, p=AE rate</p> <p>The Fisher's Exact Test is used to estimate the appropriate sample size which would provide sufficient to detect differences in the proportion of participants with Grade 3 and 4 AEs, and related Grade 2 AEs between the two arms.</p> <p>Using a Fisher's Exact Test under 0.05 type I error, a trial with 1,000 participants assigned to the active arm and 500 participants assigned to the placebo arm would provide approximately 91% power to detect a difference of 4% or larger if the AE rate in the placebo arm were 1%. The figure below is a power curve that demonstrates the change in power for detecting the difference in the AE rates between the placebo arm (assumed 1% rate) and the active arm (varying rates). The vertical axis displays power, and the horizontal axis displays the AE rate in the active arm. In the figure, P1 and N1 denote the AE rate and sample size in the active arm, respectively; P2 and N2 denote the AE rate and sample size in the control arm, respectively. All calculations are based on 2-sided Fisher's Exact Test, alpha = 0.05, and were computed using PASS 2008.</p>	AE rate	Probability* of detecting			at least 1 event	at least 2 events	at least 3 events	0.003	95%	80%	58%	0.004	98%	91%	76%	0.005	99%	96%	88%	0.006	100%	98%	94%	<ul style="list-style-type: none"> <li>• <u>proportional hazards among the two groups,</u></li> <li>• <u>microbicide efficacy of <math>\geq 50\%</math> in preventing HIV-1 infection,</u></li> <li>• <u>randomisation ratio of 2:1 (dapivirine vaginal ring vs. placebo ring),</u></li> <li>• <u>a two-sided log-rank test statistic, with alpha = 0.05,</u></li> <li>• <u><math>\geq 4\%</math> average annual HIV incidence in the placebo arm (assumes a reduction in incidence in the trial population due to risk reduction counseling), and</u></li> <li>• <u><math>\leq 10\%</math> loss-to-follow-up rate over the duration of the trial period.</u></li> </ul> <p><u>Below is a table which provides the estimated power to detect 40%, 50% and 60% microbicide efficacy with a sample size of 1,650 and under the assumptions as stated above.</u></p> <table border="1" data-bbox="1061 592 1805 818"> <thead> <tr> <th><u>Microbicide efficacy</u></th> <th><u># Expected HIV-1 seroconversions</u></th> <th><u>Power</u></th> </tr> </thead> <tbody> <tr> <td><u>40%</u></td> <td><u>88</u></td> <td><u>61.8%</u></td> </tr> <tr> <td><u>50%</u></td> <td><u>80</u></td> <td><u>83.2%</u></td> </tr> <tr> <td><u>60%</u></td> <td><u>72</u></td> <td><u>95.6%</u></td> </tr> </tbody> </table> <p><u>A trial with the proposed design will provide approximately 83% power to detect a 50% reduction in the rate of HIV-1 seroconversions in the active arm, assuming an annual HIV-1 seroconversion rate of 4% in the placebo arm, and a 10% lost-to-follow-up rate.</u></p> <p><u>Moreover, in a trial with this number of participants assigned to the investigational product, there is a 95% probability of detecting an AE occurring at a rate of 0.3% or higher.</u></p>	<u>Microbicide efficacy</u>	<u># Expected HIV-1 seroconversions</u>	<u>Power</u>	<u>40%</u>	<u>88</u>	<u>61.8%</u>	<u>50%</u>	<u>80</u>	<u>83.2%</u>	<u>60%</u>	<u>72</u>	<u>95.6%</u>	
AE rate		Probability* of detecting																																			
	at least 1 event	at least 2 events	at least 3 events																																		
0.003	95%	80%	58%																																		
0.004	98%	91%	76%																																		
0.005	99%	96%	88%																																		
0.006	100%	98%	94%																																		
<u>Microbicide efficacy</u>	<u># Expected HIV-1 seroconversions</u>	<u>Power</u>																																			
<u>40%</u>	<u>88</u>	<u>61.8%</u>																																			
<u>50%</u>	<u>80</u>	<u>83.2%</u>																																			
<u>60%</u>	<u>72</u>	<u>95.6%</u>																																			

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE												
<p>Power vs P1 with P2=0.01 A=0.05 N1=1000 N2=500 2-Sided Exact Test</p>  <table border="1" data-bbox="129 188 817 742"> <caption>Data points for Power vs P1 graph</caption> <thead> <tr> <th>P1</th> <th>Power</th> </tr> </thead> <tbody> <tr> <td>0.02</td> <td>0.20</td> </tr> <tr> <td>0.03</td> <td>0.63</td> </tr> <tr> <td>0.04</td> <td>0.91</td> </tr> <tr> <td>0.05</td> <td>0.99</td> </tr> <tr> <td>0.06</td> <td>1.00</td> </tr> </tbody> </table> <p>To adjust for loss to follow-up and product discontinuation the sample size of N = 1,500 is inflated by 10% for a final sample size of 1,650.</p>	P1	Power	0.02	0.20	0.03	0.63	0.04	0.91	0.05	0.99	0.06	1.00	<p>SECTION 9.5 Statistical Analysis</p> <p><b><u>The primary analysis will focus on efficacy as well as safety assessments.</u></b></p> <p><b><u>As stated in the ICH E9 guidance document, “the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject rather than the actual treatment given”<sup>13</sup>. The intent-to-treat (ITT) population is defined as all participants randomised to either treatment, and under their planned treatment assignment. However, due to the time between HIV-1 infection and the ability to detect antibodies, it is possible that participants who tested negative at screening were infected with HIV. Therefore, the primary analysis will be conducted using a modification of the intent-to-treat (ITT) principle. The modified intent-to-treat (m-ITT) population will exclude all participants that were determined at any point during or after the trial to have been HIV-infected based on the stored HIV-RNA PCR sample taken at the time of enrolment.</u></b></p> <p><b><u>As it is possible that the inclusion of non-adherent participants or</u></b></p>	<p>The addition of efficacy assessment as a primary endpoint necessitated amendment of the Statistical Analysis section.</p>
P1	Power													
0.02	0.20													
0.03	0.63													
0.04	0.91													
0.05	0.99													
0.06	1.00													
<p>SECTION 9.5 Statistical Analysis</p> <p>The primary analysis will focus on safety assessments. The primary analysis will be conducted using the safety population, which will include all participants who received at least one dose of the IP. 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.</p> <p>The active and placebo arms will be compared to assess the safety of the dapivirine ring. As this is a randomised trial, it is anticipated that the two groups will be comparable at baseline with respect to pre-existing conditions, and furthermore, that women with pre-existing conditions will be treated and evaluated before being enrolled into the trial. For this reason, no baseline adjustments are planned prospectively, but the data will be thoroughly reviewed to assess any potentially relevant baseline imbalances. Chi-square tests of association will be used to evaluate differences in categorical variables between the two groups under a 0.05 alpha level. For categorical variables with small sample size (&lt;30),</p>	<p>SECTION 9.5 Statistical Analysis</p> <p><b><u>The primary analysis will focus on efficacy as well as safety assessments.</u></b></p> <p><b><u>As stated in the ICH E9 guidance document, “the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject rather than the actual treatment given”<sup>13</sup>. The intent-to-treat (ITT) population is defined as all participants randomised to either treatment, and under their planned treatment assignment. However, due to the time between HIV-1 infection and the ability to detect antibodies, it is possible that participants who tested negative at screening were infected with HIV. Therefore, the primary analysis will be conducted using a modification of the intent-to-treat (ITT) principle. The modified intent-to-treat (m-ITT) population will exclude all participants that were determined at any point during or after the trial to have been HIV-infected based on the stored HIV-RNA PCR sample taken at the time of enrolment.</u></b></p> <p><b><u>As it is possible that the inclusion of non-adherent participants or</u></b></p>	<p>The addition of efficacy assessment as a primary endpoint necessitated amendment of the Statistical Analysis section.</p>												



OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>Fisher's Exact test may be used. Continuous data may be compared between the two treatment arms using student t-tests or Wilcoxon signed rank tests.</p> <p>The safety profile is not expected to differ across research centres and it is unlikely that the difference in the safety profile between the active and control arms is affected by the research centre. However, for each analysis subsequently discussed, research centres will be evaluated via inclusion as a main effect and with a treatment-centre interaction term in appropriate regression models.</p> <p>For the secondary analyses, the incidence density rates of seroconversions (HIV-1 and HIV-2) and pregnancies will be compared between treatment groups. Additional analyses will be performed to evaluate adherence and acceptability to 4-weekly use of the vaginal ring over the IP use period as well as additional predictors of adherence (including sexual behaviour and condom use of women using a vaginal ring). The frequency of HIV-1 drug resistance in women who seroconvert while using the IP will also be assessed.</p> <p>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.</p>	<p><b><u>participants removed from the trial product may artificially lower the rates of safety outcomes, additional analyses will be conducted on the per-protocol population, where time off-product is removed from the analysis. 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 written in a SAP, which will be finalised prior to unblinding of trial data.</u></b></p> <p><b><u>For the secondary analyses, the incidence density rates of HIV-2 seroconversions, curable STIs, changes in vaginal flora and pregnancies will be compared between treatment groups.</u></b> Additional analyses will be performed to evaluate adherence and acceptability to 4-weekly use of the vaginal ring over the IP use period as well as additional predictors of adherence (including sexual behaviour and condom use of women using a vaginal ring). The frequency of HIV-1 drug resistance in women who seroconvert while using the IP will also be assessed. The data will be presented using appropriate statistical measures including, but not limited to: mean, standard deviation, median, and interquartile range for continuous data; <b><u>and the</u></b> frequency and relative frequency for categorical data. When appropriate, 95% confidence intervals will be presented.</p>	
<p>SECTION 9.5.1 Primary Safety Analysis</p> <p>The primary safety analysis will include the risk ratio, which is the ratio of the proportion of participants with Grade 3 and 4 AEs, and related Grade 2 AEs in the active arm versus in the placebo arm. The corresponding 95% CIs will also be presented. Fisher's Exact test will be provided to compare the proportion of participants, in the active and placebo arms, with Grade 3 and 4 AEs, and related Grade 2 AEs; at a 0.05 significance level. Similar analyses will be performed using the per-protocol population.</p> <p>Although balance of baseline characteristics is expected across trial arms, a Poisson regression model may be used to provide risk ratios adjusted for unbalance in any baseline characteristics.</p> <p>In addition to the analyses described above, all AEs reported during the trial will be presented in tables, overall, by treatment arm, and by research centre.</p>	<p>SECTION 9.5.1 Primary <b><u>Efficacy</u></b> Analysis</p> <p><b><u>As stated earlier, the primary analysis will be performed on the m-ITT population, i.e., all trial participants that were HIV-1 negative at enrolment and were randomised to either the trial product or placebo. The primary efficacy analysis of the primary endpoint will be the comparison of the incidence rate of HIV-1 seroconversion, as determined by the HIV testing algorithm in Appendix C, between the active and placebo arms. For participants who were reported to HIV-1 seroconvert at the exit visit, HIV-RNA PCR tests will be performed on stored samples in reverse sequential order to estimate the time point of HIV infection. If the infection is determined to have been acquired while the participant was on product, the seroconversion will be included in the primary analysis. However, if the infection is determined to have been acquired during the time between the last product visit and the exit visit, the seroconversion will not be included in the primary analysis.</u></b></p> <p><b><u>The primary analysis will include the estimation of the incidence density rate of HIV-1 seroconversion, with corresponding 95% CIs. The formal statistical test used to evaluate the efficacy of the dapivirine ring will evaluate the null</u></b></p>	<p>The addition of efficacy assessment as a primary endpoint necessitated amendment of the Statistical Analysis section.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
	<p><u>hypothesis of no difference in the population survival curves (i.e. the probability of an HIV-1 seroconversion occurring at any time point is the same for the active and placebo arms) via a log-rank test stratified by research centre and evaluated at a 5% significance level. This analysis will be accompanied with Kaplan-Meier survival curves of the two trial arms for visual inspection of the proportional hazards assumption. Trial participants will be followed on the IP for 24 months, and will be tested for HIV-1 infection at 4-weekly visits. Participants that are not diagnosed with HIV-1 at the end of the trial participation period will be censored at the earliest date of any of the following events: completion of investigational product use, trial drop-out, a positive pregnancy test followed by permanent product discontinuation, or death.</u></p> <p><u>9.5.2 Primary Safety Analysis</u>  <u>A descriptive analysis of all AEs will be presented in tables and listings. Data will be presented by MedDRA System Organ Class (SOC) and Preferred term (PT), by treatment arm. Fisher's Exact test will be performed to compare the proportion of participants in the active and placebo arms, with regard to all Grade 3 and 4 AEs, all SAEs, and AEs leading to IP discontinuation, at a 0.05 significance level. Similar analyses will be conducted on the m-ITT and Per-Protocol populations.</u></p> <p><u>As this is a randomised trial, it is anticipated that the two groups will be comparable at baseline with respect to pre-existing conditions, and furthermore, that women with pre-existing conditions will be treated and evaluated before being enrolled into the trial. For this reason, no baseline adjustments are planned prospectively, but the data will be thoroughly reviewed to assess any potentially relevant baseline imbalances. Chi-square tests of association will be used to evaluate differences in categorical variables between the two groups under a 0.05 alpha level. For categorical variables with small sample size (&lt; 30), Fisher's Exact test may be used. Continuous data may be compared between the two treatment arms using Student t-tests or Wilcoxon signed rank tests. Comparisons between measurements taken during the trial and prior to or at enrolment may also be made; comparisons of continuous data will be performed using paired t-tests and comparisons of categorical data will be performed using McNemar's test.</u></p> <p><u>The safety profile is not expected to differ across research centres and it is unlikely that the difference in the safety profile between the active and control arms is affected by the research centre. However, for each analysis subsequently discussed, research centres will be evaluated via inclusion as a main effect and with a treatment-by-centre interaction term in appropriate</u></p>	

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
	<b><u>regression models. Although balance of baseline characteristics is expected across trial arms, a Poisson regression model may be used to provide risk ratios adjusted for imbalance in any baseline characteristics.</u></b>	
<p>SECTION 9.5.2 Secondary Analyses</p> <ul style="list-style-type: none"> <li><b>Incidence of HIV-1 and HIV-2 seroconversion</b></li> </ul> <p>Hazard ratios will be estimated with corresponding 95% CIs to quantify the effect of the dapivirine ring on HIV-1 and HIV-2 seroconversion. Time to HIV-1 seroconversion will be calculated as the number of days between the date of HIV-1 seroconversion and the randomisation date. Participants who do not seroconvert before the last product visit will be censored on the day of their last negative HIV test, and time to censoring will be calculated as the number of days between the date of censoring and the randomisation date. Kaplan-Meier survival curves will be provided to graphically describe the probability of remaining HIV-1 negative over the trial duration for each treatment arm, and will be used to assess the assumption of proportional hazards. The log-rank test (two-sided, alpha=0.05) will be used to evaluate the effect of the dapivirine ring on HIV-1 incidence, and will be stratified by research centre. Cox proportional hazards will be used to estimate the median time to HIV-1 seroconversion in the treatment groups adjusting for any imbalance in baseline covariates.</p> <p>HIV-1 seroconversions detected at the exit visit are not included in the analysis described previously but, because they may be a result of infections acquired while the participant was off-product between the last product use visit and the exit visit, they are considered a safety concern. To ensure that IP use is not associated with higher risk of HIV-1 seroconversion following extended use of the IP, an additional analysis will be performed which will include all HIV-1 seroconversions detected during the trial following randomisation and will include the period between the last product use visit and the exit visit. For this analysis, time to HIV-1 seroconversion will be calculated as the number of days between the date of HIV-1 seroconversion and the randomisation date. Participants who do not seroconvert before the exit visit will be censored on the day of their last negative HIV test. Time to censoring will be calculated as the number of days between the date of censoring and the randomisation date.</p> <p>Similar analyses will be conducted for HIV-2 seroconversion.</p>	<p>SECTION 9.5.3 Secondary Analyses</p> <ul style="list-style-type: none"> <li><b><u>Incidence rate of HIV-2 seroconversion</u></b></li> </ul> <p><b><u>The incidence density rates of HIV-2 seroconversion in the active and placebo arms will be provided with 95% CIs. The log-rank test will be used to test the null hypothesis that there is no difference between the population survival curves (i.e. the probability of an HIV-2 seroconversion occurring at any time point is the same for the active and placebo arms), and will be stratified by research centre and evaluated at a 5% significance level.</u></b></p>	<p>The addition of efficacy assessment as a primary endpoint necessitated amendment of the Statistical Analysis section.</p>
<p>SECTION 9.5.3 Subgroup Analysis of Participants over 45 Years of Age</p> <p>IPM 027 will enrol participants over 40 years of age to assess the safety of dapivirine in a silicone elastomer vaginal matrix ring inserted once every 4 weeks</p> <p>IPM 027 Version 1.0 Amendment 1.0 Summary of Changes 23 January 2012</p>	<p><del>SECTION 9.5.3 Subgroup Analysis of Participants over 45 Years of Age</del></p> <p><del>IPM 027 will enrol participants over 40 years of age to assess the safety of dapivirine in a silicone elastomer vaginal matrix ring inserted once every 4 weeks</del></p>	<p>As the enrolment age was limited to ≤ 45 years, no subgroup analysis for women</p>

~~Strikethrough~~ text is deleted text  
Underlined text is new text

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE																																																																																																																										
<p>in older women, when compared to a placebo vaginal ring. An assessment of the primary, secondary and exploratory endpoints will be performed in a subgroup of participants over 40 years of age.</p> <p>A subgroup with approximately 200 participants over 40 years of age in the active arm, or approximately 300 participants in both arms, would be sufficient to detect at least one AE with a rate of 2% and at least three events if the AE rate was 5%. The table below presents the probabilities of detecting at least one, two, and three AEs of varying rates for a total of 150 and 200 participants over 40 years of age in the active arm.</p>	<p><del>in older women, when compared to a placebo vaginal ring. An assessment of the primary, secondary and exploratory endpoints will be performed in a subgroup of participants over 40 years of age.</del></p> <p><del>A subgroup with approximately 200 participants over 40 years of age in the active arm, or approximately 300 participants in both arms, would be sufficient to detect at least one AE with a rate of 2% and at least three events if the AE rate was 5%. The table below presents the probabilities of detecting at least one, two, and three AEs of varying rates for a total of 150 and 200 participants over 40 years of age in the active arm.</del></p>	<p>over 40 years will be conducted.</p> <p>Due the addition of efficacy assessment as a primary endpoint, an interim efficacy analysis will now be performed when 50% of the endpoints have been observed.</p>																																																																																																																										
<table border="1"> <thead> <tr> <th rowspan="3">AE rate</th> <th colspan="3">N=225 (150 on active)</th> <th colspan="3">N=300 (200 on active)</th> </tr> <tr> <th colspan="3">Probability* of detecting</th> <th colspan="3">Probability* of detecting</th> </tr> <tr> <th>at least 1 event</th> <th>at least 2 events</th> <th>at least 3 events</th> <th>at least 1 event</th> <th>at least 2 events</th> <th>at least 3 events</th> </tr> </thead> <tbody> <tr> <td>0.01</td> <td>78%</td> <td>44%</td> <td>19%</td> <td>87%</td> <td>60%</td> <td>32%</td> </tr> <tr> <td>0.02</td> <td>95%</td> <td>80%</td> <td>58%</td> <td>98%</td> <td>91%</td> <td>76%</td> </tr> <tr> <td>0.03</td> <td>99%</td> <td>94%</td> <td>83%</td> <td>100%</td> <td>98%</td> <td>94%</td> </tr> <tr> <td>0.04</td> <td>100%</td> <td>98%</td> <td>94%</td> <td>100%</td> <td>100%</td> <td>99%</td> </tr> <tr> <td>0.05</td> <td>100%</td> <td>100%</td> <td>98%</td> <td>100%</td> <td>100%</td> <td>100%</td> </tr> <tr> <td>0.06</td> <td>100%</td> <td>100%</td> <td>99%</td> <td>100%</td> <td>100%</td> <td>100%</td> </tr> </tbody> </table>	AE rate	N=225 (150 on active)			N=300 (200 on active)			Probability* of detecting			Probability* of detecting			at least 1 event	at least 2 events	at least 3 events	at least 1 event	at least 2 events	at least 3 events	0.01	78%	44%	19%	87%	60%	32%	0.02	95%	80%	58%	98%	91%	76%	0.03	99%	94%	83%	100%	98%	94%	0.04	100%	98%	94%	100%	100%	99%	0.05	100%	100%	98%	100%	100%	100%	0.06	100%	100%	99%	100%	100%	100%	<table border="1"> <thead> <tr> <th rowspan="3">AE rate</th> <th colspan="3">N=225 (150 on active)</th> <th colspan="3">N=300 (200 on active)</th> </tr> <tr> <th colspan="3">Probability* of detecting</th> <th colspan="3">Probability* of detecting</th> </tr> <tr> <th>at least 1 event</th> <th>at least 2 events</th> <th>at least 3 events</th> <th>at least 1 event</th> <th>at least 2 events</th> <th>at least 3 events</th> </tr> </thead> <tbody> <tr> <td><del>0.01</del></td> <td><del>78%</del></td> <td><del>44%</del></td> <td><del>19%</del></td> <td><del>87%</del></td> <td><del>60%</del></td> <td><del>32%</del></td> </tr> <tr> <td><del>0.02</del></td> <td><del>95%</del></td> <td><del>80%</del></td> <td><del>58%</del></td> <td><del>98%</del></td> <td><del>91%</del></td> <td><del>76%</del></td> </tr> <tr> <td><del>0.03</del></td> <td><del>99%</del></td> <td><del>94%</del></td> <td><del>83%</del></td> <td><del>100%</del></td> <td><del>98%</del></td> <td><del>94%</del></td> </tr> <tr> <td><del>0.04</del></td> <td><del>100%</del></td> <td><del>98%</del></td> <td><del>94%</del></td> <td><del>100%</del></td> <td><del>100%</del></td> <td><del>99%</del></td> </tr> <tr> <td><del>0.05</del></td> <td><del>100%</del></td> <td><del>100%</del></td> <td><del>98%</del></td> <td><del>100%</del></td> <td><del>100%</del></td> <td><del>100%</del></td> </tr> <tr> <td><del>0.06</del></td> <td><del>100%</del></td> <td><del>100%</del></td> <td><del>99%</del></td> <td><del>100%</del></td> <td><del>100%</del></td> <td><del>100%</del></td> </tr> </tbody> </table>	AE rate	N=225 (150 on active)			N=300 (200 on active)			Probability* of detecting			Probability* of detecting			at least 1 event	at least 2 events	at least 3 events	at least 1 event	at least 2 events	at least 3 events	<del>0.01</del>	<del>78%</del>	<del>44%</del>	<del>19%</del>	<del>87%</del>	<del>60%</del>	<del>32%</del>	<del>0.02</del>	<del>95%</del>	<del>80%</del>	<del>58%</del>	<del>98%</del>	<del>91%</del>	<del>76%</del>	<del>0.03</del>	<del>99%</del>	<del>94%</del>	<del>83%</del>	<del>100%</del>	<del>98%</del>	<del>94%</del>	<del>0.04</del>	<del>100%</del>	<del>98%</del>	<del>94%</del>	<del>100%</del>	<del>100%</del>	<del>99%</del>	<del>0.05</del>	<del>100%</del>	<del>100%</del>	<del>98%</del>	<del>100%</del>	<del>100%</del>	<del>100%</del>	<del>0.06</del>	<del>100%</del>	<del>100%</del>	<del>99%</del>	<del>100%</del>	<del>100%</del>	<del>100%</del>	
AE rate		N=225 (150 on active)			N=300 (200 on active)																																																																																																																							
		Probability* of detecting			Probability* of detecting																																																																																																																							
	at least 1 event	at least 2 events	at least 3 events	at least 1 event	at least 2 events	at least 3 events																																																																																																																						
0.01	78%	44%	19%	87%	60%	32%																																																																																																																						
0.02	95%	80%	58%	98%	91%	76%																																																																																																																						
0.03	99%	94%	83%	100%	98%	94%																																																																																																																						
0.04	100%	98%	94%	100%	100%	99%																																																																																																																						
0.05	100%	100%	98%	100%	100%	100%																																																																																																																						
0.06	100%	100%	99%	100%	100%	100%																																																																																																																						
AE rate	N=225 (150 on active)			N=300 (200 on active)																																																																																																																								
	Probability* of detecting			Probability* of detecting																																																																																																																								
	at least 1 event	at least 2 events	at least 3 events	at least 1 event	at least 2 events	at least 3 events																																																																																																																						
<del>0.01</del>	<del>78%</del>	<del>44%</del>	<del>19%</del>	<del>87%</del>	<del>60%</del>	<del>32%</del>																																																																																																																						
<del>0.02</del>	<del>95%</del>	<del>80%</del>	<del>58%</del>	<del>98%</del>	<del>91%</del>	<del>76%</del>																																																																																																																						
<del>0.03</del>	<del>99%</del>	<del>94%</del>	<del>83%</del>	<del>100%</del>	<del>98%</del>	<del>94%</del>																																																																																																																						
<del>0.04</del>	<del>100%</del>	<del>98%</del>	<del>94%</del>	<del>100%</del>	<del>100%</del>	<del>99%</del>																																																																																																																						
<del>0.05</del>	<del>100%</del>	<del>100%</del>	<del>98%</del>	<del>100%</del>	<del>100%</del>	<del>100%</del>																																																																																																																						
<del>0.06</del>	<del>100%</del>	<del>100%</del>	<del>99%</del>	<del>100%</del>	<del>100%</del>	<del>100%</del>																																																																																																																						
<p>The subgroup analysis will not be powered to detect small differences in the safety profile between the active and placebo arms. However, with 300 participants in the subgroup, the trial has 94% power to detect a difference when the AE rate in the active arm is 20% and the AE rate in the placebo arm is 5%.</p>	<p><del>The subgroup analysis will not be powered to detect small differences in the safety profile between the active and placebo arms. However, with 300 participants in the subgroup, the trial has 94% power to detect a difference when the AE rate in the active arm is 20% and the AE rate in the placebo arm is 5%.</del></p> <p><b><u>9.6 Interim Analysis</u></b></p> <p><b><u>Regular safety reviews will be conducted by the Data and Safety Monitoring Board (DSMB) at predetermined intervals during the trial (refer to Section 9.7). A single interim efficacy analysis is planned when 50% of the required events have occurred (i.e. 40 HIV-1 seroconversions in either treatment group). The interim analysis will be performed by an independent statistician that is otherwise not involved in the trial and will include descriptive statistics of baseline variables, safety data (i.e., AEs), and STI and HIV incidence. To maintain the proposed Type I error rate (<math>\alpha = 0.05</math>), which will be inflated due to multiple testing of the efficacy hypothesis, the interim and</u></b></p>																																																																																																																											

~~Strikethrough~~ text is deleted text  
Underlined text is new text

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
	<p><u>final analyses will be adjusted using a Lan-DeMets spending function with O'Brien-Fleming grouped sequential stopping boundary<sup>14, 15</sup>.</u></p> <p><u>In addition, the DSMB may recommend early termination of the trial on the basis of: 1) safety concerns, or 2) demonstrating futility:</u></p> <p><u>1) Safety concern – an increased risk of safety outcomes in the dapivirine ring arm as compared to the placebo ring arm.</u></p> <p><u>2) Demonstrating futility – evidence that the trial is highly unlikely to show that the new intervention is superior, given current evidence and the added information that would become available if the trial continued.</u></p> <p><u>A separate SAP will be drafted after the protocol is finalised. This plan will provide specific details about:</u></p> <p><u>1) the parameterisation of variables,</u></p> <p><u>2) the statistical assumptions required,</u></p> <p><u>3) the statistical methods to be employed,</u></p> <p><u>4) specifications of the stopping boundaries used in the interim analysis, and</u></p> <p><u>5) the Type I error at the interim look.</u></p> <p><u>The Sponsor will review and approve the SAP before any analyses are undertaken.</u></p>	
<p>SECTION 9.6 Data Safety Monitoring Board (DSMB)</p> <p>An independent DSMB will be established. The DSMB will meet via conference call at predetermined intervals during the trial; ad hoc calls may be convened if requested by the DSMB or IPM. DSMB members will include individuals not associated with this trial, but who have expertise in conducting clinical trials, experience working in developing countries, and/or a history of working in the microbicide arena. Prior to each DSMB meeting, the data management group will prepare a summary report of all AEs and SAEs for the DSMB to assess safety. The DSMB has the option to recommend pausing or stopping the trial at any point, if warranted, based on AEs observed during the trial, or other safety concerns identified during the course of the trial. DSMB members will remain blinded to the treatment groups unless it is necessary to unblind an individual or stop the trial for safety reasons.</p> <p>A separate DSMB charter will describe the DSMB composition and its charges</p>	<p>Section <u>9.7</u> Data <u>and</u> Safety Monitoring Board (DSMB)</p> <p>An independent DSMB will be established. The DSMB will meet via conference call at predetermined intervals during the trial; <i>ad hoc</i> calls <u>or face-to-face meetings</u> may be convened if requested by the DSMB or IPM. DSMB members will include individuals not associated with this trial, but who have expertise in conducting clinical trials, experience working in developing countries, and/or a history of working in the microbicide arena. Prior to each DSMB meeting, the data management group will prepare a summary report of all AEs and SAEs for the DSMB to assess safety. The DSMB has the option to recommend pausing or stopping the trial at any point, if warranted, based on AEs observed during the trial, or other safety concerns identified during the course of the trial. DSMB members will remain blinded to the treatment groups unless it is necessary to unblind an individual or stop the trial for safety reasons.</p> <p>A separate DSMB charter will describe the DSMB composition and its charges</p>	<p>The sentence describing DSMB meetings was revised to indicate that face-to-face meetings might also be held.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<p>related to the trial.</p> <p>This trial will be conducted under US Food &amp; Drug Administration IND regulations (21 CFR Part 312), and in accordance with the ethical principles of the World Medical Association Declaration of Helsinki, the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the U.S. Code of Federal Regulations (CFR) Title 21 and applicable local regulatory requirements.</p>	<p>related to the trial.</p> <p>This trial will be conducted under US Food &amp; Drug Administration IND regulations (21 CFR Part 312), and in accordance with the ethical principles of the World Medical Association Declaration of Helsinki, the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the U.S. Code of Federal Regulations (CFR) Title 21 and applicable local regulatory requirements.</p>	
<p>SECTION 10.1 Trial Initiation</p> <p>The trial can be initiated at the research centre once all relevant IRB/IEC and regulatory approvals have been obtained as per country requirements and IP shipment has been authorised by the Sponsor. Following Sponsor approval, IPM will notify the research centre in writing via letter correspondence to begin trial operations according to the protocol.</p>	<p>SECTION 10.1 Trial Initiation</p> <p>The trial can be initiated at the research centre once all relevant IRB/IEC and regulatory approvals have been obtained as per country requirements, <u>and all essential documents are available on file</u> and IP shipment has been authorised by the Sponsor. Following Sponsor approval, IPM will notify the research centre in writing via letter correspondence to begin trial operations according to the protocol.</p>	<p>Reference to essential documents was made as per ICH GCP 8.2 (which includes shipping records for IP and trial-related materials).</p>
<p>SECTION 10.5 Disclosure of Data</p> <p>Participant medical information is confidential and disclosure to third parties other than those described in Section 10.3 is strictly prohibited. All trial data will be stored securely at the trial research centre. All participant information including laboratory reports, forms, lists, logbooks, appointment books and administrative forms will be stored in locked file cabinets in areas with access limited to trial staff.</p> <p>Participants' trial information will not be released without written permission of the participant, except as necessary for monitoring by the Sponsor, Sponsor's designated monitors, or regulatory authorities.</p>	<p>SECTION 10.5 Disclosure of Data</p> <p>Participant medical information is confidential and disclosure to third parties other than those described in Section 10.3 is strictly prohibited. All trial data will be stored securely at the trial research centre. All participant information including laboratory reports, forms, lists, logbooks, appointment books and administrative forms will be stored in locked file cabinets <u>or rooms</u> in areas with access limited to trial staff.</p> <p>Participants' trial information will not be released without written permission of the participant, except as necessary for monitoring by the Sponsor, Sponsor's designated monitors, <del>or</del> regulatory authorities, <u>or local IRBs/IECs</u>.</p>	<p>The section was updated to ensure consistency between the protocol and the Participant Information Sheet that will be used for this clinical trial.</p>
<p>SECTION 11.1 Ethical Review</p> <p>This protocol, research centre-specific informed consent forms, 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.</p> <p>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 the ethical principles of:</p> <ul style="list-style-type: none"> <li>World Medical Association Declaration of Helsinki<sup>13</sup></li> </ul>	<p>SECTION 11.1 Ethical Review</p> <p>This protocol, research centre-specific informed consent <u>documents</u>, 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.</p> <p>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 the ethical principles of:</p> <ul style="list-style-type: none"> <li>World Medical Association Declaration of Helsinki<sup>13</sup></li> </ul>	<p>Typographical error corrected.</p>

OLD TEXT (Final Protocol Version 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 1.0)	MOTIVATION FOR CHANGE
<ul style="list-style-type: none"> <li>• ICH GCP guidelines<sup>14</sup></li> <li>• Applicable national ethics and regulatory requirements in countries where the trial is being conducted, e.g. <i>Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa</i><sup>15</sup>.</li> </ul>	<ul style="list-style-type: none"> <li>• ICH GCP guidelines<sup>14</sup></li> <li>• Applicable national ethics and regulatory requirements in countries where the trial is being conducted, e.g. <i>Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa</i><sup>15</sup>.</li> </ul>	

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>PROTOCOL SYNOPSIS</p> <p>METHODS</p> <p><u>Screening and enrolment:</u> Potential participants who consent will be invited to screen for the trial. At screening 1, these potential participants will provide information on inclusion and exclusion criteria, including locator and menses information, demographic information, 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 condoms), contraceptive counselling and HIV pre- and post-test counselling, and tested for pregnancy, HIV, STIs and cervical cytology, as well as safety laboratory assessments. At screening 2, further information will be collected on medical history, concomitant medication, locator and menses information. Those women who meet specified inclusion criteria and no exclusion criteria, have a normal pelvic examination, negative pregnancy and HIV rapid tests, and consent to participate in the trial, will be invited to enrol in the trial. Eligible women will be randomly assigned in a 2:1 ratio to one of the two trial arms. At enrolment, each participant will receive a baseline behavioural questionnaire and a diary card to record sexual activity and ring experiences over the upcoming 4-week period. Blood samples will be collected for storage, and will be tested retrospectively for HIV-RNA PCR, HIV viral genotyping and HSV-2 serology subsequent to HIV-1 seroconversion. In addition, vaginal specimens will be taken prior to ring insertion to determine vaginal pH and assess vaginal flora.</p> <p>At enrolment, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled visit.</p> <p><u>Trial visits:</u> Dapivirine or placebo vaginal rings will be inserted at 4-weekly intervals for the duration of the IP use trial period. Similar to the enrolment visit, at each regularly scheduled trial visit while on the IP, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled visit. All participants will receive pre- and post-test HIV counselling, HIV/STI risk reduction counselling, condom and vaginal ring adherence counselling, HIV and pregnancy testing, and collection of locator, menses, and concomitant medication information. Male condoms will be provided at all visits as part of HIV/STI risk reduction counselling. Contraceptive counselling will be provided at all visits.</p> <p>Blood and vaginal fluid samples will be collected for storage at all visits, including the last product use visit. These stored blood samples will be tested for HIV-RNA</p>	<p>PROTOCOL SYNOPSIS</p> <p>METHODS</p> <p><u>Screening and enrolment:</u> Potential participants who consent will be invited to screen for the trial. At screening 1, these potential participants will provide information on inclusion and exclusion criteria, including locator and menses information, demographic information, 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 condoms), contraceptive counselling and HIV pre- and post-test counselling, and tested for pregnancy, HIV, STIs and cervical cytology, as well as safety laboratory assessments. At screening 2, further information will be collected on medical history, concomitant medication, locator and menses information. Those women who meet specified inclusion criteria and no exclusion criteria, have a normal pelvic examination, negative pregnancy and HIV rapid tests, and consent to participate in the trial, will be invited to enrol in the trial. Eligible women will be randomly assigned in a 2:1 ratio to one of the two trial arms. At enrolment, each participant will receive a baseline behavioural questionnaire and a diary card to record sexual activity and ring experiences over the upcoming 4-week period. Blood samples will be collected for storage, and will be tested retrospectively for HIV-RNA PCR, HIV viral genotyping and HSV-2 serology subsequent to <b>confirmed</b> HIV-1 seroconversion. In addition, vaginal specimens will be taken prior to ring insertion to determine vaginal pH and assess vaginal flora.</p> <p>At enrolment, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled visit.</p> <p><u>Trial visits:</u> Dapivirine or placebo vaginal rings will be inserted at 4-weekly intervals for the duration of the IP use trial period. Similar to the enrolment visit, at each regularly scheduled trial visit while on the IP, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled visit. All participants will receive pre- and post-test HIV counselling, HIV/STI risk reduction counselling, condom and vaginal ring adherence counselling, HIV and pregnancy testing, and collection of locator, menses, and concomitant medication information. Male condoms will be provided at all visits as part of HIV/STI risk reduction counselling. Contraceptive counselling will be provided at all visits.</p> <p>Blood and vaginal fluid samples will be collected for storage at all visits, including the last product use visit. These stored blood samples will be tested for HIV-RNA</p>	<p>Text was added to clarify that retrospective testing for HIV-RNA PCR, HIV viral genotyping and HSV-2 serology will only be performed for participants who are confirmed to have been infected with HIV.</p> <p>The window for individual qualitative interviews was extended from 36 weeks after trial initiation to 42 weeks after research centre activation, as recruitment is slower than initially anticipated.</p>



OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>PCR and viral genotyping only in HIV-1 seroconverters, while HSV-2 serology, blood and vaginal fluid dapivirine concentration measurement will be conducted in confirmed HIV-1 seroconverters and a randomly selected control group of HIV-negative participants.</p> <p>The rapid and confirmatory laboratory tests used in the HIV testing algorithm will be able to detect both subtypes, HIV-1 and HIV-2.</p> <p>At the point of HIV seroconversion, the IP will be discontinued, and additional samples will be collected and tested for viral genotyping (blood), dapivirine concentrations (blood and vaginal fluid) and HSV-2 serology (blood). In addition, blood samples for viral genotyping will also be collected at the scheduled exit visit, approximately 6 weeks following seroconversion. No further storage samples will be collected in these participants.</p> <p>Adherence assessments will be conducted through an interviewer-administered questionnaire at all 4-weekly trial visits, except the exit visit. Participants will be provided with diary cards at all 4-weekly visits except the last product use and exit visits. The participant may consult the diary card during the adherence assessments and the adherence counselling sessions at each 4-weekly visit. The cards will be collected at each visit. Acceptability questionnaires will be administered at the second trial visit (week 4), and at 24-weekly intervals thereafter, until the last product use visit.</p> <p>Twenty-four (24) to 36 weeks after trial initiation, each research centre will conduct 6 – 10 qualitative individual interviews with participants, and 6 – 10 qualitative individual interviews with male partners. These interviews will provide data on acceptability, sexual behaviour and adherence issues. The recruitment and sampling strategy will be specified in the Statistical Analysis Plan (SAP).</p> <p>AEs will be assessed at all visits post-randomisation. In addition, safety laboratory assessments, pelvic examination, vaginal pH and vaginal flora as well as STI tests will be performed at 12-weekly intervals. Cervical cytology will be repeated at the end of the first and second year of IP use. Residual dapivirine levels in returned rings will be measured for a selected group of participants at predetermined time-points.</p>	<p>PCR and viral genotyping only in HIV-1 seroconverters, while HSV-2 serology, blood and vaginal fluid dapivirine concentration measurement will be conducted in confirmed HIV-1 seroconverters and a randomly selected control group of HIV-negative participants.</p> <p>The rapid and confirmatory laboratory tests used in the HIV testing algorithm will be able to detect both subtypes, HIV-1 and HIV-2.</p> <p>At the point of HIV seroconversion, the IP will be discontinued, and additional samples will be collected and tested for viral genotyping (blood), dapivirine concentrations (blood and vaginal fluid) and HSV-2 serology (blood). In addition, blood samples for viral genotyping will also be collected at the scheduled exit visit, approximately 6 weeks following seroconversion. No further storage samples will be collected in these participants.</p> <p>Adherence assessments will be conducted through an interviewer-administered questionnaire at all 4-weekly trial visits, except the exit visit. Participants will be provided with diary cards at all 4-weekly visits except the last product use and exit visits. The participant may consult the diary card during the adherence assessments and the adherence counselling sessions at each 4-weekly visit. The cards will be collected at each visit. Acceptability questionnaires will be administered at the second trial visit (week 4), and at 24-weekly intervals thereafter, until the last product use visit.</p> <p>Twenty-four (24) to <u>42</u> weeks after <b>research centre activation</b>, each research centre will conduct 6 – 10 qualitative individual interviews with participants, and 6 – 10 qualitative individual interviews with male partners. These interviews will provide data on acceptability, sexual behaviour and adherence issues. The recruitment and sampling strategy will be specified in the Statistical Analysis Plan (SAP).</p> <p>AEs will be assessed at all visits post-randomisation. In addition, safety laboratory assessments, pelvic examination, vaginal pH and vaginal flora as well as STI tests will be performed at 12-weekly intervals. Cervical cytology will be repeated at the end of the first and second year of IP use. Residual dapivirine levels in returned rings will be measured for a selected group of participants at predetermined time-points.</p>	
<p>SECTION 3.1 Trial Design</p> <p><b><u>Trial visits (during investigational product use)</u></b> Dapivirine or placebo vaginal rings, according to the allocated randomisation group, will be inserted at 4-weekly intervals for the duration of the IP use period.</p>	<p>SECTION 3.1 Trial Design</p> <p><b><u>Trial visits (during investigational product use)</u></b> Dapivirine or placebo vaginal rings, according to the allocated randomisation group, will be inserted at 4-weekly intervals for the duration of the IP use period.</p>	<p>The window for individual qualitative interviews was extended from 36 weeks after trial</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>Similar to enrolment, at each regularly scheduled trial visit while on the IP, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled trial visit. All participants will receive pre- and post-test HIV counselling, HIV/STI risk reduction counselling, condom and vaginal ring adherence counselling, HIV and pregnancy testing, and collection of locator, menses, and concomitant medication information. Male condoms will be provided at all visits as part of HIV/STI risk reduction counselling. Contraceptive counselling will be provided at all visits. Blood samples and vaginal fluid samples will be collected for storage at all visits. These stored blood samples will be tested for HIV-RNA PCR and viral genotyping only in HIV-1 seroconverters, while HSV-2 serology, blood and vaginal fluid dapivirine concentration measurement will be conducted in these seroconverters and a randomly selected control group of HIV-negative participants.</p> <p>The rapid and confirmatory laboratory tests used in the HIV testing algorithm will detect both subtypes, HIV-1 and HIV-2. At the point of HIV seroconversion, the IP will be discontinued, and additional samples will be collected and tested for viral genotyping (blood), dapivirine concentrations (blood and vaginal fluid) and HSV-2 serology (blood). In addition, blood samples for viral genotyping will also be collected at the scheduled exit visit approximately 6 weeks following seroconversion. No further storage samples will be taken in these participants.</p> <p>Adherence assessments will be conducted through an interviewer-administered questionnaire at all 4-weekly trial visits, except the exit visit. Participants will be provided with a diary card at each 4-weekly visit except the last product use and exit visits. The diary card will be self-administered, and record the participant's sexual activity and ring use during the 4-week period. The diary card is meant to be completed daily by the participant, and returned to the research centre at each 4-weekly visit, to serve as a memory aid for participants to review during adherence counselling, and the adherence questionnaires. Acceptability questionnaires will be administered at the second trial visit (week 4), and 24-weekly intervals from week 24 thereafter, until the last product use visit.</p> <p>Twenty-four (24) to 36 weeks after trial initiation, each research centre will conduct 6 – 10 qualitative individual interviews with participants, and 6 – 10 qualitative individual interviews with male partners. These interviews will provide data on acceptability, sexual behaviour and adherence issues. The recruitment and sampling strategy will be specified in the SAP.</p> <p>AEs will be assessed at all visits post-randomisation. In addition, safety laboratory assessments, pelvic examination, vaginal pH and vaginal flora as well as STI tests will be performed at 12-weekly intervals. Cervical cytology will be repeated at the</p>	<p>Similar to enrolment, at each regularly scheduled trial visit while on the IP, each participant will be instructed to self-insert a newly-dispensed vaginal ring, which will be removed at the next scheduled trial visit. All participants will receive pre- and post-test HIV counselling, HIV/STI risk reduction counselling, condom and vaginal ring adherence counselling, HIV and pregnancy testing, and collection of locator, menses, and concomitant medication information. Male condoms will be provided at all visits as part of HIV/STI risk reduction counselling. Contraceptive counselling will be provided at all visits. Blood samples and vaginal fluid samples will be collected for storage at all visits. These stored blood samples will be tested for HIV-RNA PCR and viral genotyping only in HIV-1 seroconverters, while HSV-2 serology, blood and vaginal fluid dapivirine concentration measurement will be conducted in these seroconverters and a randomly selected control group of HIV-negative participants.</p> <p>The rapid and confirmatory laboratory tests used in the HIV testing algorithm will detect both subtypes, HIV-1 and HIV-2. At the point of HIV seroconversion, the IP will be discontinued, and additional samples will be collected and tested for viral genotyping (blood), dapivirine concentrations (blood and vaginal fluid) and HSV-2 serology (blood). In addition, blood samples for viral genotyping will also be collected at the scheduled exit visit approximately 6 weeks following seroconversion. No further storage samples will be taken in these participants.</p> <p>Adherence assessments will be conducted through an interviewer-administered questionnaire at all 4-weekly trial visits, except the exit visit. Participants will be provided with a diary card at each 4-weekly visit except the last product use and exit visits. The diary card will be self-administered, and record the participant's sexual activity and ring use during the 4-week period. The diary card is meant to be completed daily by the participant, and returned to the research centre at each 4-weekly visit, to serve as a memory aid for participants to review during adherence counselling, and the adherence questionnaires. Acceptability questionnaires will be administered at the second trial visit (week 4), and 24-weekly intervals from week 24 thereafter, until the last product use visit.</p> <p>Twenty-four (24) to <u>42</u> weeks after <u>research centre activation</u>, each research centre will conduct 6 – 10 qualitative individual interviews with participants, and 6 – 10 qualitative individual interviews with male partners. These interviews will provide data on acceptability, sexual behaviour and adherence issues. The recruitment and sampling strategy will be specified in the SAP.</p> <p>AEs will be assessed at all visits post-randomisation. In addition, safety laboratory assessments, pelvic examination, vaginal pH and vaginal flora as well as STI tests will be performed at 12-weekly intervals. Cervical cytology will be repeated at the</p>	<p>initiation to 42 weeks after research centre activation, as recruitment is slower than initially anticipated.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
end of the first and second year of IP use. Residual dapivirine levels in returned rings will be measured for a selected group of participants at pre-determined time-points.	end of the first and second year of IP use. Residual dapivirine levels in returned rings will be measured for a selected group of participants at pre-determined time-points.	
<p>SECTION 3.3.2 Exclusion Criteria</p> <p>Women who have any of the exclusion criteria below are not eligible:</p> <ol style="list-style-type: none"> <li>1. Currently pregnant or last pregnancy within 3 months prior to screening or intends to become pregnant during trial participation;</li> <li>2. Currently breast-feeding;</li> <li>3. Non-therapeutic injection drug use in the 12 months prior to screening;</li> <li>4. Participated in another research trial using drugs, medical devices, microbicides or oral pre-exposure prophylaxis agents within 60 days prior to screening;</li> <li>5. Previously participated or currently participating in any HIV vaccine trial;</li> <li>6. Untreated, clinically significant urogenital infections, e.g., urinary tract, or other sexually transmitted infections, or other gynaecological symptoms within 1 week prior to enrolment;</li> <li>7. Has a Grade 2 or higher pelvic examination finding, according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; Addendum 1 Female Genital Grading Table for Use in Microbicide Studies;</li> <li>8. History of significant urogenital or uterine prolapse, undiagnosed vaginal bleeding, diagnosed chronic and/or recurrent vulvovaginal candidiasis urethral obstruction, incontinence or urge incontinence;</li> <li>9. Any gynaecological surgery within 90 days prior to screening;</li> <li>10. Any Grade 1 or higher baseline aspartate aminotransferase (AST), alanine transaminase (ALT), or platelet count, and any Grade 2 or higher baseline haematology, chemistry or urinalysis laboratory value according to the according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events;</li> <li>11. Any history of anaphylaxis or severe allergy resulting in angioedema; or a history of sensitivity/allergy to latex or a silicone elastomer;</li> <li>12. Any history of diabetes mellitus and chronic use of oral corticosteroid therapy; and any uncontrolled serious chronic or progressive disease;</li> <li>13. Cervical cytology at screening that requires cryotherapy, biopsy or treatment (other than for infection). Women with Grade 1 cervical cytology findings can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology);</li> <li>14. Any condition(s) that, in the opinion of the investigator, might put the</li> </ol>	<p>SECTION 3.3.2 Exclusion Criteria</p> <p>Women who have any of the exclusion criteria below are not eligible:</p> <ol style="list-style-type: none"> <li>1. Currently pregnant or last pregnancy within 3 months prior to screening or intends to become pregnant during trial participation;</li> <li>2. Currently breast-feeding;</li> <li>3. Non-therapeutic injection drug use in the 12 months prior to screening;</li> <li>4. Participated in another research trial using drugs, medical devices, microbicides or oral pre-exposure prophylaxis agents within 60 days prior to screening;</li> <li>5. Previously participated or currently participating in any HIV vaccine trial;</li> <li>6. Untreated, clinically significant urogenital infections, e.g., urinary tract, or other sexually transmitted infections, or other gynaecological symptoms within 1 week prior to enrolment;</li> <li>7. Has a Grade 2 or higher pelvic examination finding, according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; Addendum 1 Female Genital Grading Table for Use in Microbicide Studies;</li> <li>8. History of significant urogenital or uterine prolapse, undiagnosed vaginal bleeding, diagnosed chronic and/or recurrent vulvovaginal candidiasis urethral obstruction, incontinence or urge incontinence;</li> <li>9. Any gynaecological surgery within 90 days prior to screening;</li> <li>10. Any Grade 1 or higher baseline aspartate aminotransferase (AST), alanine transaminase (ALT), or platelet count, and any Grade 2 or higher baseline haematology, chemistry or urinalysis laboratory value according to the <del>according to the</del> Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events;</li> <li>11. Any history of anaphylaxis or severe allergy resulting in angioedema; or a history of sensitivity/allergy to latex or a silicone elastomer;</li> <li>12. Any history of diabetes mellitus and chronic use of oral corticosteroid therapy; and any uncontrolled serious chronic or progressive disease;</li> <li>13. Cervical cytology at screening that requires cryotherapy, biopsy or treatment (other than for infection). Women with Grade 1 cervical cytology findings can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology);</li> <li>14. Any condition(s) that, in the opinion of the investigator, might put the</li> </ol>	<p>Typographical error corrected.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>participant at risk, or interfere with the trial objectives or the participant's adherence to trial requirements.</p>	<p>participant at risk, or interfere with the trial objectives or the participant's adherence to trial requirements.</p>	
<p>SECTION 4.3.1 4-Weekly Trial Visits (Weeks 4 to 100)</p> <p><b>(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 <math>\pm 7</math> days. Although the visit window is <math>\pm 7</math> days, consecutive visits should be no less than 21 days and no more than 35 days apart).</b></p> <p><b>NOTE:</b> Additional procedures for participants who test HIV-positive are described in Section 5.3 of the protocol.</p> <ul style="list-style-type: none"> <li>a. Update locator and menses information as necessary.</li> <li>b. Obtain and record any AEs and concomitant medications since the last visit.</li> <li>c. Collect and review the diary card and provide a new diary card. Administer the adherence questionnaire.</li> <li>d. Provide adherence counselling, including contraceptive adherence, adherence to trial visit schedule and requirements and vaginal ring adherence. (Refer to Sections 5.4 and 5.13). Participants will be instructed to keep the ring inserted for a period of 28 consecutive days (4 weeks). 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. Adherence counselling will include further details on actions that should be taken in the event of expulsion or removal.</li> <li>e. Administer the acceptability questionnaire <b>(NOTE: ONLY at the second trial visit (week 4) after enrolment, and at 24-weekly intervals thereafter, starting at week 24 until the last product use visit).</b></li> <li>f. Provide HIV/STI risk reduction counselling; including provision of male condoms (Refer to Section 5.2.2).</li> <li>g. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).</li> <li>h. Perform HIV rapid testing as detailed in Section 5.3. (Additional procedures for participants who test HIV-positive are also described in Section 5.3 of the protocol).</li> <li>i. Perform urine pregnancy testing.</li> </ul>	<p>SECTION 4.3.1 4-Weekly Trial Visits (Weeks 4 to 100)</p> <p><b>(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 <math>\pm 7</math> days. Although the visit window is <math>\pm 7</math> days, consecutive visits should be no less than 21 days and no more than 35 days apart).</b></p> <p><b>NOTE:</b> Additional procedures for participants who test HIV-positive are described in Section 5.3 of the protocol.</p> <ul style="list-style-type: none"> <li>a. Update locator and menses information as necessary.</li> <li>b. Obtain and record any AEs and concomitant medications since the last visit.</li> <li>c. Collect and review the diary card and provide a new diary card. Administer the adherence questionnaire.</li> <li>d. Provide adherence counselling, including contraceptive adherence, adherence to trial visit schedule and requirements and vaginal ring adherence. (Refer to Sections 5.4 and 5.13). Participants will be instructed to keep the ring inserted for a period of 28 consecutive days (4 weeks). 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. Adherence counselling will include further details on actions that should be taken in the event of expulsion or removal.</li> <li>e. Administer the acceptability questionnaire <b>(NOTE: ONLY at the second trial visit (week 4) after enrolment, and at 24-weekly intervals thereafter, starting at week 24 until the last product use visit).</b></li> <li>f. Provide HIV/STI risk reduction counselling; including provision of male condoms (Refer to Section 5.2.2).</li> <li>g. Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).</li> <li>h. Perform HIV rapid testing as detailed in Section 5.3. (Additional procedures for participants who test HIV-positive are also described in Section 5.3 of the protocol).</li> <li>i. Perform urine pregnancy testing.</li> </ul>	<p>The text specifying the timing of the blood and vaginal fluid samples for measurement of dapivirine concentrations was revised. Although it is preferable to collect the sample before ring removal, it might be difficult for some participants to undergo two speculum insertions during one visit, in which case the research centre staff may collect the vaginal fluid sample after ring removal. In addition, participants may have removed the ring prior to their visit, in which case the ring will not be in place at the time of sample collection. As these PK samples will mainly be used as measure of adherence to ring use, collection of these samples after ring removal will not greatly impact the interpretation of the data.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>j. Collect blood specimens by venipuncture for storage (Blood volume specified in Appendix D).</p> <p>k. Instruct the participant to remove the vaginal ring. Perform IP accountability.</p> <p>l. Collect vaginal fluid samples for storage (Refer to Section 5.15). <b>NOTE:</b> For dapivirine concentration measurements, blood and vaginal fluid samples must be collected prior to removal of the vaginal ring.</p> <p>m. Dispense a new vaginal ring and instruct participant to self-insert the new ring.</p> <p>n. Perform brief digital examination to ensure the ring is properly placed (Refer to Section 5.12).</p> <p>o. Schedule the next visit.</p>	<p>j. Collect blood specimens by venipuncture for storage (Blood volume specified in Appendix D).</p> <p>k. Instruct the participant to remove the vaginal ring. Perform IP accountability.</p> <p>l. Collect vaginal fluid samples for storage (Refer to Section 5.15). <b>NOTE:</b> For dapivirine concentration measurements, blood and vaginal fluid samples <u>should preferably</u> be collected prior to removal of the vaginal ring.</p> <p>m. Dispense a new vaginal ring and instruct participant to self-insert the new ring.</p> <p>n. Perform brief digital examination to ensure the ring is properly placed (Refer to Section 5.12).</p> <p>o. Schedule the next visit.</p>	
<p>SECTION 4.3.3 24-Weekly Trial Visits (Weeks 24, 48, 72 and 96)</p> <p><b>(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of <math>\pm 7</math> days. Although the visit window is <math>\pm 7</math> days, consecutive visits should be no less than 21 days and no more than 35 days apart).</b></p> <p><b>NOTE:</b> Participants will 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.</p> <p>a. Complete all 4-weekly and 12-weekly trial visit procedures as detailed above.</p> <p>b. Administer the acceptability questionnaire.</p> <p>c. Invite 6 – 10 participants to participate in an individual interview to be held at each research centre during weeks 24 – 36.</p> <p>d. Request permission from participants that have completed week 24 to recruit their male partner for an individual interview until 6 – 10 male partner interviews have been conducted at each research centre.</p>	<p>SECTION 4.3.3 24-Weekly Trial Visits (Weeks 24, 48, 72 and 96)</p> <p><b>(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of <math>\pm 7</math> days. Although the visit window is <math>\pm 7</math> days, consecutive visits should be no less than 21 days and no more than 35 days apart).</b></p> <p><b>NOTE:</b> Participants will 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.</p> <p>a. Complete all 4-weekly and 12-weekly trial visit procedures as detailed above.</p> <p>b. Administer the acceptability questionnaire.</p> <p>c. Invite 6 – 10 participants to participate in an individual interview to be held at each research centre during weeks 24 – <u>42</u>.</p> <p>d. Request permission from participants that have completed week 24 to recruit their male partner for an individual interview until 6 – 10 male partner interviews have been conducted at each research centre.</p>	<p>The window for individual qualitative interviews was extended from 36 weeks after trial initiation to 42 weeks after research centre activation, as recruitment is slower than initially anticipated.</p>
<p>SECTION 4.3.5 Last Product Use Visit (Week 104 or Early Discontinuation)</p> <p><b>(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of <math>\pm 7</math> days. Although the visit window is <math>\pm 7</math> days, consecutive visits should be no less than 21 days and</b></p>	<p>SECTION 4.3.5 Last Product Use Visit (Week 104 or Early Discontinuation)</p> <p><b>(All visit dates will be calculated from the enrolment visit as baseline date. Each scheduled visit has a window period of <math>\pm 7</math> days. Although the visit window is <math>\pm 7</math> days, consecutive visits should be no less than 21 days and</b></p>	<p>Text was added to clarify that the procedures scheduled for the last product use visit should be performed when two</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>no more than 35 days apart).</p> <p><b>NOTE:</b> <i>These trial procedures will also apply at the point of HIV seroconversion, and the visit will be considered the last product use visit for the participant.</i></p> <ol style="list-style-type: none"> <li>Update locator and menses information as necessary.</li> <li>Obtain and record any AEs and concomitant medications since the last visit.</li> <li>Collect the diary card.</li> <li>Administer the adherence questionnaire.</li> <li>Administer the acceptability questionnaire.</li> <li>Provide HIV/STI risk-reduction counselling (including dispensing of condoms) and contraceptive counselling (Refer to Sections 5.2.2 and 5.4).</li> <li>Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).</li> <li>Perform HIV rapid testing as detailed in section 5.3. (Additional procedures for participants who test HIV-positive are also described in Section 5.3 of the protocol)</li> <li>Perform pregnancy testing and urinalysis dipstick testing (microscopy only if indicated).</li> <li>Collect blood specimen by venipuncture for syphilis testing (RPR) and safety laboratory tests (haematology and chemistry). Blood volume is specified in Appendix D.</li> <li>Collect blood specimen by venipuncture for sample storage (Blood volume specified in Appendix D).</li> <li>Perform physical examination.</li> <li>Collect vaginal fluid sample for storage. <b>NOTE:</b> <i>For dapivirine concentration measurements, blood and vaginal fluid samples must be collected prior to removal of the vaginal ring.</i></li> <li>Instruct the participant to remove the last vaginal ring. Perform IP accountability.</li> <li>Perform pelvic examination (Refer to Section 5.8) and collect specimen for assessment of vaginal flora and vaginal pH, and cervicovaginal swabs for STI testing (Refer to Section 5.10). If pelvic examination indicates abnormal findings, e.g., any symptoms or evidence of genital infections, abrasions, ulcerations, etc., provide or refer for appropriate treatment.</li> <li>Collect a specimen for cervical cytology.</li> <li>Schedule the exit visit.</li> <li>Each research centre will conduct 2 – 3 focus groups with participants who have been recruited for these groups at the last product use visit. Additionally, 6 – 10 individual interviews with male partners will be conducted at each</li> </ol>	<p>no more than 35 days apart).</p> <p><b>NOTE:</b> <i>These trial procedures will also apply <u>when two positive HIV rapid tests or a positive urine pregnancy test is obtained, or when IP is permanently discontinued.</u> The applicable visit will be considered the last product use visit for the participant.</i></p> <ol style="list-style-type: none"> <li>Update locator and menses information as necessary.</li> <li>Obtain and record any AEs and concomitant medications since the last visit.</li> <li>Collect the diary card.</li> <li>Administer the adherence questionnaire.</li> <li>Administer the acceptability questionnaire.</li> <li>Provide HIV/STI risk-reduction counselling (including dispensing of condoms) and contraceptive counselling (Refer to Sections 5.2.2 and 5.4).</li> <li>Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).</li> <li>Perform HIV rapid testing as detailed in section 5.3. (Additional procedures for participants who test HIV-positive are also described in Section 5.3 of the protocol)</li> <li>Perform pregnancy testing and urinalysis dipstick testing (microscopy only if indicated).</li> <li>Collect blood specimen by venipuncture for syphilis testing (RPR) and safety laboratory tests (haematology and chemistry). Blood volume is specified in Appendix D.</li> <li>Collect blood specimen by venipuncture for sample storage (Blood volume specified in Appendix D).</li> <li>Perform physical examination.</li> <li>Collect vaginal fluid sample for storage. <b>NOTE:</b> <i>For dapivirine concentration measurements, blood and vaginal fluid samples <u>should preferably be collected prior to removal of the vaginal ring.</u></i></li> <li>Instruct the participant to remove the last vaginal ring. Perform IP accountability.</li> <li>Perform pelvic examination (Refer to Section 5.8) and collect specimen for assessment of vaginal flora and vaginal pH, and cervicovaginal swabs for STI testing (Refer to Section 5.10). If pelvic examination indicates abnormal findings, e.g., any symptoms or evidence of genital infections, abrasions, ulcerations, etc., provide or refer for appropriate treatment.</li> <li>Collect a specimen for cervical cytology. <b>NOTE:</b> <i>It is not recommended that <u>cervical cytology be repeated within six weeks of a previous sample.</u></i></li> <li>Schedule the exit visit.</li> </ol>	<p>positive HIV rapid tests or a positive urine pregnancy test was obtained, or upon permanent discontinuation of IP.</p> <p>The text specifying the timing of the blood and vaginal fluid samples for measurement of dapivirine concentrations was revised. Although it is preferable to collect the sample before ring removal, it might be difficult for some participants to undergo two speculum insertions during one visit, in which case the research centre staff may collect the vaginal fluid sample after ring removal. In addition, participants may have removed the ring prior to their visit, in which case the ring will not be in place at the time of sample collection. As these PK samples will mainly be used as measure of adherence to ring use, collection of these samples after ring removal will not greatly impact the interpretation of the data.</p> <p>Text was added to</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
research centre.	r. Each research centre will conduct 2 – 3 focus groups with participants who have been recruited for these groups at the last product use visit. Additionally, 6 – 10 individual interviews with male partners will be conducted at each research centre.	clarify that cervical cytology should not be repeated within six weeks of a previous sample, as advised by the central laboratory, due to the risk that inadequate re-epithelialisation of the cervix, if the test is repeated too soon, may produce confounding results.
<p>SECTION 4.4 Exit Visit (6 weeks after the Last Product Use Visit)</p> <p><b>(The scheduled visit has a window period of ± 7 days).</b></p> <p><i>NOTE: 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 5.3 (No further HIV counselling and testing will be done unless indicated for additional confirmatory testing).</i></p> <ol style="list-style-type: none"> <li>Update locator information as necessary.</li> <li>Obtain and record any AEs and concomitant medications since the last visit.</li> <li>Provide final safety and STI laboratory results to participant.</li> <li>Provide HIV/STI risk-reduction counselling; including provision of male condoms (Refer to Section 5.2.2).</li> <li>Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).</li> <li>Perform HIV rapid testing as detailed in Section 5.3.</li> <li>Exit the participant from the trial.</li> </ol>	<p>SECTION 4.4 Exit Visit (6 weeks after the Last Product Use Visit)</p> <p><b>(The scheduled visit has a window period of ± 7 days).</b></p> <p><i><b>NOTE: <u>If the outcome of confirmatory tests is pending, the exit visit may be conducted more than 6 weeks after the last product use visit, but should be performed as soon as possible after the results are available.</u></b> 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 5.3 (No further HIV counselling and testing will be done unless indicated for additional confirmatory testing).</i></p> <ol style="list-style-type: none"> <li>Update locator information as necessary.</li> <li>Obtain and record any AEs and concomitant medications since the last visit.</li> <li>Provide final safety and STI laboratory results to participant.</li> <li>Provide HIV/STI risk-reduction counselling; including provision of male condoms (Refer to Section 5.2.2).</li> <li>Provide HIV pre- and post-test counselling (Refer to Section 5.2.1).</li> <li>Perform HIV rapid testing as detailed in Section 5.3.</li> <li>Exit the participant from the trial.</li> </ol>	Text was added to allow the exit visit to take place more than 6 weeks after the last product use visit, in the case of pending confirmatory test results.
<p>SECTION 4.7 Missed and Late Visits</p> <p>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 clinic 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</p>	<p>SECTION 4.7 Missed and Late Visits</p> <p>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 clinic 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</p>	Text was added to make provision for telephonic contact with the participant when an additional vaginal ring was dispensed, to

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>operating procedure (SOP) and documented in the source documents and applicable CRFs.</p> <p>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 3 by the time the trial window has begun for Visit 4, i.e., within 7 days from Visit 4, Visit 3 will be considered missed. Trial procedures will be performed as scheduled for the current visit (e.g. Visit 4 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.</p> <p>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 be put back on her original visit schedule.</p>	<p>operating procedure (SOP) and documented in the source documents and applicable CRFs.</p> <p>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 3 by the time the trial window has begun for Visit 4, i.e., within 7 days from Visit 4, Visit 3 will be considered missed. Trial procedures will be performed as scheduled for the current visit (e.g. Visit 4 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.</p> <p><b><u>In the event that a participant will be away and unable to attend one of the 4-weekly visits where a new vaginal ring would be inserted, the research centre could dispense an additional ring on a case-by-case basis following discussion by the investigator with the IPM Clinical Project Manager or designee. The participant would then self-insert the new ring on the day that her 4-weekly visit was due to take place. The research centre will contact the participant telephonically, if possible, to remind her to remove the current ring and insert the new ring. The adherence questionnaire will be administered over the telephone and research centre staff will enquire about adverse events and concomitant medication; other information will be collected as appropriate.</u></b></p> <p>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 be put back on her original visit schedule.</p> <p><b><u>If a 12-weekly or 24-weekly visit is missed, safety laboratory assessments and STI testing should be performed at the next visit.</u></b></p>	<p>remind the participant to insert the new ring, and collect adverse event, concomitant medication and adherence information.</p> <p>Provision is made for safety laboratory tests to be conducted at the next clinic visit if a 12- or 24-weekly visit is missed.</p>
<p>SECTION 5.3.3 Trial Visits</p> <p>Both the 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 C) will be applied for all 4-weekly trial visits, including the last product use visit. HIV-testing while the participant is enrolled in the trial will be performed on blood samples obtained by venipuncture (blood volumes specified in Appendix D).</p>	<p>SECTION 5.3.3 Trial Visits</p> <p>Both the 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 C) will be applied for all 4-weekly trial visits, including the last product use visit. HIV-testing while the participant is enrolled in the trial will be performed on blood samples obtained by venipuncture (blood volumes specified in Appendix D).</p>	<p>Text was added to clarify the procedures to be followed by the research centre in the event of reactive HIV rapid tests, and to clarify when it would be appropriate to</p>



OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative and continue using the IP. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2 (done on the same blood sample). If Test 2 is reactive, the participant is considered to have been infected while on the trial, and will be permanently discontinued from the IP. Additional confirmatory testing will be performed by Western Blot or another confirmatory test where appropriate. Additional testing will be performed on stored samples of seroconverters as described in Section 5.15. Nucleic acid-amplification testing (NAAT) by an HIV-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.</p> <p>If Test 2 is non-reactive, the result is discordant and 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 then the participant is considered to be HIV-infected. The IP is stopped immediately and a sample drawn for endpoint confirmation (by Western Blot). Nucleic acid-amplification testing (NAAT) by an HIV-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.</p> <p>If Test 3 is non-reactive, the participant is considered to be probably HIV-negative. The participant will continue on the IP and be requested to return for repeat testing after two weeks. In such cases the research centre will notify the IPM Clinical Physician or designee. If a similar result is obtained on testing after two weeks, the process of repeat testing after 2 weeks may continue for a third cycle.</p> <p>All enrolled participants will, in addition, have blood taken at each trial visit to be stored locally or at a central laboratory, for possible HIV-RNA PCR 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 the PCR test result is negative. This will be done to approximate the period of HIV infection. If the enrolment HIV-RNA PCR test result is positive, the participant is not considered to have been infected while using the IP.</p> <p>Additional blood (blood volume as specified in Appendix D) 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</p>	<p>If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative and continue using the IP. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2 (done on the same blood sample). If Test 2 is reactive, <b><u>IP will be withheld until HIV infection has been confirmed. Trial procedures relevant to the last product use visit 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. If a pelvic examination was performed within the previous 12 weeks, it may be repeated at the investigator's discretion prior to re-introduction of IP. If confirmatory test(s) indicate(s) that the participant is HIV infected, the participant will be permanently discontinued from IP.</u></b></p> <p>Additional testing will be performed on stored samples of seroconverters as described in Section 5.15. Nucleic acid-amplification testing (NAAT) by an HIV-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.</p> <p>If Test 2 is non-reactive, the result is discordant and 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, <b><u>IP will be withheld until HIV infection has been confirmed. Trial procedures relevant to the last product use visit 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. If a pelvic examination was performed within the previous 12 weeks, it may be repeated at the investigator's discretion prior to re-introduction of IP. If confirmatory test(s) indicate(s) that the participant is HIV infected, the participant will be permanently discontinued from IP.</u></b> Nucleic acid-amplification testing (NAAT) by an HIV-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.</p> <p>If Test 3 is non-reactive, the participant is considered to be probably HIV-negative. The participant will continue on the IP and be requested to return for repeat testing</p>	<p>consider re-introduction of investigational product in cases where confirmatory testing indicates negative test results.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>section 5.15.</p> <p>Any participant who is confirmed HIV-positive while on the trial will be discontinued from the IP. Trial procedures relevant to the last product use visit as detailed in Section 4.3.5 will be performed, and an exit visit will be scheduled approximately 6 weeks 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.</p>	<p>after two weeks. In such cases the research centre will notify the IPM Clinical Physician or designee. <b><u>Additional confirmatory tests may be indicated at any stage in consultation with the IPM Clinical Project Manager or designee.</u></b> If a similar result is obtained on testing after two weeks, the process of repeat testing after 2 weeks may continue for a third cycle.</p> <p>All enrolled participants will, in addition, have blood taken at each trial visit to be stored locally or at a central laboratory, for possible HIV-RNA PCR 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 the PCR test result is negative. This will be done to approximate the period of HIV infection. If the enrolment HIV-RNA PCR test result is positive, the participant is not considered to have been infected while using the IP.</p> <p>Additional blood (blood volume as specified in Appendix D) 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 5.15.</p> <p>Any participant who is confirmed HIV-positive while on the trial will be discontinued from the IP. Trial procedures relevant to the last product use visit as detailed in Section 4.3.5 will be performed, and an exit visit will be scheduled approximately 6 weeks 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.</p>	
<p>SECTION 5.3.4 Exit Visit</p> <p>At the exit visit, the participants will be tested using the same testing algorithm. If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2. If Test 2 is reactive, this will be considered an HIV seroconversion after product discontinuation. This 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 an HIV-RNA PCR test will be performed on stored samples in reverse sequential order to estimate the time point of HIV infection.</p> <p>Initial counselling services will be provided at the research centre and women will be referred for additional counselling, support services and treatment.</p>	<p>SECTION 5.3.4 Exit Visit</p> <p><b><u>For participants confirmed as HIV-negative prior to the exit visit</u></b></p> <p>At the exit visit, the participants will be tested using the same testing algorithm. If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2. If Test 2 is reactive, this will be considered an HIV seroconversion after product discontinuation. This 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 an HIV-RNA PCR test will be performed on stored samples in reverse sequential order to estimate the time point of HIV infection.</p> <p>Initial counselling services will be provided at the research centre and women will</p>	<p>Text was added to distinguish between the HIV testing procedures to be followed at the exit visit for participants confirmed as HIV-negative prior to this visit, as opposed to participants confirmed as HIV-infected prior to this visit.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>If Test 2 is non-reactive, the result is discordant. HIV Rapid Test 3 will be performed for discordant rapid test results. If Test 3 is reactive then the participant will be considered to be HIV-infected. 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- negative and will be counselled appropriately. Refer to Appendix C: HIV Testing Algorithms.</p> <p>As stated in Section 5.3.3 above, an exit visit will be scheduled approximately 6 weeks following HIV-seroconversion and IP discontinuation. Blood samples for viral genotyping will be collected from these participants. Additional trial procedures for exit visits scheduled following HIV seroconversion are described in Section 4.4 (No further HIV counselling and testing will be done unless indicated for additional confirmatory testing).</p> <p><b>NOTE:</b> Up to 15% of all HIV rapid test samples will be retested at a central laboratory, for quality control purposes. Details of this testing will be provided in the Laboratory Manual. The Laboratory Manual will also provide details of the IPM specified Test 1; Test 2 and Test 3.</p> <p>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 (PMTCT) services.</p> <p>The research centres will inform IPM Medical Safety of any new HIV infections within 24 hours of diagnosis. The applicable regulatory authorities and ethics committees who require expedited notification of HIV seroconversions 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.</p>	<p>be referred for additional counselling, support services and treatment.</p> <p>If Test 2 is non-reactive, the result is discordant. HIV Rapid Test 3 will be performed for discordant rapid test results. If Test 3 is reactive then the participant will be considered to be HIV-infected. 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- negative and will be counselled appropriately. Refer to Appendix C: HIV Testing Algorithms, <u>and Appendix D: Visit Schedule and Blood Volumes.</u></p> <p><b><u>For participants confirmed as HIV-infected prior to the exit visit</u></b></p> <p>As stated in Section 5.3.3 above, an exit visit will be scheduled approximately 6 weeks following <b><u>confirmed</u></b> HIV-seroconversion and IP discontinuation. Blood samples for viral genotyping will be collected from these participants. Additional trial procedures for exit visits scheduled following HIV seroconversion are described in Section 4.4 (No further HIV counselling and testing will be done unless indicated for additional confirmatory testing).</p> <p><b>NOTE:</b> Up to 15% of all HIV rapid test samples will be retested at a central laboratory, for quality control purposes. Details of this testing will be provided in the Laboratory Manual. The Laboratory Manual will also provide details of the IPM specified Test 1; Test 2 and Test 3.</p> <p>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 (PMTCT) services.</p> <p>The research centres will inform IPM Medical Safety of any new HIV infections within 24 hours of diagnosis. The applicable regulatory authorities and ethics committees who require expedited notification of HIV seroconversions 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.</p>	
<p>SECTION 5.5 Pregnancy Testing and Management</p> <p>A urine pregnancy test will be performed at all scheduled trial visits while the participant is using the IP and can be performed additionally at unscheduled visits</p>	<p>SECTION 5.5 Pregnancy Testing and Management</p> <p>A urine pregnancy test will be performed at all scheduled trial visits while the participant is using the IP and can be performed additionally at unscheduled visits</p>	<p>Text was added to clarify the procedures to be followed by the research centre in the event of positive</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>if any reason exists to suspect pregnancy or, in the event of a participant defaulting on her contraception, prior to recommencing contraception.</p> <p>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.</p> <p>If a participant tests positive for pregnancy while on the IP, ring use will be discontinued immediately, and she will be referred to a local prenatal clinic for medical services. The research centres will be asked to report all pregnancies to IPM within 24 hours of confirming a positive pregnancy test. A confirmatory serum pregnancy test may be requested at the discretion of the investigator or a designated qualified 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 after discussion with the IPM Clinical Physician or designee.</p> <p>Women who become pregnant and HIV positive during the trial will be referred for appropriate Prevention of Mother-to-Child Transmission (PMTCT) services.</p> <p>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.</p>	<p>if any reason exists to suspect pregnancy or, in the event of a participant defaulting on her contraception, prior to recommencing contraception.</p> <p>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.</p> <p>If a participant tests positive for pregnancy while on the IP, ring use will be discontinued immediately. <b><u>Trial procedures relevant to the last product use visit will be performed. The participant</u></b> will be referred to a local prenatal clinic for medical services. The research centres will be asked to report all pregnancies to IPM within 24 hours of confirming a positive pregnancy test. A confirmatory serum pregnancy test may be requested at the discretion of the investigator or a designated qualified 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 <del>after discussion with the IPM Clinical Physician or designee.</del></p> <p><b><u>An exit visit will be scheduled approximately 6 weeks following a positive pregnancy test and IP discontinuation. Trial procedures for exit visits are described in Section 4.4. If the participant indicates a change in pregnancy status or the participant's clinical history indicates a change in her pregnancy status, a urine pregnancy test may be performed. If the urine pregnancy test is negative, the investigator can consider recommencing IP. The participant must have a negative pregnancy test prior to re-introduction of IP. A pelvic examination should be performed prior to re-introduction of IP.</u></b></p> <p>Women who become pregnant and HIV positive during the trial will be referred for appropriate Prevention of Mother-to-Child Transmission (PMTCT) services.</p> <p>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.</p>	<p>pregnancy tests, and to clarify when it would be appropriate to consider re-introduction of investigational product in cases where confirmatory testing indicates negative test results.</p>
<p>SECTION 5.12 Vaginal Ring Insertion and Placement Check and Ring Removal</p> <p>At the enrolment and 4-weekly trial visits, participants will insert their vaginal rings under clinic supervision. The participant will be instructed to wash her hands thoroughly, 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</p>	<p>SECTION 5.12 Vaginal Ring Insertion and Placement Check and Ring Removal</p> <p>At the enrolment and 4-weekly trial visits, participants will insert their vaginal rings under clinic supervision. The participant will be instructed to wash her hands thoroughly, 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</p>	<p>Text was revised to indicate that participants will be allowed as many attempts as needed to insert the vaginal ring.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>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 wash her hands thoroughly again. A brief digital examination will be performed immediately after by an appropriately qualified and trained trial staff member as designated by the investigator, to verify proper placement of the ring. The verification of the placement of the ring at subsequent visits will be done at the discretion of the designated trial staff. If upon digital examination the ring is not inserted correctly, the investigator or nurse will allow the participant a maximum of 2 additional attempts to re-insert the ring properly or provide assistance as required to put the ring in place. At all trial visits when a pelvic examination is performed, the participant will remove the ring prior to the examination.</p> <p>If the participant requests help with either removal or re-insertion of the vaginal ring, or after she has made a maximum of 3 attempts to remove/re-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 Study Operations Manual.</p>	<p>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 wash her hands thoroughly again. A brief digital examination will be performed immediately after by an appropriately qualified and trained trial staff member as designated by the investigator, to verify proper placement of the ring. The verification of the placement of the ring at subsequent visits will be done at the discretion of the designated trial staff. If upon digital examination the ring is not inserted correctly, the investigator or nurse will allow the participant <del>a maximum of 2</del> additional attempts to re-insert the ring properly or provide assistance as required to put the ring in place. At all trial visits when a pelvic examination is performed, the participant will remove the ring prior to the examination.</p> <p>If the participant requests help with either removal or re-insertion of the vaginal ring, or after she has made <u>several</u> attempts to remove/re-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 Study Operations Manual.</p>	
<p>SECTION 5.14.4 Qualitative Interviews</p> <p>Qualitative interviews (focus groups and individual interviews) will be conducted at two points in the trial 24 – 36 weeks after trial initiation, and following last product use visits. Focus groups and individual interviews will be conducted with a sample of trial participants, and individual interviews will be conducted with a sample of participant’s male partners. These interviews will provide further information on acceptability and adherence for the exploratory objectives.</p>	<p>SECTION 5.14.4 Qualitative Interviews</p> <p>Qualitative interviews (focus groups and individual interviews) will be conducted at two points in the trial: 24 – <u>42</u> weeks after <u>research centre activation</u>, and following last product use visits. Focus groups and individual interviews will be conducted with a sample of trial participants, and individual interviews will be conducted with a sample of participant’s male partners. These interviews will provide further information on acceptability and adherence for the exploratory objectives.</p>	<p>The window for individual qualitative interviews was extended from 36 weeks after trial initiation to 42 weeks after research centre activation, as recruitment is slower than initially anticipated.</p>
<p>SECTION 5.15 Sample Storage and Analysis</p> <p>Blood and vaginal fluid samples will be collected for storage locally or at a central laboratory at all trial visits, to be tested subsequent to confirmed HIV-1 seroconversion. Blood samples for HSV-2 serology, HIV viral genotyping and HIV-RNA PCR will be stored from enrolment (or screening 2 for research centres that use this option). Testing will be conducted on stored samples from confirmed HIV-1 seroconverters and specifically for dapivirine concentration measurements and HSV-2 serology from both HIV-1 seroconverters and a random sample of HIV-negative participants. For dapivirine concentration measurements, blood and vaginal fluid samples must be collected prior to removal of the vaginal ring. Further details regarding these procedures will be provided in the Laboratory Manual (which forms part of the Study Operations Manual).</p>	<p>SECTION 5.15 Sample Storage and Analysis</p> <p>Blood and vaginal fluid samples will be collected for storage locally or at a central laboratory at all trial visits, to be tested subsequent to confirmed HIV-1 seroconversion. Blood samples for HSV-2 serology, HIV viral genotyping and HIV-RNA PCR will be stored from enrolment (or screening 2 for research centres that use this option). Testing will be conducted on stored samples from confirmed HIV-1 seroconverters and specifically for dapivirine concentration measurements and HSV-2 serology from both HIV-1 seroconverters and a random sample of HIV-negative participants. For dapivirine concentration measurements, blood and vaginal fluid samples <u>should preferably</u> be collected prior to removal of the vaginal ring. Further details regarding these procedures will be provided in the Laboratory Manual (which forms part of the Study Operations Manual).</p>	<p>The text specifying the timing of the blood and vaginal fluid samples for measurement of dapivirine concentrations was revised. Although it is preferable to collect the sample before ring removal, it might be difficult for some participants to undergo two speculum</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>As described in Section 5.3.3 above, additional blood (blood volume as specified in Appendix D) and vaginal fluid samples will also be obtained for analysis at the point of HIV seroconversion according to the HIV testing algorithm described in Section 5.3. The blood samples will be tested retrospectively for HIV-RNA PCR, HSV-2 serology and viral genotyping, while both blood and vaginal fluid will be tested for dapivirine concentrations. Plasma and vaginal fluid drug concentrations will be used to evaluate the relationship between drug concentrations and HIV seroconversion. HSV-2 serology and dapivirine concentration analyses will be conducted in HIV-1 seroconverters and a randomly selected control group of HIV-negative participants.</p> <p>All specimens will be collected and analysed according to methods described in the Laboratory Manual and standard operating procedures (SOPs) for proper collection, processing, labelling, and transport of specimens to the laboratories conducting the assays. Where possible and appropriate, stored specimens will be re-tested to assess validity of unusual or unexpected assay results.</p> <p>Any residual specimens will be destroyed at the end of the trial after all protocol-required and quality control testing has been completed.</p>	<p>As described in Section 5.3.3 above, additional blood (blood volume as specified in Appendix D) and vaginal fluid samples will also be obtained for analysis at the point of HIV seroconversion according to the HIV testing algorithm described in Section 5.3. The blood samples will be tested retrospectively for HIV-RNA PCR, HSV-2 serology and viral genotyping, while both blood and vaginal fluid will be tested for dapivirine concentrations. Plasma and vaginal fluid drug concentrations will be used to evaluate the relationship between drug concentrations and HIV seroconversion. HSV-2 serology and dapivirine concentration analyses will be conducted in HIV-1 seroconverters and a randomly selected control group of HIV-negative participants.</p> <p>All specimens will be collected and analysed according to methods described in the Laboratory Manual and standard operating procedures (SOPs) for proper collection, processing, labelling, and transport of specimens to the laboratories conducting the assays. Where possible and appropriate, stored specimens will be re-tested to assess validity of unusual or unexpected assay results.</p> <p>Any residual specimens will be destroyed at the end of the trial after all protocol-required and quality control testing has been completed.</p>	<p>insertions during one visit, in which case the research centre staff may collect the vaginal fluid sample after ring removal. In addition, participants may have removed the ring prior to their visit, in which case the ring will not be in place at the time of sample collection. As these PK samples will mainly be used as measure of adherence to ring use, collection of these samples after ring removal will not greatly impact the interpretation of the data.</p>
<p><b>SECTION 7.4.1 Serious Adverse Event Definition</b></p> <p>A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that at any dose meets any of the following criteria:</p> <ul style="list-style-type: none"> <li>• Results in death.</li> <li>• 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.</li> <li>• Requires inpatient hospitalisation or prolongation of existing hospitalisation. This criterion applies if the event requires inpatient hospitalisation and results in an overnight stay in hospital or, in the opinion of the investigator, prolongs an existing hospitalisation. A hospitalisation (including hospitalisation for an elective procedure or routinely scheduled treatment) for a pre-existing condition which has not worsened does not constitute an SAE.</li> <li>• 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.</li> <li>• Is a congenital anomaly/birth defect. This criterion applies if a participant gives birth to a child with a congenital</li> </ul>	<p><b>SECTION 7.4.1 Serious Adverse Event Definition</b></p> <p>A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that at any dose meets any of the following criteria:</p> <ul style="list-style-type: none"> <li>• Results in death.</li> <li>• 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.</li> <li>• Requires inpatient hospitalisation or prolongation of existing hospitalisation. This criterion applies if the event requires inpatient hospitalisation and results in an overnight stay in hospital or, in the opinion of the investigator, prolongs an existing hospitalisation. A hospitalisation (including hospitalisation for an elective procedure or routinely scheduled treatment) for a pre-existing condition which has not worsened does not constitute an SAE.</li> <li>• 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.</li> <li>• Is a congenital anomaly/birth defect. This criterion applies if a participant gives birth to a child with a congenital</li> </ul>	<p>Provision is made for IPM or its appointed designee (external service provider) to process and report SAEs to Regulatory or Health Authorities.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 1.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 2.0)	MOTIVATION FOR CHANGE
<p>anomaly or birth defect.</p> <ul style="list-style-type: none"> <li>Is an important and significant medical event that may not be immediately life threatening or result in death or hospitalisation but, based upon appropriate medical judgment, may jeopardise the participant or require intervention to prevent one of the other outcomes listed above. e.g., bronchospasm requiring intensive treatment in an emergency room or at home.</li> </ul> <p><b>NOTE:</b> An SAE need not be severe in nature to meet any of the above criteria.</p> <p>All SAEs that occur from the time the participant is enrolled (receives treatment assignment) through the duration of the trial, whether considered to be associated with investigational product or not, must be reported to the IPM Medical Safety Physician or designee within 24 hours of the research centre becoming aware of the event. All SAEs should be reported using the designated Immediately Reportable Event (IRE) Report Form.</p> <p>The IRE Report Form will be completed with all available information at the time of reporting. The investigator is required to write a detailed written report and complete SAE follow-up in a timely manner until the SAE returns to baseline, the participant returns to normal health or until the investigator does not expect further improvement or worsening of the event. Medical records may be requested by IPM to assist in assessing relatedness and severity of the SAE, and for possible submission to Regulatory or Health authorities. To maintain confidentiality, the participant's name will be blacked out and replaced with the Participant Identification Number and initials on any medical records submitted.</p> <p>More details on SAE reporting requirements are described in a separate Safety Reporting Plan.</p>	<p>anomaly or birth defect.</p> <ul style="list-style-type: none"> <li>Is an important and significant medical event that may not be immediately life threatening or result in death or hospitalisation but, based upon appropriate medical judgment, may jeopardise the participant or require intervention to prevent one of the other outcomes listed above. e.g., bronchospasm requiring intensive treatment in an emergency room or at home.</li> </ul> <p><b>NOTE:</b> An SAE need not be severe in nature to meet any of the above criteria.</p> <p>All SAEs that occur from the time the participant is enrolled (receives treatment assignment) through the duration of the trial, whether considered to be associated with investigational product or not, must be reported to the IPM Medical Safety Physician or designee within 24 hours of the research centre becoming aware of the event. All SAEs should be reported using the designated Immediately Reportable Event (IRE) Report Form.</p> <p>The IRE Report Form will be completed with all available information at the time of reporting. The investigator is required to write a detailed written report and complete SAE follow-up in a timely manner until the SAE returns to baseline, the participant returns to normal health or until the investigator does not expect further improvement or worsening of the event. Medical records may be requested by IPM <u>or designee</u> to assist in assessing relatedness and severity of the SAE, and for possible submission to Regulatory or Health authorities. To maintain confidentiality, the participant's name will be blacked out and replaced with the Participant Identification Number and initials on any medical records submitted.</p> <p>More details on SAE reporting requirements are described in a separate Safety Reporting Plan.</p>	
<p>SECTION 7.4.2 Serious Adverse Event Contact Information</p> <p>SAEs will be reported to IPM within 24 hours of the research centre becoming aware of the event. If the SAE is related, and life-threatening or fatal, IPM Medical Safety should be notified immediately by email or telephone.</p> <p>The following email will be used for communication with the Medical Safety team regarding any IREs: <a href="mailto:safetyreports@ipmglobal.org">safetyreports@ipmglobal.org</a>.</p> <p>IPM will process all safety reports. The Medical Safety team will review all SAEs and generate the necessary queries.</p>	<p>SECTION 7.4.2 Serious Adverse Event Contact Information</p> <p>SAEs will be reported to IPM <u>or designee</u> within 24 hours of the research centre becoming aware of the event. If the SAE is related, and life-threatening or fatal, IPM Medical Safety should be notified immediately by email or telephone.</p> <p>The following email will be used for communication with the <b>IPM</b> Medical Safety team regarding any IREs: <a href="mailto:safetyreports@ipmglobal.org">safetyreports@ipmglobal.org</a>. <b>Contact details of relevant safety personnel are provided in the Safety Reporting Plan.</b></p> <p><u>IPM or designee</u> will process all safety reports. The Medical Safety team will review all SAEs and generate the necessary queries.</p>	<p>Text was added to make provision for an appointed IPM designee (external service provider), and to indicate that safety reporting processes and contact details are provided in a detailed safety reporting plan provided to the research centres.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 2.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 3.0)	MOTIVATION FOR CHANGE
<p>PROTOCOL SYNOPSIS</p> <p>TRIAL DESIGN</p> <p>IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled trial to assess the safety and efficacy of dapivirine in a silicone elastomer vaginal ring, inserted once every 4 weeks, in healthy, sexually active HIV-negative women, when compared to a placebo vaginal ring. Approximately 1,650 participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.</p>	<p>PROTOCOL SYNOPSIS</p> <p>TRIAL DESIGN</p> <p>IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled trial to assess the safety and efficacy of dapivirine in a silicone elastomer vaginal ring, inserted once every 4 weeks, in healthy, sexually active HIV-negative women, when compared to a placebo vaginal ring. Approximately <u>1,950</u> participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.</p>	<p>The high degree of product non-adherence observed at one of the research centres participating in the trial will impact the ability of the trial to test the study hypothesis for efficacy via ITT analysis and to detect true treatment differences in efficacy and safety. Therefore, the original sample size of 1650 participants will be increased to approximately 1950 to mitigate the potential negative impact of non-adherence at this centre on the trial outcome and to sustain the power of the trial for the primary objectives.</p>
<p>PROTOCOL SYNOPSIS</p> <p>POPULATION</p> <p>Approximately 1,650 sexually active HIV-negative women, 18 – 45 years of age, who understand the trial and can provide informed consent, will be enrolled and randomised in a 2:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a placebo vaginal ring.</p>	<p>PROTOCOL SYNOPSIS</p> <p>POPULATION</p> <p>Approximately <u>1,950</u> sexually active HIV-negative women, 18 – 45 years of age, who understand the trial and can provide informed consent, will be enrolled and randomised in a 2:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a placebo vaginal ring.</p>	<p>The high degree of product non-adherence observed at one of the research centres participating in the trial will impact the ability of the trial to test the study hypothesis for efficacy via ITT analysis and to detect true treatment differences in efficacy and safety. Therefore, the original sample size of 1650 participants will be increased to approximately 1950 to mitigate the potential negative impact of non-adherence at this centre on the trial outcome and</p>



OLD TEXT (Final Protocol Version 1.0 Amendment 2.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 3.0)	MOTIVATION FOR CHANGE
		to sustain the power of the trial for the primary objectives.
<p>PROTOCOL SYNOPSIS</p> <p>STATISTICAL CONSIDERATIONS</p> <p><u>Sample Size and Power Calculations:</u> IPM 027 will randomise approximately 1,650 HIV-negative women in a 2:1 ratio such that 1,100 participants will be assigned to the investigational product and 550 participants will be assigned to the placebo ring. Under this design, a total of 80 HIV-1 seroconversions are expected and will provide approximately 83% power to detect a 50% reduction in the rate of HIV-1 seroconversions in the active arm, assuming an annual HIV-1 seroconversion rate of 4% in the placebo arm.</p> <p><u>Statistical Analyses:</u> The analysis of the primary efficacy endpoint (HIV-1 seroconversion rate) will be performed on the modified Intent-to-Treat (m-ITT) population, which will include all participants who were HIV-1 negative at the time of enrolment, analysed according to the treatment arm to which they were randomised, regardless of adherence to the product. A per-protocol analysis may also be performed on a subset of participants who did not experience a major protocol violation.</p> <p>The primary efficacy analysis will provide an estimate of the HIV-1 seroconversion rates for the treatment and placebo arms, with 95% confidence intervals (CIs). The log-rank test, stratified by research centre, will formally evaluate at a 5% significance level the null hypothesis that the probability of an HIV-1 seroconversion occurring at any time point is the same for the active and placebo arms. Kaplan-Meier curves will also be presented, stratified by research centre.</p> <p>For the safety analysis, a descriptive analysis of all AEs will be presented in tables and listings. Fisher's Exact test will be performed to compare the proportion of participants in the active and placebo arms, with regard to all Grade 3 and 4 AEs, all SAEs, and AEs leading to IP discontinuation, at a 0.05 significance level.</p> <p>The analysis of the social and behavioural secondary endpoints will focus on the assessment of acceptability of the vaginal ring, adherence to the use of the vaginal ring, as well as investigation of possible factors influencing adherence of women participating in the trial. Data for vaginal ring acceptability, sexual behaviour, condom use and vaginal ring use will be collected by self-report</p>	<p>PROTOCOL SYNOPSIS</p> <p>STATISTICAL CONSIDERATIONS</p> <p><u>Sample Size and Power Calculations:</u> IPM 027 will randomise approximately <b>1,950</b> HIV-negative women in a 2:1 ratio such that <b>1,300</b> participants will be assigned to the investigational product and <b>650</b> participants will be assigned to the placebo ring. <b><u>The increased sample size will mitigate the potential negative impact of product non-adherence on the trial outcome and sustain the power of the trial for the primary objectives.</u></b></p> <p>Under this design, a total of <b>96</b> HIV-1 seroconversions are expected and will provide <del>approximately</del> <b>81%</b> power to detect a 50% reduction in the rate of HIV-1 seroconversions in the active arm, assuming an annual HIV-1 seroconversion rate of 4% in the placebo arm.</p> <p><u>Statistical Analyses:</u> The analysis of the primary efficacy endpoint (HIV-1 seroconversion rate) will be performed on the modified Intent-to-Treat (m-ITT) population, which will include all participants who were HIV-1 negative at the time of enrolment, analysed according to the treatment arm to which they were randomised, regardless of adherence to the product. A per-protocol analysis may also be performed on a subset of participants who did not experience a major protocol violation.</p> <p>The primary efficacy analysis will provide an estimate of the HIV-1 seroconversion rates for the treatment and placebo arms, with 95% confidence intervals (CIs). The log-rank test, stratified by research centre, will formally evaluate at a 5% significance level the null hypothesis that the probability of an HIV-1 seroconversion occurring at any time point is the same for the active and placebo arms. Kaplan-Meier curves will also be presented, stratified by research centre.</p> <p>For the safety analysis, a descriptive analysis of all AEs will be presented in tables and listings. Fisher's Exact test will be performed to compare the proportion of participants in the active and placebo arms, with regard to all Grade 3 and 4 AEs, all SAEs, and AEs leading to IP discontinuation, at a 0.05 significance level.</p>	<p>The high degree of product non-adherence observed at one of the research centres participating in the trial will impact the ability of the trial to test the study hypothesis for efficacy via ITT analysis and to detect true treatment differences in efficacy and safety. Therefore, the original sample size of 1650 participants will be increased to approximately 1950 to mitigate the potential negative impact of non-adherence at this centre on the trial outcome and to sustain the power of the trial for the primary objectives.</p> <p>Provision is made for additional interim efficacy analyses during the trial, if requested by the DSMB.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 2.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 3.0)	MOTIVATION FOR CHANGE
<p>through interviewer-administered questionnaires, focus groups and individual interviews. Comparison between the two treatment arms will be conducted and will take into account the repeated measures by using a general estimating equation (GEE) framework.</p> <p>Appropriate statistical analyses of the exploratory endpoints will be performed.</p> <p>The Data and Safety Monitoring Board (DSMB) will perform thorough reviews of the data at pre-specified time points during the trial duration. They may recommend the early termination of the trial or modification due to evidence of safety concerns among participants. An interim analysis will be conducted when 50% of the endpoints have been observed and will be based on futility and efficacy.</p>	<p>The analysis of the social and behavioural secondary endpoints will focus on the assessment of acceptability of the vaginal ring, adherence to the use of the vaginal ring, as well as investigation of possible factors influencing adherence of women participating in the trial. Data for vaginal ring acceptability, sexual behaviour, condom use and vaginal ring use will be collected by self-report through interviewer-administered questionnaires, focus groups and individual interviews. Comparison between the two treatment arms will be conducted and will take into account the repeated measures by using a general estimating equation (GEE) framework.</p> <p>Appropriate statistical analyses of the exploratory endpoints will be performed.</p> <p>The Data and Safety Monitoring Board (DSMB) will perform thorough reviews of the data at pre-specified time points during the trial duration. They may recommend the early termination of the trial or modification due to evidence of safety concerns among participants. An interim analysis <b><u>to assess for possible futility or efficacy</u></b> will be conducted when <b><u>approximately 50%</u></b> of the <b><u>expected trial</u></b> endpoints have been observed <del>and will be based on futility and efficacy.</del> <b><u>An additional interim analysis/analyses may be requested by the DSMB.</u></b></p>	
<p>SECTION 3.1 Trial Design</p> <p>IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled trial to assess the safety and efficacy of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks in healthy, sexually active HIV-negative women, when compared to a placebo vaginal ring. The trial will be conducted at approximately 7 clinical research centres in sub-Saharan Africa. Approximately 1,650 participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.</p>	<p>SECTION 3.1 Trial Design</p> <p>IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled trial to assess the safety and efficacy of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks in healthy, sexually active HIV-negative women, when compared to a placebo vaginal ring. The trial will be conducted at approximately 7 clinical research centres in sub-Saharan Africa. Approximately <b><u>1,950</u></b> participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.</p>	<p>The high degree of product non-adherence observed at one of the research centres participating in the trial will impact the ability of the trial to test the study hypothesis for efficacy via ITT analysis and to detect true treatment differences in efficacy and safety. Therefore, the original sample size of 1650 participants will be increased to approximately 1950 to mitigate the potential negative impact of non-adherence at this centre on the trial outcome and to sustain the power of the trial for the primary objectives.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 2.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 3.0)	MOTIVATION FOR CHANGE
<p>SECTION 3.3 Trial Population</p> <p>Approximately 1,650 sexually active HIV-negative women, 18 – 45 years of age, who understand the trial and can provide informed consent, will be enrolled and randomised in a 2:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a placebo vaginal ring.</p>	<p>SECTION 3.3 Trial Population</p> <p>Approximately <u>1,950</u> sexually active HIV-negative women, 18 – 45 years of age, who understand the trial and can provide informed consent, will be enrolled and randomised in a 2:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a placebo vaginal ring.</p>	<p>The high degree of product non-adherence observed at one of the research centres participating in the trial will impact the ability of the trial to test the study hypothesis for efficacy via ITT analysis and to detect true treatment differences in efficacy and safety. Therefore, the original sample size of 1650 participants will be increased to approximately 1950 to mitigate the potential negative impact of non-adherence at this centre on the trial outcome and to sustain the power of the trial for the primary objectives.</p>
<p>SECTION 4.7 Missed and Late Visits</p> <p>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 clinic for a scheduled visit during the trial window, e.g., within <math>\pm 7</math> 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 and applicable CRFs.</p> <p>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 3 by the time the trial window has begun for Visit 4, i.e., within 7 days from Visit 4, Visit 3 will be considered missed. Trial procedures will be performed as scheduled for the current visit (e.g. Visit 4 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.</p>	<p>SECTION 4.7 Missed and Late Visits</p> <p>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 clinic for a scheduled visit during the trial window, e.g., within <math>\pm 7</math> 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 and applicable CRFs.</p> <p>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 3 by the time the trial window has begun for Visit 4, i.e., within 7 days from Visit 4, Visit 3 will be considered missed. Trial procedures will be performed as scheduled for the current visit (e.g. Visit 4 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.</p>	<p>Provision is made for more than one additional vaginal ring to be dispensed to a participant in the event that the participant is unable to attend more than one consecutive 4-weekly ring replacement visit.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 2.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 3.0)	MOTIVATION FOR CHANGE
<p>In the event that a participant will be away and unable to attend one of the 4-weekly visits where a new vaginal ring would be inserted, the research centre could dispense an additional ring on a case-by-case basis following discussion by the investigator with the IPM Clinical Project Manager or designee. The participant would then self-insert the new ring on the day that her 4-weekly visit was due to take place. The research centre will contact the participant telephonically, if possible, to remind her to remove the current ring and insert the new ring. The adherence questionnaire will be administered over the telephone and research centre staff will enquire about adverse events and concomitant medication; other information will be collected as appropriate.</p> <p>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 be put back on her original visit schedule.</p> <p>If a 12-weekly or 24-weekly visit is missed, safety laboratory assessments and STI testing should be performed at the next visit.</p>	<p>In the event that a participant will be away and unable to attend one of the 4-weekly visits where a new vaginal ring would be inserted, the research centre could dispense an additional ring<del>(s)</del> on a case-by-case basis following discussion by the investigator with the IPM Clinical Project Manager or designee. The participant would then self-insert the new ring on the day that her 4-weekly visit was due to take place. The research centre will contact the participant telephonically, if possible, to remind her to remove the current ring and insert the new ring. The adherence questionnaire will be administered over the telephone and research centre staff will enquire about adverse events and concomitant medication; other information will be collected as appropriate.</p> <p>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 be put back on her original visit schedule.</p> <p>If a 12-weekly or 24-weekly visit is missed, safety laboratory assessments and STI testing should be performed at the next visit.</p>	
<p>SECTION 5.10.2 STI Management</p> <p>Participants will be treated at the research centre or referred to a local health facility; according to local STI Treatment Guidelines. During routine trial visits, all participants who present with STIs will be managed syndromically; however, cervicovaginal swabs will also be collected from these participants in order to document the aetiological diagnosis. Aetiological management may be applicable following 12-weekly STI testing, according to the aetiological diagnosis.</p> <p>The <i>Clinical Management of Genital Diagnoses</i> will be detailed in the Study Operations Manual for guidelines to determine whether the vaginal ring requires temporary or permanent removal, as well as follow-up recommendations. To ensure that participants are not treated with topical urogenital treatments, they will be instructed to seek treatment at the research centre and not from local physicians, should they experience any symptoms between scheduled visits. All cases of symptomatic vulvovaginal candidiasis will be treated with oral fluconazole.</p>	<p>SECTION 5.10.2 STI Management</p> <p>Participants will be treated at the research centre or referred to a local health facility; according to local STI Treatment Guidelines. During routine trial visits, all participants who present with STIs will be managed syndromically; however, cervicovaginal swabs will also be collected from these participants, <u>at the Investigator's discretion or when required by local standard of care</u>, in order to document the aetiological diagnosis. Aetiological management may be applicable following 12-weekly STI testing, according to the aetiological diagnosis.</p> <p>The <i>Clinical Management of Genital Diagnoses</i> will be detailed in the Study Operations Manual for guidelines to determine whether the vaginal ring requires temporary or permanent removal, as well as follow-up recommendations. To ensure that participants are not treated with topical urogenital treatments, they will be instructed to seek treatment at the research centre and not from local physicians, should they experience any symptoms between scheduled visits. All cases of symptomatic vulvovaginal candidiasis will be treated with oral fluconazole.</p>	<p>Text was added to clarify that further investigations in an attempt to document an aetiological diagnosis for STIs where syndromic management was applied may be performed at the discretion of the Investigator, or when required by local standard of care.</p>
<p>SECTION 6.6 Investigational Product Administration</p> <p>Participants will self-insert a new vaginal ring at enrolment and each 4-weekly</p>	<p>SECTION 6.6 Investigational Product Administration</p> <p>Participants will self-insert a new vaginal ring at enrolment and each 4-weekly</p>	<p>Text was added to align this section with Section 5.12, to indicate that if a</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 2.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 3.0)	MOTIVATION FOR CHANGE
<p>visit through the period of trial participation. A brief digital examination will be performed by an appropriately delegated trial staff member at each 4-weekly trial visit to ensure the ring is properly placed. Participants should continue ring use through menses.</p> <p>In the event that a participant will be away and unable to attend one of the 4-weekly visits where a new vaginal ring would be inserted, the research centre could dispense an additional ring, which the participant should then self-insert on the day that her 4-weekly visit was due to take place. Management thereof will be on a case by case basis following discussion by the investigator with the IPM Clinical Physician or designee.</p>	<p>visit through the period of trial participation. <b><u>Designated trial staff will perform</u></b> a brief digital examination <del>will be performed by an appropriately delegated trial staff member</del> at each 4-weekly trial visit, <b><u>at their discretion</u></b>, to ensure the ring is properly placed. Participants should continue ring use through menses.</p> <p>In the event that a participant will be away and unable to attend one of the 4-weekly visits where a new vaginal ring would be inserted, the research centre could dispense an additional ring<b><u>(s)</u></b>, which the participant should then self-insert on the day that her 4-weekly visit was due to take place. Management thereof will be on a case by case basis following discussion by the investigator with the IPM Clinical Physician or designee.</p>	<p>participant can place the ring correctly there might be no need to perform digital examinations at each ring replacement visit.</p> <p>Provision is made for more than one additional vaginal ring to be dispensed to a participant in the event that the participant is unable to attend more than one consecutive 4-weekly ring replacement visits.</p>
<p>SECTION 6.7 Investigational Product Expulsion or Loss</p> <p>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 it. If the vaginal ring is expelled and cannot be successfully reinserted, the ring should be appropriately rinsed and stored in the bag provided for this purpose, until the earliest possible opportunity the participant can return for reinsertion of a new ring at the clinic. After the second expulsion the IPM Clinical Physician should be consulted with regard to appropriate follow-up action.</p> <p>The participant 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 return to the clinic. Also in cases where a ring is removed due to a genital AE, a new ring will be dispensed and inserted. Visits associated with expulsion or loss of rings will be regarded as unscheduled visits and management thereof will be on a case by case basis following discussion by the investigator with the IPM Clinical Physician or designee, unless the visit is within the 7-day window period of the next scheduled visit.</p>	<p>SECTION 6.7 Investigational Product Expulsion or Loss</p> <p>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 it. If the vaginal ring is expelled and cannot be successfully reinserted, the ring should be appropriately rinsed and stored in the bag provided for this purpose, until the earliest possible opportunity the participant can return for reinsertion of a new ring at the clinic. <b><u>If a second expulsion occurs before the next scheduled visit, and a second replacement of a ring (with a new ring) needs to be considered</u></b>, the IPM Clinical Physician should be consulted with regard to appropriate follow-up action.</p> <p>The participant 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 return to the clinic. Also in cases where a ring is removed due to a genital AE, a new ring will be dispensed and inserted. Visits associated with expulsion or loss of rings will be regarded as unscheduled visits and management thereof will be on a case by case basis following discussion by the investigator with the IPM Clinical Physician or designee, unless the visit is within the 7-day window period of the next scheduled visit.</p>	<p>Text added to clarify in which instances of ring expulsion and replacement trial staff should consult the IPM Clinical Physician regarding the appropriate action to be taken.</p>
<p>SECTION 6.9 Investigational Product Accountability</p> <p>The Principal Investigator or designee will be responsible for adequate and accurate accounting, handling, storage and dispensing of the IP. The IP will be</p>	<p>SECTION 6.9 Investigational Product Accountability</p> <p>The Principal Investigator or designee will be responsible for adequate and accurate accounting, handling, storage and dispensing of the IP. The IP will be</p>	<p>Text was added to specify that all rings returned by participants will be subjected to visual</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 2.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 3.0)	MOTIVATION FOR CHANGE
<p>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 will be destroyed at the end of the trial according to IPM instruction and local regulatory requirements.</p>	<p>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.</p> <p><b><u>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 ring 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 levels.</u></b></p> <p>Unused and used rings <b><u>not analysed for residual levels of dapivirine</u></b> will be destroyed <del>at the end of the trial</del> according to IPM instruction and local regulatory requirements.</p>	<p>inspection by the Investigator, as subjective assessment of whether a ring appears used, which might support adherence.</p> <p>A description of the handling of the rings prior to shipment to the analytical laboratory for assessment of residual dapivirine levels was added.</p> <p>Specification of a timeframe for destruction of rings (unused and used rings, as appropriate) was removed from the text.</p>
<p>SECTION 9.1 General Design</p> <p>IPM 027 has been designed to assess the safety and efficacy of dapivirine administered in a silicone elastomer vaginal ring (Ring-004) containing 25 mg of dapivirine and inserted once every 4 weeks, among approximately 1,650 healthy, HIV-negative, sexually active women aged 18 – 45 years – as compared with a placebo vaginal ring.</p> <p>Individuals meeting all inclusion criteria and no exclusion criteria will be randomised in a 2:1 ratio to either the investigational product or a placebo vaginal ring. To maintain the treatment ratio within each research centre, randomisation, via an automated randomisation system, will be stratified by research centre, using a pre-specified block size.</p> <p>Participants will be followed on IP over a period of approximately 24 months (104 weeks). Each participant will have an additional 6 weeks of follow-up after ring discontinuation.</p>	<p>SECTION 9.1 General Design</p> <p>IPM 027 has been designed to assess the safety and efficacy of dapivirine administered in a silicone elastomer vaginal ring (Ring-004) containing 25 mg of dapivirine and inserted once every 4 weeks, among approximately <b><u>1,950</u></b> healthy, HIV-negative, sexually active women aged 18 – 45 years – as compared with a placebo vaginal ring.</p> <p>Individuals meeting all inclusion criteria and no exclusion criteria will be randomised in a 2:1 ratio to either the investigational product or a placebo vaginal ring. To maintain the treatment ratio within each research centre, randomisation, via an automated randomisation system, will be stratified by research centre, using a pre-specified block size.</p> <p>Participants will be followed on IP over a period of approximately 24 months (104 weeks). Each participant will have an additional 6 weeks of follow-up after ring discontinuation.</p>	<p>The high degree of product non-adherence observed at one of the research centres participating in the trial will impact the ability of the trial to test the study hypothesis for efficacy via ITT analysis and to detect true treatment differences in efficacy and safety. Therefore, the original sample size of 1650 participants will be increased to approximately 1950 to mitigate the potential negative impact of non-adherence at this centre on the trial outcome and to sustain the power of the trial for the primary objectives.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 2.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 3.0)	MOTIVATION FOR CHANGE																								
<p>SECTION 9.4 Sample Size and Power Calculations</p> <p>IPM 027 will be conducted in a sample of approximately 1,650 HIV-negative women in a 2:1 ratio, such that 1,100 participants will be assigned to the investigational product and 550 participants will be assigned to the placebo ring. The sample size for this trial was determined based on the primary efficacy endpoint, the incidence rate of HIV-1 seroconversions, in the two treatment arms. The statistical assumptions used in determining this sample size therefore include:</p> <ul style="list-style-type: none"> <li>• proportional hazards among the two groups,</li> <li>• microbicide efficacy of <math>\geq 50\%</math> in preventing HIV-1 infection,</li> <li>• randomisation ratio of 2:1 (dapivirine vaginal ring vs. placebo ring),</li> <li>• a two-sided log-rank test statistic, with <math>\alpha = 0.05</math>,</li> <li>• <math>&gt; 4\%</math> average annual HIV incidence in the placebo arm (assumes a reduction in incidence in the trial population due to risk reduction counseling), and</li> <li>• <math>\leq 10\%</math> loss-to-follow-up rate over the duration of the trial period.</li> </ul> <p>Below is a table which provides the estimated power to detect 40%, 50% and 60% microbicide efficacy with a sample size of 1,650 and under the assumptions as stated above.</p> <table border="1" data-bbox="152 895 896 1121"> <thead> <tr> <th>Microbicide efficacy</th> <th># Expected HIV- 1 seroconversions</th> <th>Power</th> </tr> </thead> <tbody> <tr> <td>40%</td> <td>88</td> <td>61.8%</td> </tr> <tr> <td>50%</td> <td>80</td> <td>83.2%</td> </tr> <tr> <td>60%</td> <td>72</td> <td>95.6%</td> </tr> </tbody> </table> <p>A trial with the proposed design will provide approximately 83% power to detect a 50% reduction in the rate of HIV-1 seroconversions in the active arm, assuming an annual HIV-1 seroconversion rate of 4% in the placebo arm, and a 10% lost-to-follow-up rate.</p> <p>Moreover, in a trial with this number of participants assigned to the investigational product, there is a 95% probability of detecting an AE occurring at</p>	Microbicide efficacy	# Expected HIV- 1 seroconversions	Power	40%	88	61.8%	50%	80	83.2%	60%	72	95.6%	<p>SECTION 9.4 Sample Size and Power Calculations</p> <p>IPM 027 will be conducted in a sample of approximately <u>1,950</u> HIV-negative women in a 2:1 ratio, such that <u>1,300</u> participants will be assigned to the investigational product and <u>650</u> participants will be assigned to the placebo ring. The sample size for this trial was determined based on the primary efficacy endpoint, the incidence rate of HIV-1 seroconversions, in the two treatment arms. The statistical assumptions used in determining this sample size therefore include:</p> <ul style="list-style-type: none"> <li>• proportional hazards among the two groups,</li> <li>• microbicide efficacy of <math>\geq 50\%</math> in preventing HIV-1 infection,</li> <li>• randomisation ratio of 2:1 (dapivirine vaginal ring vs. placebo ring),</li> <li>• a two-sided log-rank test statistic, with <math>\alpha = 0.05</math>,</li> <li>• <math>&gt; 4\%</math> average annual HIV incidence in the placebo arm (assumes a reduction in incidence in the trial population due to risk reduction counseling), and</li> <li>• <math>\leq 10\%</math> loss-to-follow-up rate over the duration of the trial period.</li> </ul> <p><b><u>The increased sample size will mitigate the potential negative impact of product non-adherence on the trial outcome and sustain the power of the trial for the primary objectives.</u></b></p> <p>Below is a table which provides the estimated power to detect 40%, 50% and 60% microbicide efficacy with a sample size of <u>1,950</u> and under the assumptions as stated above.</p> <table border="1" data-bbox="1037 1015 1780 1241"> <thead> <tr> <th>Microbicide efficacy</th> <th># Expected HIV- 1 seroconversions</th> <th>Power</th> </tr> </thead> <tbody> <tr> <td>40%</td> <td><u>104</u></td> <td><u>61%</u></td> </tr> <tr> <td>50%</td> <td><u>96</u></td> <td><u>81%</u></td> </tr> <tr> <td>60%</td> <td><u>88</u></td> <td><u>94%</u></td> </tr> </tbody> </table> <p>A trial with the proposed design will provide approximately <b>81%</b> power to detect a 50% reduction in the rate of HIV-1 seroconversions in the active arm, assuming an annual HIV-1 seroconversion rate of 4% in the placebo arm, and a</p>	Microbicide efficacy	# Expected HIV- 1 seroconversions	Power	40%	<u>104</u>	<u>61%</u>	50%	<u>96</u>	<u>81%</u>	60%	<u>88</u>	<u>94%</u>	<p>The high degree of product non-adherence observed at one of the research centres participating in the trial will impact the ability of the trial to test the study hypothesis for efficacy via ITT analysis and to detect true treatment differences in efficacy and safety. Therefore, the original sample size of 1650 participants will be increased to approximately 1950 to mitigate the potential negative impact of non-adherence at this centre on the trial outcome and to sustain the power of the trial for the primary objectives.</p>
Microbicide efficacy	# Expected HIV- 1 seroconversions	Power																								
40%	88	61.8%																								
50%	80	83.2%																								
60%	72	95.6%																								
Microbicide efficacy	# Expected HIV- 1 seroconversions	Power																								
40%	<u>104</u>	<u>61%</u>																								
50%	<u>96</u>	<u>81%</u>																								
60%	<u>88</u>	<u>94%</u>																								

OLD TEXT (Final Protocol Version 1.0 Amendment 2.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 3.0)	MOTIVATION FOR CHANGE
<p>a rate of 0.3% or higher.</p>	<p>10% lost-to-follow-up rate.</p> <p>Moreover, in a trial with this number of participants assigned to the investigational product, there is a 95% probability of detecting an AE occurring at a rate of 0.3% or higher.</p>	
<p>SECTION 9.6 Interim Analysis</p> <p>Regular safety reviews will be conducted by the Data and Safety Monitoring Board (DSMB) at predetermined intervals during the trial (refer to Section 9.7). A single interim efficacy analysis is planned when 50% of the required events have occurred (i.e. 40 HIV-1 seroconversions in either treatment group). The interim analysis will be performed by an independent statistician that is otherwise not involved in the trial and will include descriptive statistics of baseline variables, safety data (i.e., AEs), and STI and HIV incidence. To maintain the proposed Type I error rate (<math>\alpha = 0.05</math>), which will be inflated due to multiple testing of the efficacy hypothesis, the interim and final analyses will be adjusted using a Lan-DeMets spending function with O'Brien-Fleming grouped sequential stopping boundary<sup>14, 15</sup>.</p> <p>In addition, the DSMB may recommend early termination of the trial on the basis of: 1) safety concerns, or 2) demonstrating futility:</p> <ol style="list-style-type: none"> <li>1) Safety concern – an increased risk of safety outcomes in the dapivirine ring arm as compared to the placebo ring arm.</li> <li>2) Demonstrating futility – evidence that the trial is highly unlikely to show that the new intervention is superior, given current evidence and the added information that would become available if the trial continued.</li> </ol> <p>A separate SAP will be drafted after the protocol is finalised. This plan will provide specific details about:</p> <ol style="list-style-type: none"> <li>1) the parameterisation of variables,</li> <li>2) the statistical assumptions required,</li> <li>3) the statistical methods to be employed,</li> <li>4) specifications of the stopping boundaries used in the interim analysis, and</li> <li>5) the Type I error at the interim look.</li> </ol> <p>The Sponsor will review and approve the SAP before any analyses are undertaken.</p>	<p>SECTION 9.6 Interim Analysis</p> <p>Regular safety reviews will be conducted by the Data and Safety Monitoring Board (DSMB) at predetermined intervals during the trial (refer to Section 9.7). A <del>single</del> <u>An</u> interim efficacy analysis is planned when <u>approximately</u> 50% of the <del>required events</del> <u>expected trial endpoints</u> have occurred (i.e. 40 HIV-1 <del>seroconversions in either treatment group</del>). The interim analysis will be performed by an independent statistician that is otherwise not involved in the trial and will include descriptive statistics of baseline variables, safety data (i.e., AEs), and STI and HIV incidence. To maintain the proposed Type I error rate (<math>\alpha = 0.05</math>), which will be inflated due to multiple testing of the efficacy hypothesis, the interim and final analyses will be adjusted using a Lan-DeMets spending function with O'Brien-Fleming grouped sequential stopping boundary<sup>14, 15</sup>.</p> <p>In addition, the DSMB may recommend early termination of the trial on the basis of: 1) safety concerns, or 2) demonstrating futility:</p> <ol style="list-style-type: none"> <li>1) Safety concern – an increased risk of safety outcomes in the dapivirine ring arm as compared to the placebo ring arm.</li> <li>2) Demonstrating futility – evidence that the trial is highly unlikely to show that the new intervention is superior, given current evidence and the added information that would become available if the trial continued.</li> </ol> <p><u>An additional interim analysis/analyses may be requested by the DSMB.</u></p> <p>A separate SAP <u>for the interim analysis/analyses</u> will be drafted after the protocol is finalised. This plan will provide specific details about:</p> <ol style="list-style-type: none"> <li>1) the parameterisation of variables,</li> <li>2) the statistical assumptions required,</li> <li>3) the statistical methods to be employed,</li> <li>4) specifications of the stopping boundaries used in the interim analysis, and</li> <li>5) the Type I error at the interim look.</li> </ol> <p>The Sponsor will review and approve the SAP <u>for any interim analysis</u> before any analyses are undertaken.</p>	<p>Provision is made for additional interim efficacy analyses during the trial, if requested by the DSMB.</p>



OLD TEXT (Final Protocol Version 1.0 Amendment 3.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 4.0)	MOTIVATION FOR CHANGE
<p>SECTION 5.3.3 Trial Visits (last paragraph)</p> <p>Any participant who is confirmed HIV-positive while on the trial will be discontinued from the IP. Trial procedures relevant to the last product use visit as detailed in Section 4.3.5 will be performed, and an exit visit will be scheduled approximately 6 weeks 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.</p>	<p>SECTION 5.3.3 Trial Visits (last paragraph)</p> <p>Any participant who is confirmed HIV-<del>positive</del> <u>infected</u> while on the trial will be <u>permanently</u> discontinued from the IP. Trial procedures relevant to the last product use visit as detailed in Section 4.3.5 will be performed, and an exit visit will be scheduled approximately 6 weeks 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.</p> <p><u>In an instance where a participant is determined to be HIV-positive but cannot be confirmed as HIV-infected the participant will be discontinued from IP and the protocol-required procedures as stipulated for 4-, 12- and 24-weekly visits will be performed at the Investigator's discretion. Samples for measurement of dapivirine levels will no longer be collected and adherence and acceptability questionnaires will not be completed. Additional testing to demonstrate HIV infection may be performed. Participants will be followed up until the exit visit according to the original enrolment date.</u></p>	<p>To clarify that only participants who are confirmed to be HIV infected (as opposed to those with positive rapid or other serological tests) will be discontinued from the trial.</p> <p>Information added on how participants will be managed who test HIV-positive but who are not confirmed as HIV-infected.</p>
<p>SECTION 5.3.4 Exit Visit</p> <p><b><u>For participants confirmed as HIV-negative prior to the exit visit</u></b></p> <p>At the exit visit, the participants will be tested using the same testing algorithm. If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2. If Test 2 is reactive, this will be considered an HIV seroconversion after product discontinuation. This 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 an HIV-RNA PCR test will be performed on stored samples in reverse sequential order to estimate the time point of HIV infection.</p> <p>Initial counselling services will be provided at the research centre and women will be referred for additional counselling, support services and treatment.</p> <p>If Test 2 is non-reactive, the result is discordant. HIV Rapid Test 3 will be performed for discordant rapid test results. If Test 3 is reactive then the participant will be considered to be HIV-infected. 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-negative and will be counselled appropriately. Refer to</p>	<p>SECTION 5.3.4 Exit Visit</p> <p><b><u>For participants confirmed as HIV-negative prior to the exit visit</u></b></p> <p>At the exit visit, the participants will be tested using the same testing algorithm. If the HIV Rapid Test 1 is non-reactive, the participant will be considered HIV-negative. If Test 1 is reactive, the participant will be tested using HIV Rapid Test 2. If Test 2 is reactive, <u>additional confirmatory testing will be performed by Western Blot and other confirmatory tests, where appropriate. Samples for possible viral genotype analysis and HIV-RNA PCR testing will be collected.</u> <u>Once HIV infection has been confirmed,</u> this will be considered an HIV seroconversion after product discontinuation. This 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 an HIV-RNA PCR test will be performed on stored samples in reverse sequential order to estimate the time point of HIV infection.</p> <p>Initial counselling services will be provided at the research centre and women will be referred for additional counselling, support services and treatment.</p> <p>If Test 2 is non-reactive, the result is discordant. HIV Rapid Test 3 will be performed for discordant rapid test results. If Test 3 is reactive then the participant will be considered to be HIV-infected. <u>Additional confirmatory testing</u></p>	<p>Text added to clarify that the seroconverter tests are also collected if a participant seroconverts at the exit visit.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 3.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 4.0)	MOTIVATION FOR CHANGE
Appendix C: HIV Testing Algorithms, and Appendix D: Visit Schedule and Blood Volumes.	will be performed by <u>Western Blot and other confirmatory tests, where appropriate. Samples for possible viral genotype analysis and HIV-RNA PCR testing will be collected.</u> 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-negative and will be counselled appropriately. Refer to Appendix C: HIV Testing Algorithms, and Appendix D: Visit Schedule and Blood Volumes.	
<p>SECTION 5.4 Management of Contraception</p> <p>Stable contraception is defined, for the purposes of the trial, as surgical sterilisation at least 3 months prior to enrolment OR one of the following: Participants who have used contraceptives for at least the preceding year should be on the same:</p> <ul style="list-style-type: none"> <li>• Oral contraceptive regimen for at least 2 months prior to enrolment, OR</li> <li>• Transdermal contraceptive patch for at least 2 months prior to enrolment, OR,</li> <li>• Long-acting injectable progestins for at least 2 consecutive injections, OR,</li> <li>• Subcutaneous implant inserted at least 3 months prior to enrolment, OR</li> <li>• An IUD inserted at least 3 months prior to enrolment.</li> </ul> <p>Participants who have newly commenced contraceptive use or have recommenced contraceptive use after a period of greater than 6 months should be on the same:</p> <ul style="list-style-type: none"> <li>• Oral contraceptive regimen for at least 3 months prior to enrolment, OR</li> <li>• Transdermal contraceptive patch for at least 3 months prior to enrolment, OR,</li> <li>• Long-acting injectable progestins for at least 6 months, OR,</li> <li>• Subcutaneous implant inserted at least 3 months prior to enrolment, OR</li> <li>• An IUD inserted at least 3 months prior to enrolment.</li> </ul>	<p>SECTION 5.4 Management of Contraception</p> <p>Stable contraception is defined, for the purposes of the trial, as surgical sterilisation at least 3 months prior to enrolment OR one of the following: Participants who have used contraceptives for at least the preceding year should be on the same <u>contraceptive method</u>:</p> <ul style="list-style-type: none"> <li>• Oral contraceptive regimen for at least 2 months prior to enrolment, OR</li> <li>• Transdermal contraceptive patch for at least 2 months prior to enrolment, OR,</li> <li>• Long-acting injectable progestins for at least 2 consecutive injections, OR,</li> <li>• Subcutaneous implant inserted at least 3 months prior to enrolment, OR</li> <li>• An IUD inserted at least 3 months prior to enrolment.</li> </ul> <p>Participants who have newly commenced contraceptive use or have recommenced contraceptive use after a period of greater than 6 months should be on the same <u>contraceptive method</u>:</p> <ul style="list-style-type: none"> <li>• Oral contraceptive regimen for at least 3 months prior to enrolment, OR</li> <li>• Transdermal contraceptive patch for at least 3 months prior to enrolment, OR,</li> <li>• Long-acting injectable progestins for at least 6 months, OR,</li> <li>• Subcutaneous implant inserted at least 3 months prior to enrolment, OR</li> <li>• An IUD inserted at least 3 months prior to enrolment.</li> </ul>	Text was added to align the enrolment requirements with the contraception requirements during trial conduct and to accommodate the inconsistent availability of long-acting injectable progestins from family planning service providers.
SECTION 5.5 Pregnancy Testing and Management	SECTION 5.5 Pregnancy Testing and Management	Text added to clarify that seroconverted

OLD TEXT (Final Protocol Version 1.0 Amendment 3.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 4.0)	MOTIVATION FOR CHANGE
<p>A urine pregnancy test will be performed at all scheduled trial visits while the participant is using the IP 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.</p> <p>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.</p> <p>If a participant tests positive for pregnancy while on the IP, ring use will be discontinued immediately. Trial procedures relevant to the last product use visit will be performed. 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 24 hours of confirming a positive pregnancy test. A confirmatory serum pregnancy test may be requested at the discretion of the investigator or a designated qualified 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.</p> <p>An exit visit will be scheduled approximately 6 weeks following a positive pregnancy test and IP discontinuation. Trial procedures for exit visits are described in Section 4.4. If the participant indicates a change in pregnancy status or the participant's clinical history indicates a change in her pregnancy status, a urine pregnancy test may be performed. If the urine pregnancy test is negative, the investigator can consider recommencing IP. The participant must have a negative pregnancy test prior to re-introduction of IP. A pelvic examination should be performed prior to re-introduction of IP.</p> <p>Women who become pregnant and HIV positive during the trial will be referred for appropriate Prevention of Mother-to-Child Transmission (PMTCT) services.</p> <p>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.</p>	<p>A urine pregnancy test will be performed at all scheduled trial visits while the participant is using the IP 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.</p> <p>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.</p> <p>If a participant tests positive for pregnancy while on the IP, ring use will be discontinued immediately. Trial procedures relevant to the last product use visit will be performed. 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 24 hours of confirming a positive pregnancy test. A confirmatory serum pregnancy test may be requested at the discretion of the investigator or a designated qualified 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.</p> <p>An exit visit will be scheduled approximately 6 weeks following a positive pregnancy test and IP discontinuation. Trial procedures for exit visits are described in Section 4.4. If the participant indicates a change in pregnancy status or the participant's clinical history indicates a change in her pregnancy status, a urine pregnancy test may be performed. If the urine pregnancy test is negative, the investigator can consider recommencing IP. The participant must have a negative pregnancy test prior to re-introduction of IP. A pelvic examination should be performed prior to re-introduction of IP.</p> <p>Women who become pregnant and HIV positive during the trial will be referred for appropriate Prevention of Mother-to-Child Transmission (PMTCT) services. <u>Should a participant have a positive pregnancy test in an instance where she was determined to be HIV-positive 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.</u></p> <p>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.</p>	<p>participants without confirmed HIV infection would be allowed to continue in the trial if they become pregnant.</p>

OLD TEXT (Final Protocol Version 1.0 Amendment 3.0)	NEW TEXT (Final Protocol Version 1.0 Amendment 4.0)	MOTIVATION FOR CHANGE
<p>SECTION 5.17 Reimbursement</p> <p>Participants will be reimbursed for any travel costs incurred as per local regulations. Reimbursements will be made after the completion of each trial visit. Research centre specific reimbursement amounts will be documented in the trial informed consent approved by the applicable IRB/IEC.</p>	<p>SECTION 5.17 Reimbursement</p> <p>Participants will be reimbursed for any travel costs incurred as per local regulations. Reimbursements will be made after the completion of each trial visit. <u>Upfront reimbursement for travel expenses may be made if this has been approved by the relevant ethics committee.</u> Research centre specific reimbursement amounts will be documented in the trial informed consent approved by the applicable IRB/IEC.</p>	<p>Text added to allow for reimbursement of a trial visit before the visit occurs.</p>



**INTERNATIONAL PARTNERSHIP *for* MICROBICIDES**

---

# STATISTICAL ANALYSIS PLAN FOR INTERIM ANALYSIS

---

**A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND,  
PLACEBO-CONTROLLED SAFETY AND EFFICACY  
TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN  
HEALTHY HIV-NEGATIVE WOMEN**

IPM 027

(Based on: Protocol Version 1.0, Amendment 2.0, dated 07 November 2012)

**Version 1.0**

International Partnership for Microbicides  
8401 Colesville Road, Suite 200  
Silver Spring, MD 20910 USA

**APPROVAL SIGNATURE PAGE**

**IPM 027– Statistical Analysis Plan for Interim Analysis**

**A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED SAFETY  
AND EFFICACY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-  
NEGATIVE WOMEN**

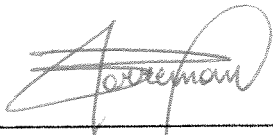
I have read the above referenced Statistical Analysis Plan and approve its contents.



Annalène Nel, MBChB PhD  
Chief Medical Officer  
International Partnership for Microbicides

09 October 2013

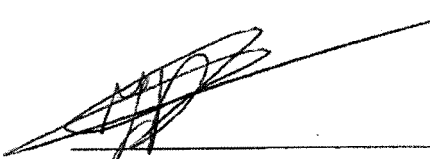
Date



Maarten Borremans, MSc  
Biostatistical Coordinator - Senior Biostatistician  
SGS Life Science Services – Biometrics

10 October 2013

Date



Joachim Dejonckheere, MSc  
Independent Biostatistician  
SGS Life Science Services – Biometrics

09 Oct 2013

Date

M. N.

Neliëtte van Niekerk, MCom  
Biometrics Specialist  
International Partnership for Microbicides

09 October 2013

Date

### **Abbreviations**

AE	Adverse Event
BMI	Body Mass Index
BV	Bacterial Vaginosis
CRF	Case Report Form
DAIDS	Division of Acquired Immunodeficiency Syndrome
DSMB	Data and Safety Monitoring Board
HIV	Human Immunodeficiency Virus
HSMC	HIV Seroconversion Monitoring Committee
ICH	International Conference on Harmonisation
IP	Investigational Product
IPM	International Partnership for Microbicides
IRE	Immediately Reportable Event
ITT	Intent-to-Treat
LOWESS	Locally Weighted Scatterplot Smoothing
MedDRA	Medical Dictionary for Regulatory Activities
m-ITT	Modified Intent-to-Treat
PID	Participant Identification Number
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
STI	Sexually Transmitted Infection
TEAE	Treatment Emergent Adverse Event

## Table of Contents

1	INTRODUCTION .....	6
2	RATIONALE .....	6
3	TRIAL DESIGN .....	6
3.1	General Design and Sample size .....	6
3.2	Randomisation .....	7
3.3	Blinding .....	7
4	SEQUENCE OF PLANNED ANALYSES .....	8
4.1	Safety Monitoring .....	8
4.2	Interim Analyses .....	8
4.3	Final Analysis and Reporting .....	9
5	ANALYSIS POPULATIONS .....	9
5.1	Safety Population .....	9
5.2	Modified Intent-to-treat (m-ITT) POPULATION .....	9
6	GENERAL STATISTICAL CONSIDERATIONS .....	10
6.1	Analysis Software .....	10
6.2	Methods for Handling Missing Data .....	10
6.3	Multiple Comparisons and Multiplicity .....	10
6.4	Multicentre Trials .....	10
6.5	Planned Subgroups, Interactions, and Covariates .....	10
6.6	Data Presentations .....	10
7	DISPOSITION OF TRIAL PARTICIPANTS .....	11
8	EVALUATION OF DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS .....	11
8.1	Demographic data .....	12
8.2	Obstetric History .....	12
8.3	Sexually transmitted infections (STIs), other genital tract infections and vaginal flora/pH test .....	12
8.4	Pelvic/Speculum examination data .....	12
9	EVALUATION OF HIV-1 SEROCONVERSION .....	13
9.1	HIV-1 seroconversion rate .....	13



9.2	Trial pausing and stopping guidelines: Early termination for proven efficacy or lack of efficacy (futility) .....	15
10	EVALUATION OF ACCRUAL, RETENTION AND ADHERENCE DATA.....	18
10.1	Accrual data .....	18
10.2	Retention data .....	18
10.3	Adherence data .....	18
10.3.1	Dapivirine Ring Residual Levels.....	19
10.3.2	Plasma and Vaginal Fluid Concentrations of Dapivirine .....	19
10.3.3	Self-reported Adherence by Questionnaire .....	20
11	EVALUATION OF SAFETY PARAMETERS.....	20
11.1	Adverse Events .....	20
11.2	Clinical Laboratory Evaluation .....	21
11.3	Pelvic examinations.....	22
11.4	Genital infections and STI assessments .....	22
11.5	Social Harms .....	22
12	PROTOCOL DEVIATIONS.....	22
13	REFERENCES.....	23
14	APPENDICES .....	23
	Appendix 1 – Table Shells .....	23
	Appendix 2 – Figure Shells.....	23
	Appendix 3 – Listing Shells.....	23
	Appendix 4 – Listing Shells for Report Appendices.....	23

## 1 INTRODUCTION

This document serves as the Statistical Analysis Plan (SAP) for the interim analysis for protocol IPM 027. Specifically, this document describes the statistical methods that will be used to analyse the interim efficacy and safety data from IPM 027 and provides templates for all tables, figures and listings that will be used to present the trial results. The planned analyses described in this SAP will be included in regulatory submissions.

Table shells, example figures and listings shells that will accompany the analysis are provided in Appendices 1 to 4. The appendices are viewed as supporting material to the analysis and will not require signature approval if formatting changes are made.

This document is based on the final version of the IPM 027 trial protocol Version 1.0, Amendment 2.0, which was finalised on 07 November 2012, and refers to Case Report Forms (CRFs) Version 1, dated 07 February 2012.

## 2 RATIONALE

An interim analysis will be conducted for IPM 027 when 50% of the 80 expected efficacy endpoints (40 HIV-1 seroconversions that have been confirmed as trial endpoints) have been observed. This analysis will involve breaking the blind to perform treatment comparisons for review by an independent Data and Safety Monitoring Board (DSMB), and will be conducted for the purpose of making a decision(s) on whether or not to stop the trial early for lack of intended efficacy (futility), or for overwhelming efficacy results. Only individuals as detailed in the IPM 027 DSMB charter will have access to the results of the interim analysis.

A complete overview of the following is presented in the Statistical Analysis Plan for the final analysis:

- Introduction to the trial
- Trial objectives
- Trial design.

## 3 TRIAL DESIGN

### 3.1 GENERAL DESIGN AND SAMPLE SIZE

IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled trial to assess the safety and efficacy of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks, in healthy, sexually active HIV-negative women, when compared to a placebo vaginal ring. Approximately 1650 participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.

Each participant will engage in the screening process for up to 4 weeks (28 days) prior to enrolment and will use the investigational product (IP) for a period of approximately 24 months (104 weeks).

Each participant will have an additional 6 weeks of follow-up after ring discontinuation, to assess safety and identify HIV seroconversions after product discontinuation.

### **3.2 RANDOMISATION**

Participants who meet all of the trial inclusion criteria and no exclusion criterion at baseline will be randomly assigned in a 2:1 ratio to one of two groups, receiving either the vaginal ring containing dapivirine or the placebo vaginal ring. Randomisation will be stratified by research centre at the time of enrolment, using a pre-specified block size, and will be determined via the use of an automated randomisation system to ensure balance of the treatment assignments. Both groups will use a ring inserted at 4-weekly intervals on a continuous basis for the duration of trial participation and have a follow-up visit 6 weeks after final ring removal.

A master randomisation list, linking each participant identification number to a trial treatment assignment (dapivirine ring or placebo ring), will be generated for the trial. At each research centre, as each new participant enters the trial, a unique participant identification number will be assigned to that participant using an automated response system.

### **3.3 BLINDING**

The Principal Investigator or his/her designee will be able to unblind each enrolled participant, through the automated system, if necessary. If, during the course of the trial a medical emergency requires knowledge of the test agent used by a particular participant, the trial blind or code may be broken for that specific participant, after discussion with IPM's Clinical Trial Physician or designee, whenever possible. Any unblinding of participant treatment assignments will be justified and explained in the source documents and applicable CRF and reporting forms. If the blinding code is broken by the Principal Investigator or his/her designee, the participant will be withdrawn from the trial and followed up as appropriate. The blinding and unblinding process will be performed by the automated response system.

An interim analysis will be conducted when 50% of the expected efficacy endpoints have been observed. This analysis will involve breaking the blind to perform treatment comparisons – see Section 4 for more details. Only individuals as detailed in the IPM 027 DSMB charter will have access to the results of the interim analysis.

## 4 SEQUENCE OF PLANNED ANALYSES

### 4.1 SAFETY MONITORING

An independent DSMB has been established for IPM 027. The DSMB members meet bi-annually via conference call during the trial. In addition, *ad hoc* calls or face-to-face meetings may be convened if requested by the DSMB Chair or IPM. DSMB members include individuals not associated with this trial, but who have expertise in conducting clinical trials, experience working in developing countries, and/or a history of working in the microbicide arena. Prior to each DSMB meeting, a data package of all available clinical and safety data will be prepared for the DSMB for their review; these data packages, containing blinded and unblinded data (masked treatment groups), will be prepared by an independent statistician not otherwise involved in the trial.

The DSMB has the option to recommend pausing or stopping the trial at any point for any of the following:

- Proven efficacy – if there is clear evidence that the risk of HIV-1 seroconversion is significantly lower in the dapivirine arm than in the placebo arm
- Lack of efficacy (futility) – if there is clear evidence that the trial is highly unlikely to show that the dapivirine ring is superior to placebo in reducing HIV-1 seroconversions, given current evidence and the additional information that would become available if the trial continued
- Ring-related safety outcomes observed in the dapivirine arm are greater than those observed in the placebo arm, and differ in a significant way as judged by the DSMB
- Trial performance standards are not acceptable.

The pausing and stopping rules that the DSMB will use as basis for recommending early termination of the trial due to proven efficacy, or lack of efficacy, are described in Section 9.2.

The DSMB composition and its charges related to the trial are described in a separate DSMB charter.

### 4.2 INTERIM ANALYSES

An interim analysis will be conducted for IPM 027 when 50% of the 80 expected efficacy endpoints (40 HIV-1 seroconversions that have been confirmed as trial endpoints) have been observed. This analysis will involve breaking the blind to perform treatment comparisons and will be conducted for the purpose of making a decision(s) on whether or not to stop the trial early for lack of intended efficacy (futility), or for overwhelming efficacy results. The interim analysis will be performed by an independent statistician who is not otherwise involved in the trial and will include all data available in the clinical

database at the time point when at least 40 HIV-1 seroconversions (confirmed trial endpoints) have occurred. The results of the interim analysis will be reviewed by the DSMB; only individuals as detailed in the IPM 027 DSMB charter will have access to the results of the interim analysis.

Full details of the efficacy analysis that will be performed at the interim analysis, including the statistical hypothesis to be tested, and the trial pausing or stopping rules that will be followed for this analysis, are presented in Section 9. Details of the safety analysis that will be performed are given in Section 11.

#### **4.3 FINAL ANALYSIS AND REPORTING**

A separate SAP has been prepared, detailing the final efficacy and safety analyses. This SAP will be finalised and approved prior to final database lock and unblinding.

### **5 ANALYSIS POPULATIONS**

#### **5.1 SAFETY POPULATION**

All participants who have been randomised to IP and received at least one dapivirine or placebo vaginal ring will be included in the safety population.

#### **5.2 MODIFIED INTENT-TO-TREAT (M-ITT) POPULATION**

As defined in ICH Guideline E9 (*Statistical Principles for Clinical Trials*)<sup>5</sup> the intent-to-treat (ITT) principle states that the effect of a treatment can be best assessed by evaluating the treatment on the planned treatment group, rather than the actual treatment given. The intent-to-treat population will include all trial participants who were randomised to one of the two treatment arms, dapivirine ring or placebo ring. All participants randomised to a treatment group will be analysed as members of the treatment group (dapivirine or placebo) to which they were randomised, regardless of adherence to the planned course of treatment.

Some participants may not have detectable levels of HIV antibodies at the enrolment visit, and as such, HIV-positive women who are assumed to be HIV-negative may be enrolled in the trial. To accommodate this situation, a modified intent-to-treat (m-ITT) population will be determined and used for the analysis of the primary efficacy endpoint. This population will include all participants that are included in the ITT population but will exclude those who were determined to be HIV-infected at the enrolment visit. These women who have seroconverted after enrolment will be excluded from the m-ITT population on the basis of baseline information collected prior to randomisation and which only became available after randomisation.

## **6 GENERAL STATISTICAL CONSIDERATIONS**

### **6.1 ANALYSIS SOFTWARE**

Statistical analyses will be conducted by an independent statistical vendor not otherwise involved in the trial. The statistical analyses will be performed using SAS<sup>®</sup> for Windows XP or Linux/Unix (version 9.1 or higher, SAS Institute Inc, Cary, North Carolina, USA).

### **6.2 METHODS FOR HANDLING MISSING DATA**

All participants in the m-ITT population will be included in the analysis of the primary efficacy endpoint. While every effort will be made to minimise the amount of missing data, some degree of missing data, primarily associated with missed visits, is expected. No imputation for missing data will be done for the interim analysis.

### **6.3 MULTIPLE COMPARISONS AND MULTIPLICITY**

Section 9.2 describes the method for adjusting the significance level for multiple evaluations of the efficacy data.

### **6.4 MULTICENTRE TRIALS**

Differences in participant safety and efficacy of the dapivirine vaginal ring across research centres will be explored graphically and descriptively. The key efficacy and safety analyses will be summarised overall and for each research centre separately.

### **6.5 PLANNED SUBGROUPS, INTERACTIONS, AND COVARIATES**

As stated in Section 5, the analysis of the primary efficacy endpoint will be based on the m-ITT population, which will include all participants who were HIV-negative at baseline and who were randomised to IP.

As this is a randomised trial in healthy HIV-negative women, it is anticipated that the treatment arms will be comparable at baseline with respect to pre-existing conditions. Furthermore, it is expected that women with pre-existing conditions will be treated and evaluated before being enrolled into the trial. For this reason, no baseline adjustments are planned or will be performed for the interim analysis.

### **6.6 DATA PRESENTATIONS**

Descriptive statistics will be presented overall, by research centre and by treatment arm (dapivirine ring and placebo ring).

For continuous variables, the descriptive statistics include: mean and standard deviation (when appropriate), quartiles, range, and number of non-missing data values. For

categorical variables, descriptive statistics may include frequencies, relative frequencies, and the number of missing data values. Percentages will be presented to one decimal place. The subsequent sections discuss the planned analyses beyond the listings and simple descriptive analyses.

Baseline is defined as the last available measurement before the first insertion of the IP. This measurement may be made at Screening 1, Screening 2, or Visit 1 (prior to ring insertion).

In accordance with the protocol, each scheduled visit while the participant is on IP has a window period of  $\pm 7$  days. However, consecutive visits should be no less than 21 days and no more than 35 days apart. If any repeat observations are made within any given window period, the repeat values will be captured as pertaining to unscheduled visits. Data from scheduled and unscheduled visits will be shown, and listings will be appropriately labelled when data arise from unscheduled visits.

Tables and figures of trial results will accompany the text of the interim analysis report. Listings will be sorted by treatment arm, research centre and participant identification number (PID), and key variables such as visit date and/or trial visit number will be presented in each listing.

## **7 DISPOSITION OF TRIAL PARTICIPANTS**

All participants who provide informed consent for this trial will be accounted for in accordance with ICH guideline E3 (*Structure and Content of Clinical Study Reports*)<sup>4</sup>.

The number and percentage of trial participants who were screened, randomised to IP, permanently discontinued IP, permanently discontinued the trial, and who completed the trial will be presented.

For those participants who discontinued prematurely, the time to permanent discontinuation of IP and the time to permanent discontinuation of the trial will be calculated, and presented together with Kaplan-Meier curves by treatment and research centre-by-treatment.

A figure will also be presented to depict the cumulative enrolment per research centre and treatment arm.

## **8 EVALUATION OF DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS**

Unless otherwise specified, demographic data and other baseline characteristics will be summarised descriptively overall, by research centre, and by treatment arm, using appropriate summary statistics as described in Section 6.6.

## 8.1 DEMOGRAPHIC DATA

The following baseline demographic characteristics will be summarised: age, race, height, weight and body mass index (BMI), as well as information on education level and relationship history. Age and BMI will be derived as described in Table 1.

**Table 1 Derived and Computed Demographic Variables**

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes, or Equation(s)
Age	Age (years)	18 to 45 (inclusive)	INT((date of enrolment – date of birth)/365.25)
BMI	Body Mass Index (kg/m <sup>2</sup> )		(Participant body weight in kg)/ (Participant height in m) <sup>2</sup>

Qualitative demographic characteristics (nominal or ordinal categories) will be summarised using absolute and relative frequencies. Quantitative demographic characteristics (continuous) will be summarised using the appropriate summary statistics.

## 8.2 OBSTETRIC HISTORY

Obstetric history data will be collected during the Screening 1 visit. These data will be presented descriptively per research centre and treatment arm.

## 8.3 SEXUALLY TRANSMITTED INFECTIONS (STIs), OTHER GENITAL TRACT INFECTIONS AND VAGINAL FLORA/pH TEST

Cervicovaginal samples will be collected for genital infection and STI testing (bacterial vaginosis (BV), Trichomonas, Gonorrhoea, Chlamydia and Syphilis) at Screening Visit 1 and every 12 weeks until the last product use visit. Assessments of vaginal flora and vaginal pH will be done at the Enrolment visit and every 12 weeks until the last product use visit, to assess changes in vaginal flora as measured by the Nugent score for three pathogens (*Lactobacilli*, *Gardnerella* and anaerobic gram negative rods morphotype, *Mobiluncus Spp*), and overall.

STIs and other genital tract infections will be summarised using absolute and relative frequencies. Vaginal pH, total numeric Nugent score and different gram stain results for the three pathogens mentioned above will be summarised using appropriate summary statistics. A listing will also be presented for all STIs and other genital tract infections findings.

## 8.4 PELVIC/SPECULUM EXAMINATION DATA

Pelvic examinations will be performed at Screening Visits 1 and 2, and every 12 weeks until the last product use visit. A summary of pelvic examination data will be presented



overall, by research centre, treatment arm, and by trial visit in tabular form. By-participant listings will also be provided.

## **9 EVALUATION OF HIV-1 SEROCONVERSION**

The analysis of the primary efficacy endpoint will be performed on the m-ITT population, *i.e.* all trial participants who were HIV-1 negative at enrolment and who were randomised to either the dapivirine or placebo vaginal ring.

A blinded review of the data for the May 2013 DSMB meeting (data cut-off date: 28 February 2013), confirmed a suspicion of product non-adherence in the trial. Specifically, at Research Centre 03 in KwaZulu-Natal, South Africa, a high incidence of protocol non-adherence (primarily missed and late visits, and early trial discontinuations) was observed in December 2012 – a finding which prompted the Sponsor to analyse all used rings returned to all research centres as of 28 February 2013 for residual dapivirine amounts. This (blinded) analysis revealed that during any given month of ring use, the majority (50-80%) of women assigned to the dapivirine ring at Research Centre 03 had drug residuals in used rings of 24 mg or more (*i.e.* essentially all of the initial drug load), indicating limited ring use.

For this reason, an additional analysis on the m-ITT population, excluding all participants enrolled at Research Centre 03, will be performed as complementary analysis.

Based on the outcome of the two analyses performed on the primary efficacy endpoint (refer to Section 9.1) and the stopping or pausing criteria as set out in Section 9.2, the DSMB will make a recommendation regarding continuing, pausing or stopping the trial, also taking into account the treatment effect observed at each research centre, and the results of the analysis of the ring residual levels of dapivirine in the returned rings (refer to Section 10.3.1).

### **9.1 HIV-1 SEROCONVERSION RATE**

Trial participants will be followed on IP for 24 months, and will be tested for HIV-1 infection at 4-weekly visits until the last product use visit, as well as at the exit visit 6 weeks after ring discontinuation. HIV seroconversion will be determined per the HIV testing algorithm presented in Appendix C of the IPM 027 protocol<sup>6</sup>. However, the statistical analyses will be performed on confirmed trial endpoints only, *i.e.* HIV-1 seroconversions confirmed by the independent IPM 027 HIV Seroconversion Monitoring Committee (HSMC) as occurring after enrolment into the trial. The point of HIV-1 infection is determined by performing reverse sequential HIV RNA PCR testing (on stored samples collected at each visit) until a negative test result is achieved.

The following statistical analyses will be performed:

- Analysis on the m-ITT population, with censoring applied for those participants who have not been diagnosed with HIV-1 infection by the data cut-off date for the interim analysis. Censoring will be applied at the date of trial termination (for any reason), or the data cut-off date for the interim analysis, and will be assumed to be unrelated to HIV-1 acquisition; it will also be assumed that survival probabilities are the same for participants recruited early and late in the trial.
- Analysis on the m-ITT population, excluding all participants enrolled at Research Centre 03 (both adherent and non-adherent women in both the active and placebo arms).

The number of HIV-1 seroconversions (confirmed trial endpoints), the incidence density rate of HIV-1 seroconversion, *i.e.* HIV-1 seroconversion rate per 100 person-years of product use, as well as a 95% confidence interval for the HIV-1 seroconversion rate per 100 person-years, will be presented for each treatment arm and research centre.

The formal statistical test that will be used to evaluate the difference in time to seroconversion between the dapivirine ring and placebo ring will be the log-rank test, stratified by research centre. The log-rank test is a non-parametric statistical method for comparing distributions of time until the occurrence of an event of interest among independent groups. In this case, the event will be HIV-1 seroconversion. The event time will be defined as the elapsed time from enrolment to HIV-1 seroconversion.

The log-rank test assumes a constant hazard ratio over time. The analysis will include presentation of Kaplan-Meier survival curves, in addition to an evaluation of Schoenfeld residuals,  $\log(-\log(\text{survival}))$  versus  $\log$  of survival time plots, and the LOWESS smooth for visual inspection of the proportional hazards assumption.

The LIFETEST SAS procedure will be used to apply the log-rank test to the data. The output from this procedure will provide a Chi-square value with an associated p-value, as well as a Kaplan-Meier survival curve (representing the estimated proportion of HIV-negative participants at every time point).

A listing will be presented for all positive HIV test results.

The bi-annual HIV-1 incidence rate per 100 person-years (based on confirmed trial endpoints) will be plotted by DSMB reporting period, and per research centre and treatment group.

Calculation methods of the derived variables that will be used in the analyses are provided in Table 2.

**Table 2 Derived and Computed Variables – HIV Seroconversion**

Variable Name	Description	Computation Methods, Notes, or Equation(s)
HIV_TTS	Time to HIV-1 seroconversion	Date_HIV_seroconversion* – Date_enrolment
HIV_TDP	Time to discontinuation of IP	Date_LPU – Date_enrolment
HIV_TDT	Time to discontinuation of trial	Date_trial completion – Date_enrolment
HIV_C	Censor variable	

\* Date of first trial visit with an HIV-positive test result.  
 LPU = Last recorded date of product use.

### **9.2 TRIAL PAUSING AND STOPPING GUIDELINES: EARLY TERMINATION FOR PROVEN EFFICACY OR LACK OF EFFICACY (FUTILITY)**

The IPM 027 trial has 83.2% power to detect a reduction of 50% in the HIV-1 seroconversion rate for the dapivirine ring relative to placebo. The primary null and alternative hypotheses for this trial are:

- $H_0$ : HIV-1 seroconversion hazard rate of active product relative to placebo = 1  
 (hazard ratio = 1)
- $H_1$ : HIV-1 seroconversion hazard rate of active product relative to placebo < 1  
 (hazard ratio < 1)

However, at the interim analysis, a more stringent efficacy evaluation will be performed. The efficacy of the dapivirine ring will be evaluated against the null hypothesis that the hazard ratio = 0.75:

- $H_0$ : HIV-1 seroconversion hazard rate of active product relative to placebo = 0.75  
 (hazard ratio = 0.75)
- $H_1$ : HIV-1 seroconversion hazard rate of active product relative to placebo < 0.75  
 (hazard ratio < 0.75)

The null hypothesis will be evaluated at a nominal, one-sided 2.5% significance level, and the stopping criteria will be as follows:

- Stopping for efficacy will be allowed when the hazard ratio < 0.75
- Stopping for futility will be allowed when the hazard ratio = 1, or for harm when the hazard ratio > 1

The DSMB will review the results of the interim analysis, and has the option to recommend pausing or stopping the trial at any point for any of the following:

- Proven efficacy – if there is clear evidence that the risk of HIV-1 seroconversion is significantly lower in the dapivirine arm than in the placebo arm ( $H_0$ : HR = 0.75 is rejected in favour of  $H_1$ )

- Lack of efficacy (futility) – if there is clear evidence that the trial is highly unlikely to show that the dapivirine ring is superior to placebo in reducing HIV-1 seroconversions, given current evidence and the additional information that would become available if the trial continued.

The null hypothesis will be evaluated at a nominal, one-sided 2.5% significance level. To avoid inflation of the Type I error rate when evaluating superiority both at the interim and the final analysis, the Lan and De-Met's implementation of the O'Brien-Fleming grouped sequential stopping boundary, with the time scale measured on the cumulative number of HIV-1 seroconversions, will be used.

With 50% of the expected number of events available, the adjusted one-sided significance levels are equal to 0.0015 at the interim analysis and 0.0245 at the final analysis, with -2.9626 and -1.9686 the respective, corresponding critical values for the test statistic (on the Z-scale). If the actual number of events at the interim analysis is different from 40 (50% of expected trial endpoints), the O'Brien-Fleming-adjusted critical values/significance levels corresponding to the actual fraction of information will be used.

To evaluate the null hypothesis for efficacy, the log-rank test stratified for research centre will be used, including the available data up to the data cut-off point. If the (one-sided) p-value obtained with this stratified log-rank test is below 0.0015, the null hypothesis of  $HR = 0.75$  will be rejected and it will be concluded that the HIV-1 seroconversion rate for dapivirine is superior, compared to placebo.

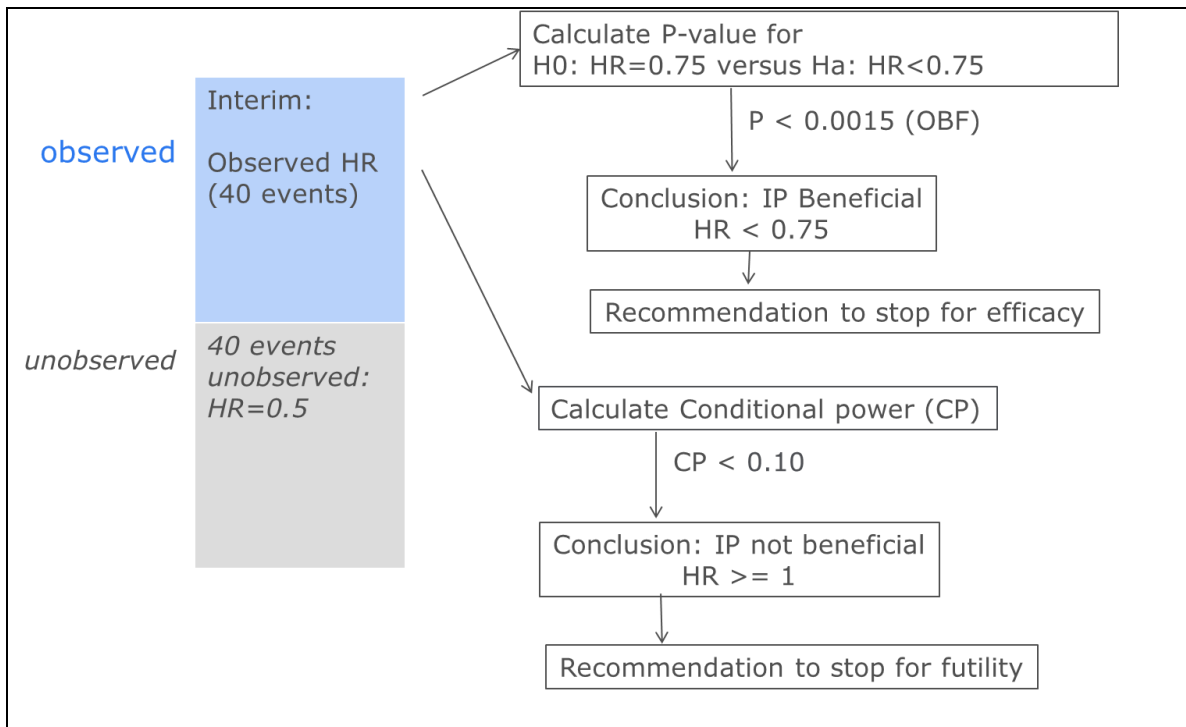
At the same time, futility will be evaluated using methods of stochastic curtailment. Specifically, at the interim analysis the conditional power to reject  $H_0: HR = 1$  at trial end (final analysis) will be calculated based on the log-rank test, conditional on the observed value of the stratified log-rank test statistic for the observed data and assuming the hazard ratio equals 0.5 (with an annual HIV incidence rate of 4% for placebo, and an annual loss-to-follow-up rate of 10%, as specified in the protocol) for the unobserved data. When the conditional power appears smaller than 0.10 (10%) the trial will be stopped to accept  $H_0$ , and futility will be concluded.

In summary, implementation of the analysis methods specified above will permit early stopping only for a very strong positive effect (proven efficacy, *i.e.* clear evidence that the risk of HIV-1 seroconversion is significantly lower in the dapivirine arm than in the placebo arm) or a strong negative effect (futility or harm, *i.e.* clear evidence that the trial is highly unlikely to show that the dapivirine ring is superior to placebo in reducing HIV-1 seroconversions, given current evidence and the added information that would become available if the trial continued).

**Note:** Based on the outcome of the two analyses performed on the primary efficacy endpoint (refer to Section 9.1) and the stopping or pausing criteria as set out above, the DSMB will make a recommendation regarding continuing, pausing or stopping the trial:

- Stopping for futility should only be recommended if the conditional power to reject  $H_0: HR = 1$  at trial end (final analysis) for both analyses appears smaller than 0.10
- Stopping the trial for efficacy should only be recommended if the p-value of the stratified log-rank test of both analyses is below the O'Brien-Fleming-adjusted significance level corresponding to the actual number of trial endpoints included in the analyses ( $p < 0.0015$  if 40 trial endpoints are included in the analyses)
- Any recommendation on pausing or stopping the trial should also take into account the treatment effect observed at each individual research centre, and the results of the analysis of the ring residual levels of dapivirine in the returned rings (refer to Section 10.3.1).

**Overview of interim analysis (assuming 40 confirmed trial endpoints are available)**



OBF = O'Brien-Fleming; IP = Investigational product; HR = Hazard ratio; CP = Conditional power

## 10 EVALUATION OF ACCRUAL, RETENTION AND ADHERENCE DATA

### 10.1 ACCRUAL DATA

A figure will be presented where the actual accrual rate as of the data cut-off date for the interim analysis will be plotted along with the expected accrual rate.

### 10.2 RETENTION DATA

Retention rates will be calculated per visit and overall and presented descriptively per research centre and treatment arm. The following calculations will be used:

- Retention rate per visit will be calculated as:

$100 \times (\text{Number of participants expected for the visit and who completed the visit within the allowable timeframe} / \text{Number of participants expected per visit}).$

Note that for this calculation, a participant is not considered “expected” once she has HIV seroconverted, but is considered “expected” for every visit after enrolment, regardless of loss-to-follow-up or termination.

- Overall (cumulative) retention rate will be calculated as:

$100 \times (\text{Total number of completed visits within the allowable timeframe per visit as of the data cut-off date} / \text{Total number of expected study visits}).$

Note that for this calculation, a participant is not considered “expected” once she has HIV seroconverted and “expected visits” is the number of visits expected to be completed, assuming no missed visits or loss-to-follow-up.

### 10.3 ADHERENCE DATA

The data collected in IPM 027 allow both subjective and objective assessments of adherence to ring use by the participants in this trial. The subjective adherence measures include self-reported ring use as collected by adherence questionnaires, and/or feedback from participants or male partners following qualitative individual interviews or focus group discussions. Missed and/or late clinical trial visits (outside protocol-allowed visits windows – refer to Section 6.6) will also be used as indicator of non-adherence to prescribed product use. Objective, quantitative measures of adherence include plasma and vaginal fluid concentrations of dapivirine in samples collected at the 4-weekly trial visits, as well as the residual levels of dapivirine in all used rings returned to the research centres.

### **10.3.1 DAPIVIRINE RING RESIDUAL LEVELS**

All used vaginal rings returned to the research centres at each trial visit are collected and shipped at regular, pre-defined intervals to an analytical laboratory, where the rings of those participants assigned to the active ring are analysed to determine the residual amounts of dapivirine in the rings.

The following summaries will be produced on these data:

- A summary of ring residual levels at each trial visit, with standard descriptive statistics – presented overall and by research centre. Corresponding box plots will be prepared.
- A descriptive summary of the ring residual levels by trial visit and by category of residual amount (0-5, 6-10, 11-15, 16-17, 18-19, 20-21, 22-23, and 24-25+ mg). This summary will be prepared overall and by research centre, with corresponding bar charts.
- A summary relating the ring residual amounts to time intervals (in days) between consecutive trial visits (<7, 7-14, 14-21, 21-28, 28-35, 35-42, 42-49, 49-56, and >56 days), to determine whether a trend between residual amounts and visits outside the permitted window periods is apparent. Corresponding box plots will be prepared.

In addition, a listing of those trial participants who HIV-1 seroconverted (confirmed trial endpoints), together with the number of days since their last trial visit, and corresponding ring residual levels of dapivirine, will be produced. A scatter plot of the residual levels of dapivirine in the last ring returned by these participants prior to HIV seroconversion will be produced and compared visually with the average ring residual levels of those participants who were HIV-negative as of the data cut-off date for the interim analysis.

### **10.3.2 PLASMA AND VAGINAL FLUID CONCENTRATIONS OF DAPIVIRINE**

All blood and vaginal fluid samples collected at each trial visit are shipped to a bio-analytical laboratory, where the samples of all participants assigned to active rings are analysed for plasma and vaginal fluid levels of dapivirine.

These data will be summarised and presented graphically by box plots for each visit, by research centre and overall. A summary, relating the plasma and vaginal fluid concentrations of dapivirine to time intervals (in days) between consecutive trial visits (<7, 7-14, 14-21, 21-28, 28-35, 35-42, 42-49, 49-56, and >56 days), will be produced to determine whether a trend is apparent between these levels and visits outside the permitted visit window periods. These results will be presented graphically by box plots.

In addition, a listing of those trial participants who HIV-1 seroconverted (confirmed trial endpoints), together with the number of days since their last trial visit, dapivirine ring residual levels, and corresponding plasma and vaginal fluid levels of dapivirine, will be produced. Scatter plots of the plasma and vaginal fluid levels of dapivirine measured prior to HIV seroconversion for these participants will be produced and compared visually with the average plasma and vaginal fluid levels of dapivirine of those participants who were HIV-negative as of the data cut-off date for the interim analysis.

The correlation between the amount of residual dapivirine in the used rings and the corresponding plasma and vaginal fluid levels of dapivirine will be explored graphically and summarised descriptively.

### **10.3.3 SELF-REPORTED ADHERENCE BY QUESTIONNAIRE**

Self-reported adherence to the ring regimen will be calculated per visit and overall, and presented descriptively per research centre and treatment group. The adherence rate per visit will be calculated as:

- $100 \times (\text{Number of days that the participant reportedly wore the ring} / \text{the total number of days that the participant was expected to wear the ring})$ .

The self-reported adherence rates will be presented in the following categories:

- > 80%
- 60% to 80%
- 40% to 60%
- < 40%.

## **11 EVALUATION OF SAFETY PARAMETERS**

### **11.1 ADVERSE EVENTS**

The safety analyses will be performed based on the safety population only.

An adverse event (AE) is defined as any untoward medical occurrence during the course of a clinical trial in a participant who received an investigational product at any dose, which does not necessarily have a causal relationship with the investigational product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding considered clinically significant by the Investigator), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the IP. Any condition occurring prior to enrolment will be recorded as medical history. All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.0.



### *Treatment Emergent Adverse Events (TEAEs)*

TEAEs are defined as those AEs that started on or worsened after the first application of the IP. Only TEAEs will be recorded in the CRF.

### *Product-related Adverse Events*

Product-relatedness is reported as “Related” or “Not Related”. While every effort is made to ensure that this field is not missing through data reviews and queries, if the relationship with the IP is missing on the CRF, it will be assumed that the AE was “related” to the IP.

### *Immediately Reportable Events (IREs)*

IREs are defined as:

- Serious adverse events (SAEs)
- Pregnancies
- HIV seroconversions
- Non-serious adverse events leading to permanent discontinuation of IP.

Frequencies of all IREs and other selected adverse events, including DAIDS<sup>2</sup> Grade 2 or higher AEs, DAIDS Grade 3 or higher AEs, AEs judged by the Investigator as product-related, urogenital AEs, and deaths, will be summarised by research centre and treatment arm.

The incidence of all adverse events will be reported by MedDRA system organ class (SOC) and preferred term (PT), and presented by treatment arm and research centre. The incidence of adverse events by worst severity, all product-related adverse events by worst severity and all urogenital adverse events by worst severity will be presented by SOC, PT and treatment group.

Listings will be presented for all reported adverse events, all DAIDS Grade 2 or higher adverse events and all adverse events leading to trial and/or IP discontinuation.

## **11.2 CLINICAL LABORATORY EVALUATION**

Collection of blood specimens for haematology and biochemistry (including electrolytes, liver function and renal function), and urine specimens for urinalysis and microscopy tests, takes place at Screening Visit 1, and every 12 weeks until the last product use visit.

Shift tables will be used to present the percentage of individuals with DAIDS Grade 1 to 4 haematology and biochemistry laboratory findings for each parameter under investigation, using the maximum severity at the Screening visit *versus* each of the visits during which clinical evaluations are performed. The tables will be presented for each laboratory parameter, by treatment arm.

A separate by-participant listing will be presented for all DAIDS Grade 1 or higher post-enrolment laboratory values.

### **11.3 PELVIC EXAMINATIONS**

Please refer to Section 8.4.

### **11.4 GENITAL INFECTIONS AND STI ASSESSMENTS**

Please refer to Section 8.3.

### **11.5 SOCIAL HARMS**

During each HIV counselling session, participants are asked questions to assess the occurrence of social harms. Participants who experience social harms 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.

By-participant listings of all social harms data will be provided as well as summary tables of such occurrences.

## **12 PROTOCOL DEVIATIONS**

The number of participants with protocol deviations will be presented using appropriate summary statistics overall, by research centre, and by treatment arm. A listing of all recorded protocol deviations will also be produced.

A protocol violation is a major deviation from the protocol which may impact the integrity of the data and/or the safety of the trial participant(s). A list of categorised protocol violations has been developed before the start of the trial and will be included in the SAP for the final efficacy and safety analysis, for purposes of defining the per-protocol analysis population prior to final database lock and unblinding.

## 13 REFERENCES

1. Chow S, Liu J. Design and Analysis of Clinical Trials: Concepts and Methodologies. 2<sup>nd</sup> Edition. Hoboken, NJ: Wiley-Interscience; 2004.
2. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 December, 2004; Clarification 1 August 2009.
3. Hosmer DW, Lemeshow S. Applied Survival Analysis: Regression Modeling of Time to Event Data. New York: Wiley; 1999.
4. ICH (1996). International Conference on Harmonisation. Guideline E3 Structure and Content of Clinical Trial Reports.
5. ICH (1998). International Conference on Harmonisation. Guideline E9 Statistical Principles for Clinical Trials.
6. IPM 027 Protocol: *A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED SAFETY AND EFFICACY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-NEGATIVE WOMEN* Version 1.0, Amendment 2.0; 07 November 2012.

## 14 APPENDICES

### APPENDIX 1 – TABLE SHELLS

### APPENDIX 2 – FIGURE SHELLS

### APPENDIX 3 – LISTING SHELLS

### APPENDIX 4 – LISTING SHELLS FOR REPORT APPENDICES



**INTERNATIONAL PARTNERSHIP *for* MICROBICIDES**

---

# STATISTICAL ANALYSIS PLAN

---

## **A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED SAFETY AND EFFICACY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-NEGATIVE WOMEN**

**IPM 027**

(Based on: Version 1.0, Amendment 3.0, dated 12 September 2013)

**Version 0.11**

International Partnership for Microbicides  
8401 Colesville Road, Suite 200  
Silver Spring, MD 20910 USA

**APPROVAL SIGNATURE PAGE**  
**IPM 027– Statistical Analysis Plan**

**A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED SAFETY  
AND EFFICACY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-  
NEGATIVE WOMEN**

I have read the above referenced Statistical Analysis Plan and approve its contents.

---

Annaléne Nel, MBChB PhD  
Chief Medical Officer  
**International Partnership for Microbicides**

---

Date

---

Maarten Borremans, MSc  
Biostatistical Coordinator - Senior Biostatistician  
**SGS Life Science Services – Biometrics**

---

Date

---

Allison Carter, MBChB  
Clinical Trial Physician  
**International Partnership for Microbicides**

---

Date

---

Neliëtte van Niekerk, MCom  
Biometrics Specialist  
**International Partnership for Microbicides**

---

Date

### Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CRF	Case Report Form
CSR	Clinical Study Report
DAIDS	Division of Acquired Immunodeficiency Syndrome
DSMB	Data and Safety Monitoring Board
HIV	Human Immunodeficiency Virus
HSMC	HIV Seroconversion Monitoring Committee
HSV-2	Herpes Simplex Virus-2
ICH	International Conference on Harmonisation
IP	Investigational Product
IPM	International Partnership for Microbicides
IRE	Immediately Reportable Event
ITT	Intent-to-Treat
LOWESS	Locally Weighted Scatterplot Smoothing
MedDRA	Medical Dictionary for Regulatory Activities
m-ITT	Modified Intent-to-Treat
PID	Participant Identification Number
PP	Per-Protocol
PT	Preferred Term
RAM	Resistance Associated Mutation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
STI	Sexually Transmitted Infection
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization

## Table of Contents

1. INTRODUCTION .....	7
2. TRIAL OBJECTIVES .....	7
2.1 Primary Objectives .....	7
2.2 Secondary Objectives .....	7
2.3 Exploratory Objectives .....	8
2.4 Assessment of Objectives .....	8
3 TRIAL DESIGN .....	9
3.1 General Design and Plan .....	9
3.2 Sample Size .....	10
3.3 Randomisation .....	11
3.4 Blinding .....	11
4 SEQUENCE OF PLANNED ANALYSES .....	11
4.1 Safety Monitoring .....	11
4.2 Interim Analyses .....	12
4.3 Final Analysis and Reporting .....	13
5 ANALYSIS POPULATIONS .....	13
5.1 Safety Population .....	13
5.2 Intent-to-treat (ITT) Population .....	13
5.3 Modified Intent-to-treat (m-ITT) Population .....	13
5.4 Per-protocol (PP) Population .....	14
6 GENERAL STATISTICAL CONSIDERATIONS .....	14
6.1 Analysis Software .....	14
6.2 Methods for Handling Missing Data .....	14
6.3 Multiple Comparisons and Multiplicity .....	14
6.4 Multicentre Trials .....	15
6.5 Planned Subgroups, Interactions, and Covariates .....	15
6.6 Data Presentations .....	15
7. TRIAL PARTICIPANTS .....	16
7.1 Disposition of Trial Participants .....	16

7.2	Protocol Deviations and Violations.....	17
7.3	Adherence to Ring Regimen.....	17
7.3.1	Adherence Measures Applying to Both Treatment Arms.....	18
7.3.2	Adherence Measures Applying to Active Arm Only.....	18
7.3.3	Self-reported Adherence by Questionnaire.....	20
8.	EVALUATION OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS.....	20
8.1	Baseline Demographics, and Relationship and Sexual History.....	21
8.2	Baseline Medical and Surgical History.....	21
8.3	Baseline Screening Assessments.....	21
8.4	Obstetrics and Gynaecological History.....	21
9.	EVALUATION OF TRIAL ENDPOINTS.....	22
9.1	Primary Endpoint 1 – Efficacy.....	22
9.1.1	Complementary Analyses on the Primary Efficacy Endpoint.....	24
9.2	Primary Endpoint 2 – Safety.....	25
9.3	Secondary Endpoints.....	26
9.3.1	Secondary Endpoint 1: Seroconversion rate of HIV-2 per 100 person-years of product use at the end of the IP use period.....	26
9.3.2	Secondary Endpoint 2: The incidence of curable STIs, and changes in vaginal flora in each trial arm over the IP use period.....	27
9.3.3	Secondary Endpoint 3: Incidence of pregnancy in each trial arm over the IP use period.....	28
9.3.4	Secondary Endpoint 4: Proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period.....	28
9.3.5	Secondary Endpoint 5: The proportion of women who report the use of the vaginal ring as acceptable.....	29
9.3.6	Secondary Endpoint 6: HIV-1 drug resistance mutations among participants who acquire HIV-1.....	30
10.	EVALUATION OF SAFETY PARAMETERS.....	31
10.1	Adverse Events.....	31
10.1.1	Treatment Emergent Adverse Events (TEAEs).....	31
10.1.2	Product-related Adverse Events.....	31
10.1.3	Summary Tables.....	31



10.2	Clinical Laboratory Evaluation.....	34
10.2.1	Assessments .....	34
10.2.2	Summary Tables.....	35
10.3	Pelvic examinations .....	36
10.3.1	Assessments .....	36
10.3.2	Summary Tables.....	36
10.4	Genital infections and other STI assessments .....	37
10.4.1	Assessments .....	37
10.4.2	Summary Tables.....	37
10.5	Immediately Reportable Events .....	38
10.5.1	Assessments .....	38
10.5.2	Summary Tables.....	38
10.6	Concomitant Medications.....	39
10.7	Physical Examination Findings and Vital Signs.....	40
10.8	Social Harms .....	40
11.	REFERENCES .....	42
12.	APPENDICES.....	42
12.1	Appendix 1 – Consort Flow Diagram.....	42
12.2	Appendix 2 – Table Shells .....	42
12.3	Appendix 3 – Figure Shells .....	42
12.4	Appendix 4 – List of Individual Participant Listings.....	42
12.5	Appendix 5 – IAS-USA Update of the Drug Resistance Mutations in HIV-1: March 2013 .....	42

## 1. INTRODUCTION

This document serves as the Statistical Analysis Plan (SAP) for the primary and secondary endpoints for protocol IPM 027. Specifically, this document describes the statistical methods that will be used to analyse the final data from IPM 027 to support the completion of the Clinical Study Report (CSR). The planned analyses described in this SAP will be included in regulatory submissions and/or future manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program.

Table shells, example figures, and listing shells that will accompany the analysis are provided in Appendices 2, 3, and 4, respectively. The appendices are viewed as supporting material of the analysis and will not require signature approval if formatting changes are made.

This document is based on the final version of the IPM 027 trial protocol Version 1.0, Amendment 3.0, which was finalised on 12 September 2013, and refers to Case Report Forms (CRFs) Version 1, dated 07 February 2012.

## 2. TRIAL OBJECTIVES

### 2.1 Primary Objectives

The primary objectives of this trial are:

- To determine the efficacy of dapivirine administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks), in preventing HIV-1 infection among healthy, sexually active HIV-negative women
- To assess the safety of dapivirine administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks).

### 2.2 Secondary Objectives

The secondary objectives of this trial are:

- To assess and compare the incidence of HIV-2 in the dapivirine and placebo vaginal ring groups
- To assess and compare the incidence of curable sexually transmitted infections (STIs), and changes in vaginal flora in the dapivirine and placebo vaginal ring groups
- To determine the incidence of pregnancy in both trial arms
- To assess reported adherence to the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period

- To assess reported acceptability of the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period
- To assess the frequency and type of HIV-1 drug resistance in women who acquire HIV-1 infection while using the investigational product.

### **2.3 Exploratory Objectives**

The exploratory objectives of this trial are:

- To evaluate the association between HSV-2 and HIV-1 infection in both trial arms
- To explore the potential relationship between method of contraception, pregnancy incidence and HIV seroconversion in both trial arms
- To explore the relationship between drug concentrations and trial outcomes (HIV-1 seroconversion and viral resistance)
- To explore the correlation of drug concentrations and self-reported adherence measures.

### **2.4 Assessment of Objectives**

Consistent with the primary objectives, the primary endpoints are:

- The incidence rate of HIV-1 serconversion
- All adverse events (AEs) (full descriptive evaluation).

The primary endpoints will be assessed by:

- Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm
- Self-reports, physical examination, gynaecological assessments, including pelvic/speculum examination, laboratory tests and other indicated investigations. All AEs will be reported, regardless of grade or relatedness.

Consistent with the secondary objectives, the secondary endpoints are:

- The incidence rate of HIV-2 seroconversion
- The incidence of curable STIs (*i.e. N.gonorrhoeae, C.trachomatis and T.vaginalis*), and changes in vaginal flora in each trial arm over the IP use period
- The incidence of pregnancy in each trial arm over the IP use period
- The proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period
- The proportion of women who report the use of the vaginal ring as acceptable
- The proportion of participants with HIV-1 drug resistance mutations among participants who acquire HIV-1.

The secondary endpoints will be assessed through:

- Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C of the trial protocol
- STI testing, vaginal flora and vaginal pH testing
- Pregnancy testing
- Questionnaires and qualitative data regarding sexual behaviour and adherence to the use of a vaginal ring inserted once every 4 weeks over the trial period
- Questionnaires and qualitative data regarding the acceptability of the use of a vaginal ring inserted once every 4 weeks over the trial period
- Viral genotyping methods.

Consistent with the exploratory objectives, the exploratory endpoints include:

- The proportion of HSV-2 among analysed samples
- Incidence of pregnancy in correlation with HIV seroconversion rates and method(s) of contraception used by participants
- Steady-state drug concentrations in blood and vaginal fluid
- Steady-state drug concentrations in correlation with self-reported adherence as outlined above for the secondary objective.

The exploratory endpoints will be assessed by:

- HSV-2 testing
- Pregnancy testing and HIV testing as outlined above for the secondary objective, and documentation of participant contraceptive method(s)
- Drug concentrations in blood and vaginal fluid
- Vaginal fluid, plasma and/or ring residual drug concentrations and self-reported behavioural measures as outlined above for the secondary objective.

### **3 TRIAL DESIGN**

#### **3.1 General Design and Plan**

IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled trial to assess the safety and efficacy of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks, in healthy, sexually active HIV-negative women, when compared to a placebo vaginal ring. Approximately 1950 participants will be randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.

Each participant will engage in the screening process for up to 4 weeks (28 days) prior to enrolment and will use the IP for a period of approximately 24 months (104 weeks).

Each participant will have an additional 6 weeks of follow-up after ring discontinuation, to assess safety (adverse events) and identify HIV seroconversions after product discontinuation.

### 3.2 Sample Size

IPM 027 will be conducted in a sample of approximately 1950 HIV-negative women in a 2:1 ratio, such that 1300 participants will be assigned to the dapivirine ring and 650 participants will be assigned to the placebo ring. The sample size and power calculations for this trial were based on the primary efficacy endpoint, the incidence rate of HIV-1 seroconversions, in the two treatment arms. The statistical assumptions used in determining this sample size include:

- proportional hazards among the two groups
- microbicide efficacy of  $\geq 50\%$  in preventing HIV-1 infection
- randomisation ratio of 2:1 (dapivirine vaginal ring *versus* placebo ring)
- a two-sided log-rank test statistic, with  $\alpha = 0.05$
- $> 4\%$  average annual HIV incidence in the placebo arm (assumes a reduction in incidence in the trial population due to risk reduction counselling)
- $\leq 10\%$  loss-to-follow-up rate over the duration of the trial period.

The increased sample size of 1950 (from 1650, as planned in IPM 027 protocol version 1.0 and amendments 1.0 and 2.0) will mitigate the potential negative impact of product non-adherence on the trial outcome and sustain the power of the trial for the primary objectives.

Table 1 below provides the estimated power to detect 40%, 50% and 60% microbicide efficacy with a sample size of 1950 based on the assumptions as stated above.

**Table 1 Estimated Power for Varying Microbicide Efficacy Levels**

Microbicide efficacy	# Expected HIV-1 seroconversions	Power
40%	104	61%
50%	96	81%
60%	88	94%

A trial with the proposed design will provide approximately 81% power to detect a 50% reduction in the rate of HIV-1 seroconversions in the active arm, assuming an annual HIV-1 seroconversion rate of 4% in the placebo arm, and a 10% loss-to-follow-up rate.

In a trial with this number of participants assigned to the IP, there is a 95% probability of detecting an AE occurring at a rate of 0.3% or higher.

### **3.3 Randomisation**

Participants who meet all of the trial inclusion criteria and no exclusion criterion at baseline will be randomly assigned in a 2:1 ratio to one of two groups, receiving either the vaginal ring containing dapivirine or the placebo vaginal ring. Randomisation will be stratified by research centre at the time of enrolment, using a pre-specified block size, and will be determined via the use of an automated randomisation system to ensure balance of the treatment assignments. Both groups will use a ring inserted at 4-weekly intervals on a continuous basis for the duration of trial participation and have a follow-up visit 6 weeks after ring removal.

A master randomisation list, linking each participant identification number to a trial treatment assignment (dapivirine ring or placebo ring) will be generated for the trial. At each research centre, as each new participant enters the trial, a unique participant identification number will be assigned to that participant using an automated response system.

### **3.4 Blinding**

The Principal Investigator or his/her designee will be able to unblind each enrolled participant, through the automated system, if necessary. If, during the course of the trial a medical emergency requires knowledge of the test agent used by a particular participant, the trial blind or code may be broken for that specific participant, after discussion with IPM's Clinical Trial Physician or designee, whenever possible. Any unblinding of participant treatment assignments will be justified and explained in the source documents and applicable CRF and reporting forms. If the blinding code is broken by the Principal Investigator or his/her designee, the participant will be withdrawn from the trial and followed up as appropriate. The blinding and unblinding process will be performed by the automated response system.

An interim analysis is planned to be conducted when approximately 50% of the expected efficacy endpoints have been observed. This analysis will involve breaking the blind to perform treatment comparisons – see Section 4.2 for more details. Only individuals as detailed in the Data and Safety Monitoring Board (DSMB) charter will have access to the results of the interim analysis.

## **4 SEQUENCE OF PLANNED ANALYSES**

### **4.1 Safety Monitoring**

An independent DSMB has been established for IPM 027. The DSMB members meet bi-annually via conference call during the trial. In addition, *ad hoc* calls or face-to-face meetings may be convened if requested by the DSMB Chair or IPM. DSMB members include individuals not associated with this trial, but who have expertise in conducting clinical trials, experience working in developing countries, and/or a history of working in the microbicide arena. Prior to each DSMB meeting, a data package of

all available clinical and safety data will be prepared for the DSMB for their review; these data packages, containing blinded and unblinded data (masked treatment groups), will be prepared by an independent statistician not otherwise involved in the trial.

The DSMB has the option to recommend pausing or stopping the trial at any point for any of the following:

- Proven efficacy – if there is clear evidence that the risk of HIV-1 seroconversion is significantly lower in the dapivirine arm than in the placebo arm
- Lack of efficacy (futility) – if there is clear evidence that the trial is highly unlikely to show that the dapivirine ring is superior to placebo in reducing HIV-1 seroconversions, given current evidence and the added information that would become available if the trial continued
- Ring-related safety outcomes observed in the dapivirine arm are greater than those observed in the placebo arm, and differ in a significant way as judged by the DSMB
- Trial performance standards are not acceptable.

The DSMB composition and its charges related to the trial are described in a separate DSMB charter.

#### **4.2 Interim Analyses**

An interim efficacy analysis is planned to be conducted when approximately 50% of the expected trial endpoints have been observed. The interim analysis will involve breaking the blind to perform treatment comparisons and will be conducted for the purpose of making a decision(s) on whether or not to stop the trial early for lack of intended efficacy (futility), or for overwhelming efficacy results. A separate SAP has been compiled for the interim analysis. The analysis will be performed by an independent statistician who is not otherwise involved in the trial and will include all data available in the clinical database at the time point when 50% of the expected number of trial endpoints have occurred. The results of the interim analysis will be reviewed by the DSMB; only individuals as detailed in the DSMB charter will have access to the results of the interim analysis.

Full details of the efficacy analysis that will be performed at the interim analysis, including the statistical hypothesis to be tested, and the trial pausing or stopping rules that will be followed for this analysis, are presented in the SAP for the interim analysis.

Additional interim analyses may be requested by the DSMB.

### **4.3 Final Analysis and Reporting**

All final and planned analyses identified in the protocol and in this SAP will be performed only after the database has been locked. A blinded review of the data will be performed prior to database lock. In addition, treatment codes will only be released after database lock.

## **5 ANALYSIS POPULATIONS**

Four analysis populations have been defined for this trial: a safety population, an intent-to-treat population, a modified intent-to-treat population, and a per-protocol population. The number of participants valid for each population, and when appropriate, the reasons for excluding trial participants from these populations, will be presented overall, by research centre, and by treatment arm using relevant summary statistics.

### **5.1 Safety Population**

The safety population includes all participants who have been randomised to IP and received at least one dapivirine or placebo vaginal ring.

### **5.2 Intent-to-treat (ITT) Population**

As defined in ICH guideline E9 (*Statistical Principles for Clinical Trials*)<sup>4</sup>, the intent-to-treat (ITT) principle states that the effect of a treatment can be best assessed by evaluating the treatment on the planned treatment arm, rather than the actual treatment given. The intent-to-treat population will include all trial participants who were randomised to one of the two treatment arms, dapivirine ring or placebo ring. All participants randomised to a treatment arm will be analysed as members of the treatment arm (dapivirine and placebo) to which they were randomised, regardless of adherence to the planned course of treatment.

### **5.3 Modified Intent-to-treat (m-ITT) Population**

Some participants may not have detectable levels of HIV antibodies at the enrolment visit, and therefore, HIV-positive women who are assumed to be HIV-negative may be enrolled in the trial. To accommodate this situation, a modified intent-to-treat (m-ITT) population will be determined and used for analysis of the primary efficacy endpoint. This population will include all participants that are included in the ITT population but who were never determined to be HIV-seropositive at the enrolment visit. Women who have seroconverted after enrolment will be excluded from the m-ITT population on the basis of baseline information collected prior to randomisation and which only became available after randomisation.



#### **5.4 Per-protocol (PP) Population**

The per-protocol population is a subset of the m-ITT population, *i.e.* all trial participants who are HIV-1 negative at the enrolment visit, with no major protocol deviations (refer to Section 7.2 for a definition of major protocol deviations).

## **6 GENERAL STATISTICAL CONSIDERATIONS**

### **6.1 Analysis Software**

Statistical analyses will be conducted by a statistical vendor and reviewed by the International Partnership for Microbicides. The analyses will be performed using SAS<sup>®</sup> for Windows XP or Linux/Unix (version 9.1 or higher, SAS Institute Inc., Cary, North Carolina, USA).

### **6.2 Methods for Handling Missing Data**

All participants in the m-ITT population will be included in the analysis of the primary efficacy endpoint (refer to Sections 9.1 and 9.1.1). While every effort will be made to minimise the amount of missing data, some degree of missing data, primarily associated with missed visits, is expected. For the analysis of adherence to 4-week ring use, patterns of missing data may be informative. As the effect of missed visits is expected to be balanced across the treatment arms, no imputation for missing data is planned prospectively.

If more than 10% of participants (protocol-assumed loss-to-follow-up rate) discontinue from the trial early, potential covariates that may be associated with time to discontinuation will be investigated. These results may be useful in identifying factors that influenced trial participation. The time of discontinuation will be defined as the time from baseline until the first missed visit after which the participant did not return for any subsequent visits.

### **6.3 Multiple Comparisons and Multiplicity**

Section 4.2 describes the planned interim analysis when approximately 50% of the expected efficacy endpoints are available. The plan for adjusting for multiple reviews of the efficacy data is as follows (also detailed in the SAP for the interim analysis):

At the interim analysis, the null hypothesis that the HIV-1 seroconversion hazard rate of active product relative to placebo equals 0.75 ( $H_0: HR = 0.75$ ) will be evaluated at a nominal, one-sided 2.5% significance level. To avoid inflation of the Type I error rate when evaluating superiority both at the interim and the final analysis, the Lan and De-Met's implementation of the O'Brien-Fleming grouped sequential stopping boundary, with the time scale measured on the cumulative number of HIV-1 seroconversions, will be used. With 40 of the expected efficacy endpoints available, the adjusted one-sided significance levels are equal to 0.0015 at the interim analysis and 0.0245 at the final analysis, with -2.9626 and -1.9686 the respective,

corresponding critical values for the test statistic (on the Z-scale). If the actual number of events at the interim analysis is different from 40, the O'Brien-Fleming-adjusted critical values/significance levels corresponding to the actual fraction of information will be used.

The final analysis of the primary efficacy endpoint only involves a single treatment comparison, which does not require further adjustment.

#### **6.4 Multicentre Trials**

Differences in participant safety and efficacy of the dapivirine vaginal ring across research centres will be explored graphically and descriptively. The key efficacy and safety analysis will be summarised overall and for each research centre separately. For the primary efficacy endpoint and primary safety endpoint, a formal comparison of the data will be performed to evaluate for homogeneity of the treatment effect across research centres.

#### **6.5 Planned Subgroups, Interactions, and Covariates**

As stated in Section 5, the analysis of the primary efficacy endpoint will be based on the m-ITT population, which will include all participants who were HIV-negative at baseline and who were randomised to IP.

As this is a randomised trial in healthy HIV-negative women, it is anticipated that the treatment arms will be comparable at baseline with respect to pre-existing conditions. Furthermore, it is expected that women with pre-existing conditions will be treated and evaluated before being enrolled into the trial. For this reason, no baseline adjustments are planned prospectively; however, all data will be reviewed to assess any potentially relevant baseline imbalances. Variables that emerge as potentially relevant covariates (e.g. number of male sex partners, or presence of genital symptoms at baseline) will be included in all analyses. Where appropriate, the statistical model will include treatment, research centre and the covariate(s) as main effects, with interaction terms for treatment-by-covariate and centre-by-covariate. Covariates that prove to be non-significant at the 5% level will be excluded from the final model.

Multivariate logistic regression models may be employed to assess the effect of multiple covariates. Comparisons between measurements taken during the trial and prior to or at enrolment may also be made; comparisons of continuous data will be performed using paired t-tests and comparisons of categorical data will be performed using McNemar's test.

#### **6.6 Data Presentations**

Descriptive statistics will be presented overall, by research centre and by treatment arm (dapivirine ring or placebo ring).

For continuous variables, the descriptive statistics will include: mean and standard deviation (when appropriate), quartiles, range, and number of non-missing and missing data values. For categorical variables, descriptive statistics may include frequencies, relative frequencies, and the number of non-missing and missing data values. Percentages will be presented to one decimal place. The subsequent sections discuss the planned analyses beyond the listings and simple descriptive analyses.

Baseline is defined as the last available measurement before the first insertion of the IP. This measurement may be made at Screening 1, Screening 2, or Visit 1 (prior to ring insertion).

In accordance with the protocol, each scheduled visit while the participant is on IP has a window period of  $\pm 7$  days. However, consecutive visits should be no less than 21 days and no more than 35 days apart. If a participant presents for a visit outside the window for a scheduled trial visit, this will be documented as a protocol deviation (refer to Section 7.2); however, the data recorded at this visit will be analysed as pertaining to the scheduled visit. Unscheduled visits may be performed at any time during the trial. If an unscheduled visit takes place within any given window period and any repeat observations are made within the given window period, the repeat values will be captured as pertaining to the unscheduled visit. Data from scheduled and unscheduled visits will be shown, and listings will be appropriately labelled when data arise from unscheduled visits.

Tables, figures, and listings of trial results will accompany the text of the Clinical Study Report. Listings of all clinical data recorded in the CRFs will be provided, except for those CRFs which are used for administrative purposes, such as the Participant Encounter Forms (PEC, PEC-1, and PEC-2) and the End of Study Inventory (ESI). Listings will be sorted by research centre and participant identification number (PID), and key variables such as treatment arm, visit date and/or trial visit number will be presented in each listing.

## **7. TRIAL PARTICIPANTS**

All participants who provide informed consent for this trial will be accounted for, in accordance with ICH guideline E3 (*Structure and Content of Clinical Study Reports*)<sup>3</sup>.

### **7.1 Disposition of Trial Participants**

The number and percentage of trial participants who were screened, randomised to IP, permanently discontinued IP, permanently discontinued the trial, and who completed the trial will be presented.

For those participants who discontinued prematurely, the time to permanent discontinuation of IP and the time to permanent discontinuation of the trial will be

calculated, and presented together with Kaplan-Meier curves by treatment, research centre-by-treatment, and baseline covariates.

For participants who temporarily discontinued IP during the course of the trial the frequency of product-hold, the duration of time off product, and the reasons for product-hold will be listed and summarised descriptively.

A listing reflecting each participant's screening date, enrolment date, and scheduled and unscheduled visit dates, as documented in the PEC CRF, will be provided. The CONSORT flow diagram in Appendix 1 may also be used to depict the disposition of trial participants.

## **7.2 Protocol Deviations and Violations**

All recorded protocol deviations will be listed and summarised overall, by research centre, and by treatment arm.

A protocol violation is a major deviation from the protocol which may impact the integrity of the data and/or the safety of the trial participant(s). A list of categorised protocol violations has been developed at the start of the trial, and prior to database lock and unblinding, the Clinical Trial Physician and trial statistician will review and finalise the list of protocol violations for purposes of defining the per-protocol analysis population.

Some protocol violations that will result in exclusion of a participant from the PP analysis will include:

- Inappropriate enrolment into the trial (e.g. participant met an exclusion criterion, or participant failed to meet all inclusion criteria) as documented in the DL CRF
- Pregnancy was confirmed but participant continued participating in the trial
- Errors in IP initiation, IP dispensing, or IP withdrawal. For example, IP was incorrectly withheld from participants, participants incorrectly resumed IP use, or inappropriate IP was dispensed to a participant
- The participant demonstrated an IP adherence rate of less than 80% over the duration of the trial (based on self-reported ring use and objective, quantitative adherence measures)
- The participant missed three or more consecutive trial visits at any stage during the course of the trial.

The number of participants with protocol violations will be presented using appropriate summary statistics overall, by research centre, and by treatment arm.

## **7.3 Adherence to Ring Regimen**

The data collected in IPM 027 allow both subjective and objective assessments of adherence to ring use by the participants in this trial. The subjective adherence measures include self-reported ring use as collected by adherence questionnaires,

and/or feedback from participants or male partners following qualitative individual interviews or focus group discussions. Missed and/or late clinical trial visits (outside protocol-allowed visits windows – refer to Section 6.6) will also be used as indicator of non-adherence to prescribed product use. Objective, quantitative measures of adherence include plasma and vaginal fluid concentrations of dapivirine in samples collected at the 4-weekly trial visits, as well as the residual levels of dapivirine in all used rings returned to the research centres.

### **7.3.1 Adherence Measures Applying to Both Treatment Arms**

As described in Section 9.1.1, three complementary analyses on the primary efficacy endpoint will be performed on the m-ITT population. For the analysis excluding non-adherent participants, one set of criteria will be applied for all participants (in a blinded manner, prior to database lock) to define non-adherence, *i.e.* the same criteria will apply to both the dapivirine ring and placebo arms, so as not to introduce bias in the analysis. The criteria that will be used are the following:

- Errors in IP initiation, IP dispensing, or IP withdrawal. For example, IP was incorrectly withheld from participants, participants incorrectly resumed IP use, or inappropriate IP was dispensed to a participant
- The participant missed three or more consecutive trial visits at any stage during the course of the trial
- The participant attended less than 80% of the scheduled trial visits over the duration of the trial.

### **7.3.2 Adherence Measures Applying to Active Arm Only**

Residual levels of dapivirine in used rings, and plasma and vaginal fluid concentrations of dapivirine will be determined for those participants assigned to the active arm, as measure of adherence to ring use. The data will be listed, summarised and presented graphically, as described below.

#### **Dapivirine Ring Residual Levels**

All used vaginal rings that are returned to the research centres at each trial visit are collected and shipped at regular, pre-defined intervals to an analytical laboratory, where the rings of those participants assigned to the active ring are analysed to determine the residual amounts of dapivirine in the rings.

For this trial, a reported ring residual level of  $\geq 24$  mg dapivirine will be used as indication of non-adherence to ring use over the 28-day period ( $\pm 7$  days) that a woman was to keep the ring *in situ*.

The following summaries and graphical presentations will be produced on these data:

- A summary of ring residual levels at each trial visit, with standard descriptive statistics – presented overall and by research centre. Corresponding box plots will be prepared.
- A descriptive summary of the ring residual levels by trial visit and by category of residual amount (0-5, 6-10, 11-15, 16-17, 18-19, 20-21, 22-23, and 24-25+ mg). This summary will be prepared overall and by research centre, with corresponding bar charts.
- A summary relating the ring residual amounts to time intervals (in days) between consecutive trial visits (<21 days, 21-35 days, and >35 days), to determine whether a trend between residual amounts and visits outside the permitted window periods is apparent. Corresponding box plots will be prepared.

In addition, a listing of those trial participants who HIV seroconverted (confirmed trial endpoints), together with the number of days since their last trial visit, and corresponding ring residual levels of dapivirine, will be produced. A scatter plot of the residual levels of dapivirine in the last ring returned by these participants prior to HIV seroconversion will be produced and compared visually with the average ring residual levels of those participants who remained HIV-negative over the duration of the trial.

#### **Plasma and Vaginal Fluid Concentrations of Dapivirine**

All blood and vaginal fluid samples collected at each trial visit are shipped to a bio-analytical laboratory, where the samples of all participants assigned to active rings are analysed for plasma and vaginal fluid levels of dapivirine.

A population pharmacokinetic model for dapivirine is in development. This model will be used to simulate the effect of different ring use/removal scenarios on plasma and/or vaginal fluid concentrations of dapivirine, which will assist in defining a range of dapivirine plasma and/or vaginal fluid levels that may be indicative of non-adherence to ring use over the 28-day period ( $\pm 7$  days) that a woman was to keep the ring *in situ*. The following scenarios will be simulated, as a minimum:

- Removal of the ring 24 hours after first insertion, and re-insertion of the same ring on Day 27, to predict the plasma and/or vaginal fluid level on Day 28
- Removal of the ring 2 weeks after first insertion, with no re-insertion for the remainder of a 28-day period
- Removal of the ring 3 weeks after first insertion, with no re-insertion for the remainder of a 28-day period.

Based on these simulations, a minimum plasma and/or vaginal fluid concentration of dapivirine will be defined (before final database lock and unblinding), below which the participant was most likely non-adherent to ring use over the intended 28 days.

The plasma and vaginal fluid data will be summarised and presented graphically by box plots for each visit, by research centre and overall. A summary, relating the plasma and vaginal fluid concentrations of dapivirine to time intervals (in days) between consecutive trial visits (<21 days, 21-35 days, and >35 days), will be produced to determine whether a trend is apparent between these levels and visits outside the permitted visit window periods. These results will be presented graphically by box plots.

In addition, a listing of those trial participants who HIV seroconverted (confirmed trial endpoints), together with the number of days since their last trial visit, dapivirine ring residual levels, and corresponding plasma and vaginal fluid levels of dapivirine, will be produced. Scatter plots of the plasma and vaginal fluid levels of dapivirine measured prior to HIV seroconversion for these participants will be produced and compared visually with the average plasma and vaginal fluid levels of dapivirine for those participants who remained HIV-negative over the duration of the trial.

The correlation between the amount of residual dapivirine in the used rings and the corresponding plasma and vaginal fluid levels of dapivirine will be explored graphically and summarised descriptively.

### **7.3.3 Self-reported Adherence by Questionnaire**

Self-reported adherence to the ring regimen will be calculated per visit and overall, and presented descriptively by research centre and treatment arm. The adherence rate per visit will be calculated as:

- $100 \times (\text{Number of days that the participant reportedly wore the ring} / \text{the total number of days that the participant was expected to wear the ring})$ .

The self-reported adherence rates will be presented in the following categories:

- > 80%
- 60% to 80%
- 40% to 60%
- < 40%.

A comprehensive description of the planned analysis of self-reported adherence data is provided in Section 9.3.4.

## **8. EVALUATION OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS**

Unless otherwise specified, demographics (DEM) and other baseline characteristics, including relationship and sexual history (BBQ), medical and surgical history (MED), and obstetrics/gynaecological history (GHX), and the physical examination obtained at the Screening visits and the Enrolment visit, will be summarised descriptively overall, by

research centre, and by treatment arm using appropriate summary statistics as described in Section 6.7.

### 8.1 Baseline Demographics, and Relationship and Sexual History

The following baseline demographic characteristics will be listed and summarised: age, race, height, weight and body mass index (BMI), as well as information on education level, and relationship and sexual history. Age and BMI will be derived as described in Table 2.

**Table 2 Derived and Computed Demographic Variables**

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes, or Equation(s)
Age	Age (years)	18 to 45 (inclusive)	INT((date of enrolment – date of birth)/365.25)
BMI	Body Mass Index (kg/m <sup>2</sup> )		(Participant body weight in kg)/ (Participant height in m) <sup>2</sup>

Qualitative demographic characteristics (nominal or ordinal categories) will be summarised using absolute and relative frequencies. Quantitative demographic characteristics (continuous) will be summarised using the appropriate summary statistics, namely number of participants, mean, standard deviation (SD), quartiles, and range. All demographic and baseline characteristics will be presented in participant listings.

### 8.2 Baseline Medical and Surgical History

Medical and surgical history will be collected during the Screening visit and Trial Visit 1 (pre-enrolment). Medical history will be presented in tabular form using appropriate descriptive statistics.

### 8.3 Baseline Screening Assessments

Laboratory assessments conducted at baseline, including cytology, syphilis testing (RPR), haematology, biochemistry, urine pregnancy tests, HSV-2 serology tests, and HIV rapid tests will be presented for all participants.

### 8.4 Obstetrics and Gynaecological History

Obstetrics and gynaecological history will be collected during the Screening visit, and gynaecological conditions will be coded using Version 15.0 of the Medical Dictionary for Regulatory Activities (MedDRA). Obstetrics and gynaecological history will be presented in tabular form with absolute and relative frequencies, and gynaecological conditions will be classified using System Organ Class (SOC) and Preferred Term (PT).

### 8.5 Prior Therapies and Medications

Prior medication is defined as any medication that started and ended before the first administration of IP. Medications will be coded using WHO Drug Dictionary. A table



summarising the number and percentage of participants using drugs within each Anatomical Therapeutic Chemical (ATC) classification will be presented.

## 9. EVALUATION OF TRIAL ENDPOINTS

### 9.1 Primary Endpoint 1 – Efficacy

The IPM 027 trial has 81% power to detect a reduction of 50% in the HIV-1 seroconversion rate for the dapivirine ring relative to placebo. The primary null and alternative hypotheses for this trial are:

$H_0$ : HIV-1 seroconversion hazard rate of active product relative to placebo = 1  
(hazard ratio = 1)

$H_1$ : HIV-1 seroconversion hazard rate of active product relative to placebo < 1  
(hazard ratio < 1)

Trial participants will be followed on IP for 24 months, and will be tested for HIV-1 infection at 4-weekly visits until the last product use visit, as well as at the exit visit 6 weeks after ring discontinuation. HIV seroconversion will be determined per the HIV testing algorithm presented in the IPM 027 protocol<sup>5</sup>. However, only HIV-1 seroconversions that have been confirmed by the independent IPM 027 HIV Seroconversion Monitoring Committee (HSMC) as occurring after enrolment into the trial will be regarded as trial endpoints. The point of HIV-1 infection is determined by performing reverse sequential HIV RNA PCR testing (on stored samples collected at each visit) until a negative test result is achieved.

Participants who are not diagnosed with HIV-1 at the end of the trial participation period will be censored at the earliest date of any of the following events: early termination of investigational product use, completion of investigational product use, trial drop-out, a positive pregnancy test followed by permanent product discontinuation, or death. Additionally, censoring will be applied at the date of trial termination (for any reason, irrespective of product use).

If HIV-1 is detected at the exit visit (6 weeks after ring discontinuation), HIV RNA PCR testing will be performed on stored samples in reverse sequential order to estimate the time point of HIV-1 infection. If HIV-1 infection is detected at or prior to the last product use visit, the participant will be included in the analysis as an HIV-1 seroconverter. If the time of infection is determined to be after completion of product use, the participant will be censored on the date of the last product use visit. Refer to Table 3 for calculation methods of derived variables.

**Table 3 Derived and Computed Variables – HIV Seroconversion**

Variable Name	Description	Computation Methods, Notes, or Equation(s)
HIV_TTS	Time to HIV-1 seroconversion	Date_HIV_seroconversion* – Date_enrolment
HIV_TDP	Time to discontinuation of IP	Date_LPUV – Date_enrolment
HIV_TDT	Time to discontinuation of trial	Date_trial completion – Date_enrolment
HIV_C	Censor variable	

\* Date of first trial visit with an HIV-positive test result.  
 LPUV = Last product use visit.

The primary analyses will be performed on the m-ITT population, adherence-adjusted populations, as well as the PP population. The aggregate of the m-ITT analysis results and the three additional complementary analyses described below (Section 9.1.1) will be used to determine the efficacy of the dapivirine vaginal ring in preventing HIV-1 transmission as compared to placebo. All of these analyses will be presented in the Clinical Study Report.

The formal statistical test used to evaluate the efficacy of the dapivirine ring will be the two-sided log-rank test, stratified by research centre, and this test will be evaluated at the adjusted one-sided significance level of 0.0245 (to account for the superiority evaluation at the interim analysis; refer to Section 6.3). It will be assumed that censoring is unrelated to HIV-1 acquisition and that survival probabilities are the same for participants recruited early and late in the trial.

The test statistic for the stratified log-rank test with  $m=1, \dots, M$  strata is given by:

$$X_{MH} = \frac{[\sum_{m=1}^M (d_{1m} - \hat{e}_{1m})]^2}{\sum_{m=1}^M \hat{v}_{1m}}$$

where

- $d_1 = \sum_{k=1}^K d_{1k}$  is the number of HIV-1 seroconversions (trial endpoints),
- $e_1 = \sum_{k=1}^K e_{1k}$  is the conditional expected number of seroconverters, and
- $v_1 \sum_{k=1}^K v_{1k}$  is the conditional variance of  $d_{1k}$ , at each  $k$ -th time point.

The log-rank test is a non-parametric, fully efficient test under the assumption of a constant hazard ratio over time. The analysis will include presentation of Kaplan-Meier survival curves, in addition to an evaluation of Schoenfeld residuals, log(-log(survival)) versus log of survival time plots, and the LOWESS smooth for visual inspection of the proportional hazards assumption. In case visual inspection

indicates severe violations of the proportional hazards assumption, more appropriate models will be explored, e.g. time-by-treatment interactions in a semi-parametric Cox proportional hazards model.

The log-rank test applies equal weighting to all parts of the survival curve, and it is believed that this will be appropriate for the purpose of evaluating efficacy of the dapivirine ring.

The Cox proportional hazards model (using a discrete time scale) will also be used to estimate the effect of the dapivirine ring regimen, and to provide an estimate of the risk ratio, or hazard ratio (using SAS procedure PHREG or TPHREG). This method is selected as it yields estimates closer to those obtained using the exact partial likelihood compared to estimates obtained by using other proposed methods<sup>2</sup>.

The number of HIV-1 seroconversions (confirmed trial endpoints), the incidence density rate of HIV-1 seroconversion, *i.e.* HIV-1 seroconversion rate per 100 person-years of product use at the end of the IP use period, as well as a 95% confidence interval for the HIV-1 seroconversion rate per 100 person-years, will be presented for each treatment arm and research centre.

The LIFETEST SAS procedure will be used to apply the log-rank test to the data. The output from this procedure will provide a Chi-square value with an associated p-value, as well as a Kaplan-Meier survival curve (representing the estimated proportion of HIV-negative participants at every time point).

#### **9.1.1 Complementary Analyses on the Primary Efficacy Endpoint**

A blinded review of the data included in the May 2013 DSMB review (data cut-off date: 28 February 2013), confirmed a suspicion of product non-adherence in the trial. Specifically, at Research Centre 03 in KwaZulu-Natal, South Africa, a high incidence of protocol non-adherence (primarily missed and late visits, and early trial discontinuations) was observed in December 2012 – a finding which prompted the Sponsor to analyse all used rings returned to all research centres as of 28 February 2013 for residual dapivirine amounts. This (blinded) analysis revealed that during any given month of ring use, the majority (50-80%) of women assigned to the dapivirine ring at Research Centre 03 had drug residuals in used rings of 24 mg or more (*i.e.* essentially all of the initial drug load) indicating limited ring use.

For this reason, the following complementary analyses of the primary efficacy endpoint will be conducted:

- a) Analysis on the m-ITT population, excluding participants enrolled at Research Centre 03. All participants enrolled at this centre – both adherent and non-adherent participants in both the active and placebo arms – will be excluded from the analysis.

- b) Analysis on the m-ITT population, excluding non-adherent participants. Non-adherent participants will be identified based on blinded review of the data before database lock, and the same criteria for non-adherence will be applied to both the active and placebo arms. These criteria are defined in Section 7.3.1.
- c) As-randomised adherence-adjusted analyses on the m-ITT population. This analysis will take into account the actual level of exposure (adherence) to the dapivirine vaginal ring, as assessed by quantitative measures (*i.e.* dapivirine ring residual levels and/or plasma and vaginal fluid concentrations), and use causal methodology to estimate the effect of the dapivirine vaginal ring in comparison to placebo, allowing for adjustment for adherence in both the active and placebo arms<sup>6</sup>.

The aggregate of these analysis results (Sections 9.1 and 9.1.1) will be used to determine the efficacy of the dapivirine vaginal ring in preventing HIV-1 transmission, compared to placebo.

The effects of known risk factors for product non-adherence<sup>7</sup> (participant age, marital status, and number of sex partners) on the treatment differences will be explored.

The results of all analyses performed on the primary efficacy endpoint will be presented in the Clinical Study Report.

## **9.2 Primary Endpoint 2 – Safety**

The analysis of adverse events (AEs) will be mainly descriptive in nature. That is, the number and percentage of participants experiencing adverse events will be presented by treatment arm. Summaries of specific AEs will be produced, including the proportion of participants experiencing Grade 3 or 4 AEs, SAEs, or AEs leading to IP discontinuation.

Differences in the proportions of participants experiencing adverse events (and specific adverse events as mentioned above) will be determined based on logistic regression analysis with research centre as covariate. Corresponding 95% confidence intervals for the differences will be provided.

As this is a randomised trial in healthy HIV-negative women, it is anticipated that the treatment groups will be comparable at baseline with respect to pre-existing conditions. Furthermore, it is expected that women with pre-existing conditions will be treated and evaluated before being enrolled into the trial. For this reason, no baseline adjustments are planned prospectively; however, all data will be reviewed to assess any potentially relevant baseline imbalances (refer to Section 6.5).

### **9.3 Secondary Endpoints**

#### **9.3.1 Secondary Endpoint 1: Seroconversion rate of HIV-2 per 100 person-years of product use at the end of the IP use period**

Consistent with secondary objective 1, secondary endpoint 1 is the HIV-2 seroconversion rate per 100 person-years of product use at the end of the investigational product use period.

##### ***Assessments***

Trial participants will be tested for HIV-2 infection at 4-weekly visits until the last product use visit, and at the exit visit 6 weeks after ring discontinuation. Participants who are not diagnosed with HIV-2 at the end of the trial participation period will be censored at the earliest date of any of the following events: completion of investigational product use, trial drop-out, a positive pregnancy test followed by permanent product discontinuation, or death. Additionally, censoring will be applied at the date of trial termination (for any reason, irrespective of product use).

If HIV-2 is detected at the exit visit, HIV RNA PCR testing will be performed on stored samples in reverse sequential order to estimate the time point of HIV-2 infection. If HIV-2 infection is detected at or prior to the last product use visit, the participant will be included in the analysis as an HIV-2 seroconverter. If the time of infection is determined to be after product use, the participant will be censored on the date of the last product use visit.

##### ***Statistical hypothesis and methods***

If appropriate, dependent on the number of HIV-2 seroconversions that occur, hazard ratios will be estimated with corresponding 95% confidence intervals to quantify the effect of the dapivirine ring on HIV-2 seroconversion. Time to HIV-2 seroconversion will be calculated as the number of days between the date of HIV-2 seroconversion and the enrolment date. Participants who do not seroconvert before the last product visit will be censored on the day of their last negative HIV test, and time to censoring will be calculated as the number of days between the date of censoring and the randomisation date. Kaplan-Meier survival curves will be provided to graphically describe the probability of remaining HIV-2 negative over the trial duration for each treatment arm.

The number and percentage of participants who were reported with HIV-2 seroconversions will be presented by treatment arm. The difference in the proportion of participants between the two treatment arms will be summarised using logistic regression analysis with research centre as covariate. Corresponding 95% confidence intervals for the differences will be provided.

### **9.3.2 Secondary Endpoint 2: The incidence of curable STIs, and changes in vaginal flora in each trial arm over the IP use period**

Consistent with the secondary objective to evaluate the incidence of curable STIs (*i.e.* *N.gonorrhoeae*, *C.trachomatis* and *T.vaginalis*), and changes in vaginal flora in the dapivirine and placebo vaginal ring groups, the second secondary endpoint is the incidence of curable STIs, and changes in vaginal flora in each trial arm over the IP use period.

#### **Assessments**

Laboratory tests for *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* will be performed, and pelvic samples will be collected for assessment of vaginal flora at enrolment and 12-weekly visits until the last product use visit.

#### **Statistical hypothesis and methods**

##### Curable STIs

For each treatment arm, the incidence density rate of STIs will be provided, with a corresponding 95% confidence interval, defined by the number of participants that test positive for a curable STI. The denominator will be the sum of the durations over time that the participants in each treatment arm contribute to the trial, as determined by the ring insertion and ring removal CRFs.

##### Changes in Vaginal Flora

It will be evaluated whether the changes in vaginal flora over time are the same in the two treatment arms. A generalised estimating equation (GEE) model will be used to evaluate the longitudinal changes in total Nugent score between the trial arms. This model will be used to account for the within-participant correlation structure in Nugent scores over trial visits, and will test for a time-by-treatment interaction. If the p-value for the time-by-treatment interaction is < 0.05, it will be concluded that the changes in vaginal flora during the trial period are different between the dapivirine ring and placebo ring arms.

Additional analyses to assess the change in vaginal flora may be performed. Changes in vaginal flora will be assessed based on the incidence density rate for the first occurrence of vaginal flora changes. A change in vaginal flora is defined as a post-enrolment increase in the total Nugent score category (*i.e.* from *Normal* to *Altered vaginal flora*, from *Altered vaginal flora* to *Abnormal*, or from *Normal* to *Abnormal*). Kaplan-Meier survival curves will be presented to compare the time to the first occurrence of vaginal flora changes in each treatment arm. The log-rank test (two-sided, alpha=0.05) will be used to evaluate the effect of the dapivirine ring on the first occurrence of a change in vaginal flora, and will be stratified by research centre. Cox proportional hazards will be used to estimate the median time to a change in vaginal flora in the treatment groups, adjusting for any imbalance in baseline covariates.

### **9.3.3 Secondary Endpoint 3: Incidence of pregnancy in each trial arm over the IP use period**

Consistent with the secondary objective to evaluate the incidence of pregnancy between the two arms, secondary endpoint 3 is the incidence of women who have a positive pregnancy test at any point during the trial.

#### ***Assessments***

Urine pregnancy tests will be performed at every trial visit. Confirmatory serum pregnancy tests will be performed at the Investigator's discretion. A participant will be discontinued early from the trial if she is confirmed to be pregnant.

#### ***Statistical hypothesis and methods***

For each treatment arm, the incidence density rate of pregnancy will be determined, with a corresponding 95% confidence interval. The numerator will include the number of participants that had a positive urine or serum pregnancy test during the trial period and the denominator will include the total number of days that each participant contributed to the trial (*i.e.* from enrolment to pregnancy, or trial completion, whichever occurs first).

### **9.3.4 Secondary Endpoint 4: Proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period**

Consistent with the secondary objective to evaluate self-reported adherence, secondary endpoint 4 is the proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period.

#### ***Assessments***

Trained staff will administer adherence questionnaires at 4-weekly trial visits, from Week 4 until the last product use visit. Adherence questionnaires include questions about ring use. The diary cards will serve as a memory aid for the participant during the adherence questionnaire session, and will be collected at each 4-weekly visit.

#### ***Statistical hypothesis and methods***

For each participant, the total number of days that the participant reported removing the vaginal ring via the question: "Since your last regularly scheduled visit, how many times was the vaginal ring out of your vagina" will be summed across all trial visits and will be divided by the total number of days that the participant was expected to wear the ring. Categories of "self-reported adherent participants" (e.g. <40%, 40-60%, 60-80%, and >80% adherence) will be defined. The proportion of participants that are adherent to the ring regimen based on self-reports will be estimated and reported using a 95% confidence interval. Additional cut-off values may be useful to describe self-reported adherence and may be explored.

Multiple methods of data collection will be utilised to examine self-reported adherence; comparisons across the different methods will be exploratory. For instance, the ring removal and ring insertion CRFs may be used as an additional way to monitor adherence.

Additional exploratory and explanatory analyses will utilise the qualitative data from focus group discussions and individual interviews.

### **9.3.5 Secondary Endpoint 5: The proportion of women who report the use of the vaginal ring as acceptable**

Consistent with the secondary objective to evaluate acceptability of the dapivirine vaginal ring, secondary endpoint 5 is the proportion of women who report a willingness to use the vaginal ring if proven effective against HIV-infection.

#### **Assessments**

Acceptability questionnaires will be administered at the second trial visit (Week 4), and at 24-weekly intervals thereafter, until the last product use visit.

#### **Statistical hypothesis and methods**

The proportion of participants that respond positively (*i.e.* “likely” or “very likely”) to the question: “If in the future a vaginal ring was available that provided some protection against HIV, and it was similar to the one you used in this trial, how likely would you be to keep it inserted in your vagina every day” at any post-enrolment visit among all trial participants will be presented with a 95% confidence interval.

In addition, two types of acceptability assessments will be performed; these are referred to as (1) simple approximation of acceptability and (2) comprehensive assessment of acceptability.

Simple approximation of acceptability will be assessed by analysis of stated willingness to use the vaginal ring if proven effective against HIV infection, and reported consistent use of the vaginal ring during the trial. A participant will be classified as having found the vaginal ring acceptable if she responds positively to questions about willingness to use and consistent use. Logistic regression analysis will be performed to examine the relationship between this acceptability and other variables of interest.

For both types of assessments, cross-tabulations and simple descriptive statistics will be calculated for socio-demographic variables and psycho-social variables collected in the acceptability and adherence questionnaires. If between-group differences arise and/or there are differential rates of drop-out on potentially confounding characteristics, the variable(s) will be included as covariates in the analyses. If numerous confounders are identified, a propensity scoring approach will be used to adjust for confounding.



Comprehensive assessment of acceptability will be based on data captured in the acceptability and adherence questionnaires. Variables evaluating participants' willingness to use the vaginal ring will be adjusted by women's perceived risk of HIV-infection and sexual practices. Variables evaluating consistent use of the vaginal ring will also be used to adjust for possible confounding factors. Another aspect of comprehensive acceptability is to investigate factors influencing participants' attitudes and responses to the IP. The acceptability measures will be regressed over possible predictors via a logistic regression model at a 5% level of significance. Additional exploratory and explanatory analyses will utilise the qualitative data from focus group discussions and individual interviews.

### **9.3.6 Secondary Endpoint 6: HIV-1 drug resistance mutations among participants who acquire HIV-1**

Consistent with the secondary objective to evaluate HIV-1 drug resistance mutations among participants who acquire HIV-1 in the trial, secondary endpoint 6 is the proportion of HIV seroconverters with drug resistant mutations.

#### **Assessments**

HIV viral genotyping will be performed on all HIV seroconverters.

#### **Statistical hypothesis and methods**

The analysis of HIV-1 drug resistance will be primarily descriptive in nature, and will depend on the pattern of resistance associated mutations (RAMs) observed in the HIV-1 seroconverters. The latest IAS-USA update of Drug Resistance Mutations in HIV-1 (dated March 2013) is provided in Appendix 5.

The number of RAMs observed will be listed by participant, and a frequency tabulation of individual RAMs produced. The proportion of HIV-1 seroconverters with at least one HIV-1 drug resistant mutation will be presented overall, and by treatment arm, with corresponding 95% confidence intervals. If appropriate, differences in the distributions of RAMs between the two treatment arms will be assessed using Van Elteren's test. The distribution of HIV-1 resistance mutations will be presented graphically with a bar chart of relative frequencies, overall and by treatment arm.

It is possible that prolonged exposure and adherence to the IP may influence the development of drug resistant mutations. A box plot displaying the distribution of days on IP may be presented for each treatment arm. The number of days of IP use prior to HIV-1 seroconversion as well as adherence to the IP may be evaluated as an independent predictor of acquiring a resistant mutation.

## 10. EVALUATION OF SAFETY PARAMETERS

### 10.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial participant. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory assessment finding), symptom or disease temporally associated with the participation in this trial, whether or not considered related to the IP.

#### 10.1.1 Treatment Emergent Adverse Events (TEAEs)

TEAEs are defined as those AEs which started on or worsened after the first application of the IP. Only TEAEs are reported in the AE CRF.

#### 10.1.2 Product-related Adverse Events

Product-relatedness is reported as “Related” or “Not Related”. While every effort is made to ensure that this field is not missing through data reviews and queries, if the relationship with the IP is missing on the CRF, it will be assumed that the AE was “related” to the IP.

#### 10.1.3 Summary Tables

A summary table of AEs will be presented, indicating the frequency and proportion of participants with:

- At least one TEAE
- At least one serious TEAE
- At least one DAIDS Grade 3 or 4 TEAE
- At least one product-related TEAE
- At least one serious product-related TEAE
- A TEAE leading to death
- A TEAE leading to premature IP discontinuation.

The definitions and location of data elements to be used to define each measure are described in Table 4 below.

**Table 4 Definition and Data Sources of AEs**

<b>Measure</b>	<b>Statistic</b>	<b>Data Sources*</b>
Participants with at least one TEAE	Frequency	A participant reported with an AE in the AE CRF Source: AE
Participants with at least one serious TEAE	Frequency	A participant reported as having an SAE per the AE CRF Source: AE
Participants with at least one DAIDS Grade 3 or 4 TEAE	Frequency	A participant reported as having a DAIDS Grade 3 or 4 AE Source: AE
Participants with at least one product-related TEAE	Frequency	A participant reported as having a “related”, “not related” event, per the AE CRF Source: AE
Participants with at least one serious product-related TEAE	Frequency	A participant reported as having a “related”, “not related” SAE, per the AE CRF Source: AE
Participants with a TEAE leading to death	Frequency	A participant reported as having an AE with the reported outcome “death” per the AE CRF Source: AE
Participants with a TEAE leading to premature IP discontinuation	Frequency	A participant reported as having an AE for which the IP was discontinued and not reintroduced per the AE CRF Source: AE

\* Percentages will use the total number of enrolled participants as denominator.

Summary tables will include the following variables:

**Table 5 AE Variables**

Variable	Data Type	Data Sources
Serious AE (SAE)	Dichotomous	Yes/No Source: AE
Outcome	Nominal	Death, Worsened, Resolved/recovered w/sequelae, Resolved/recovered, Ongoing at trial end Source: AE
Severity	Ordinal	Grade 1 Mild, Grade 2 Moderate, Grade 3 Severe, Grade 4 Life-threatening Source: AE
Relationship	Ordinal	Related, Not related Source: AE
Action	Nominal, DDDMMYY	IP continued, IP discontinued, IP reintroduced, N/A Date discontinued, date reintroduced Source: AE
Other action	Nominal	None, treatment medication, non-drug therapy, hospitalisation, other Source: AE
SOC	Nominal	System Organ Class Source: AE
PT	Nominal	Preferred Term Source: AE

The incidence of the following AEs by severity will be presented by SOC and PT and by treatment arm:

- TEAE
- Serious TEAEs
- Product-related TEAEs
- Serious product-related TEAEs.

A by-participant listing of all deaths, SAEs and premature discontinuations will be presented in Appendix 16 of the Clinical Study Report. These by-participant listings will include variables described in the summary of TEAEs in addition to the following variables:

**Table 6 Additional AE Variables**

Variable	Data Type	Data Sources
AE start date	DDMMYY	Start date Source: AE
Outcome date	DDMMYY	Outcome date Source: AE
Trial day	Continuous	Trial day = (Start Date of AE – Date of First Application of IP) + 1 Source: Calculated from AE ( <i>AEStartDate</i> ) and ENR ( <i>TrialConsentDate</i> )
Duration (days)	Continuous	Duration (days) = <i>AESendDate</i> - <i>AEStartDate</i> Source: Calculated from AE
AE start date	DDMMYY	Start date Source: AE

Adverse events and abnormal observations during the gynaecological examinations may be compared to other data collected in the trial, including STI and HIV test results, since detected genital abnormalities may also be caused by medical conditions. This may be done in an exploratory manner via the data provided in participant listings.

## 10.2 Clinical Laboratory Evaluation

### 10.2.1 Assessments

Collection of blood and urine specimens for haematology, biochemistry (including electrolytes, liver function and renal function) and urinalysis tests is conducted at Screening 1, and every 12 weeks. Clinical laboratory assessments will be performed by the research centre's certified laboratory. Reference ranges will be provided by the central laboratory.

Listings of all clinical laboratory data for each participant will be provided. Laboratory test results will be categorised by DAIDS Grade, and clinical significance. In addition, urinalysis and microscopy data will be summarised. Specific haematology, biochemistry, urinalysis, and microscopy parameters assessed during the trial are listed below.

**Table 7 Haematology, Biochemistry, Urinalysis and Microscopy Parameters**

<b>Haematology (continuous)<sup>1</sup></b>	<b>Biochemistry (continuous)<sup>1</sup></b>	<b>Urinalysis (continuous)</b>	
Erythrocytes Haemoglobin Haematocrit Platelets Leukocytes Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Electrolytes Sodium Potassium Chloride Calcium Phosphate Liver Function Bilirubin Alkaline phosphatase Gamma GT ALT AST Renal Function Urea Creatinine	pH Urobilinogen	
		<b>Urinalysis (categorical)</b>	
		Specific gravity Blood Leukocytes Protein Glucose Ketones Bilirubin Nitrites	
		<b>Microscopy (categorical)</b>	
		WBC RBC Casts Squamous epithelial cells Bacteria Yeasts Crystals Parasites	

Data sources: Haematology and biochemistry reported in LTR-1 and LTR-2 CRF; urinalysis and microscopy reported in UTR CRF.

### 10.2.2 Summary Tables

Routine clinical laboratory findings will be summarised for each of the trial visits during which these data are collected, using appropriate descriptive statistics as described in Section 6.7. A five-number summary will be included by way of box plots, presented overall, by research centre, and treatment arm; absolute change from the Screening visit to each trial visit will also be summarised in tabular form. Shift tables will be used to present the percentage of individuals with DAIDS Grades 1 to 4 haematology and biochemistry laboratory findings for each parameter under investigation using the maximum severity at the Screening visit *versus* the worst-case observation of treatment-emergent abnormalities post-baseline. A table of Grade 3 and 4 laboratory abnormalities will also be provided. The frequency and proportion of clinically significant laboratory abnormalities will be displayed by trial visit in tabular form for each parameter, as reported on the LTR-1 or LTR-2 CRF,

<sup>1</sup> Graded according to the DAIDS table<sup>2</sup> (Grades 1-4).

data element: *<parameter name>sig*. By-participant listings will be provided and will present findings from each clinical assessment.

### 10.3 Pelvic examinations

#### 10.3.1 Assessments

Pelvic examinations will be performed at Screening 1 and Screening 2, and at every 12-weekly visit until the last product use visit. The examination will include naked eye examination of the vulva, speculum examination of the vagina and cervix, and digital and bi-manual examination for adnexal or fundal masses or tenderness.

#### 10.3.2 Summary Tables

A summary of pelvic examinations will be presented overall, by research centre, treatment arm, and by trial visit in tabular form. By-participant listings will also be provided. The summary tables and listings will include the following variables:

**Table 8 Pelvic Examination Variables**

Variable	Data Type	Data Sources
Presence of Vulvar findings	Categorical	Source: PE Indicator variable for: Vulvar erythema, vulvar edema, vulvar rash, vulvar tenderness, Bartholin's or Skene's gland abnormality
Presence of Vaginal findings	Categorical	Source: PE Indicator variable for: Vaginal erythema, vaginal edema, vaginal masses, vaginal abrasions or lacerations, vaginal tenderness, vaginal discharge
Presence of Cervical findings	Categorical	Source: PE Indicator variable for: Cervical erythema, cervical edema and/or friability, cervical masses, cervical motion tenderness, cervical discharge
General/other findings	Categorical	Source: PE Indicator variable for: Odour, uterine masses, adnexal masses, uterine tenderness, adnexal tenderness, condyloma, abnormal genital tract bleeding, other
Presence of Vulvar Lesions findings	Categorical	Source: PE Indicator variable for: Ulcer, blister, pustule, peeling, ecchymosis, other lesions
Presence of Vaginal Lesions findings	Categorical	Source: PE Indicator variable for: Ulcer, blister, pustule, peeling, ecchymosis, other lesions
Presence of Cervical Lesions findings	Categorical	Source: PE Indicator variable for: Ulcer, blister, pustule, peeling, ecchymosis, other lesions
Cervical ectopy	Categorical	Source: PE

## 10.4 Genital infections and other STI assessments

### 10.4.1 Assessments

Cervicovaginal samples will be collected for genital infection and STI testing (bacterial vaginosis, Trichomonas, Gonorrhoea, and Chlamydia) at Screening 1 and every 12 weeks until the last product use visit. Assessments of vaginal flora and vaginal pH will be assessed at the Enrolment visit and every 12 weeks, to assess changes in vaginal flora as measured by the Nugent score for three pathogens, and overall.

### 10.4.2 Summary Tables

In addition to tables provided in support of the safety endpoint, genital infection and STI results will be presented overall, by research centre, by treatment arm and by trial visit. By-participant listings will also be provided. Variables that will be summarised in the tables and listings include:

**Table 9 Genital Infection and STI Variables**

Variable	Data Type	Data Sources
Trichomonas rapid Test	Dichotomous	Source: GTI
Gonorrhoea	Dichotomous	Source: GTI
Chlamydia	Dichotomous	Source: GTI
Syphilis RPR screening test	Dichotomous	Source: GTI
Syphilis RPR titre	Discrete	Source: GTI
Syphilis confirmatory test TPHA/TPPA	Categorical	Source: GTI
Vaginal pH	Discrete	Source: GTI
Whiff test	Dichotomous	Source: GTI
Clue cells (WM)	Dichotomous	Source: GTI
Yeasts (WM)	Dichotomous	Source: GTI
Trichomonas	Dichotomous	Source: GTI
Homogeneous vaginal discharge	Dichotomous	Source: GTI
Bacterial vaginosis	Dichotomous	Source: GTI

In addition to the tables provided in support of this safety endpoint, appropriate statistics will be presented to describe the Nugent score for each type of bacteria (*Lactobacilli*, *G. vaginalis* and *Bacteroides Spp.*, and curved rods) overall, by research centre, treatment arm, and trial visit. Participant listings will also be provided. Bar charts will present comparisons between the number of abnormal, normal, and intermediate diagnoses based on Nugent Scores by visit and treatment arm. A five-number summary of Nugent Scores and vaginal pH will be presented by treatment arm, and by trial visit. The average paired difference in vaginal pH at each



trial visit from the Enrolment visit will be presented. Variables that will be summarised in the tables and listings include:

**Table 10 Bacteria, Nugent Score and Vaginal pH**

Variable	Data Type	Data Sources
Lactobacilli	Discrete	Source: VF
G. vaginalis and Bacteroides Spp.	Discrete	Source: VF
Curved rods	Discrete	Source: VF
Total Nugent Score (numeric)	Discrete	Source: VF
Total Nugent Score (categorical)	Categorical	Source: VF
Vaginal pH	Discrete	Source: VF

### 10.5 Immediately Reportable Events

In addition to SAEs, the following events are considered immediately reportable events:

- 1) Pregnancy
- 2) HIV seroconversion
- 3) Any non-serious adverse event leading to permanent discontinuation of the IP

#### 10.5.1 Assessments

Urine pregnancy tests are conducted at Screening Visits 1 and 2, and at every 4-weekly visit until the last product use visit. Serum pregnancy tests will be performed at the Investigator's discretion. A negative serum test after a positive urine test would overrule the positive urine test.

HIV-1 rapid tests will be conducted at Screening Visits 1 and 2, and every 4 weeks after enrolment until the last product use visit, as well as at the exit visit 6 weeks after ring discontinuation. HIV RNA PCR tests will be conducted at the Enrolment visit and every 4 weeks, but will only be analysed if there is reason to believe that the participant is HIV-positive. All adverse events (serious and non-serious) are monitored throughout the trial; analysis of AEs is discussed in Section 10.1.

#### 10.5.2 Summary Tables

Results from pregnancy tests will be presented in tabular form overall, by research centre, treatment arm, and trial visit and will include appropriate statistics. By-participant listings will be provided for each participant.

**Table 11 Pregnancy Tests**

Variable	Data Type	Data Sources
Type of test (urine or serum)	Dichotomous	Source: PTR
Pregnancy Test	Dichotomous	Source: PTR

Results from HIV tests will be presented in tabular form overall, by research centre, treatment arm, and trial visit and will include appropriate statistics. By-participant listings will be provided for each participant.

**Table 12 HIV Tests**

Variable	Data Type	Data Sources
HIV Test Result (Test #1)	Dichotomous	Source: SER
HIV Test Result (Test #2)	Dichotomous	Source: SER
Repeat Testing (Test #1)	Dichotomous	Source: SER
Repeat Testing (Test #2)	Dichotomous	Source: SER
Western Blot	Nominal	Source: SER
RNA PCR Testing	Nominal	Source: SER *Only tested for HIV seroconverters

### 10.6 Concomitant Medications

Concomitant medication is defined as any medication taken in conjunction with the IP, that is medication that either:

- 1) Started after the first application of the IP, or
- 2) Started before the first application of the IP, but ended on or after the first application of the IP. This includes medication indicated as “Ongoing” at the end of the trial.

Concomitant medications will be coded using WHO Drug Dictionary; a table displaying the frequency and proportion of participants using medications during the trial overall, by treatment group, and by ATC categories will be presented. Concomitant medication will also be presented in the form of listings which will contain information for each medication used.

**Table 13 Concomitant Medication Variables**

Variable	Data Type	Data Sources
Drug Name	Text	Verbatim; Source: CM, <i>MedName1-3</i>
ATC category	Text	Verbatim
Indication	Text	Verbatim; Source: CM, <i>MedIndication1-3</i>
Dose/Unit/Route	Text	Verbatim; Source: CM, <i>MedDose1-3</i>
Frequency	Text	Verbatim; Source: CM, <i>MedFreq1-3</i>
Start date	DDMMYY	Source: CM, <i>MedStartDate1-3</i>
Stop date	DDMMYY	Source: CM, <i>MedStopDate1-3</i>
Ongoing at last visit	Dichotomous	Source: CM, <i>MedOngoing1-3</i>

### 10.7 Physical Examination Findings and Vital Signs

A physical examination will be conducted at Screening 1 and at the last product use visit. At these visits, vital signs will be recorded and body systems will be evaluated for abnormal/normal findings. Data will be summarised overall, by research centre, and treatment arm using appropriate descriptive statistics, as described in Section 6.7.

Listings of all vital signs data will be provided. Variables that will be summarised in the tables and listings include:

**Table 14 Physical Examination and Vital Signs Parameters**

Variable	Data Type	Data Sources
Height	Continuous	Source: PX
Weight	Continuous	Source: PX
Temperature	Continuous; Dichotomous	Source: PX
Pulse	Continuous; Dichotomous	Source: PX
Respiratory rate	Continuous; Dichotomous	Source: PX
Blood pressure	Continuous; Dichotomous	Source: PX
<i>General Examination of Body Systems:</i> General Appearance, skin and mucous membranes, cardiovascular, respiratory, gastrointestinal, and neurological systems, lymph nodes, eyes, ears, nose and throat, musculoskeletal system, and other (1-3).	Nominal	Source: PX

### 10.8 Social Harms

During each HIV counselling session, participants will be asked questions to assess the occurrence of social harms. Participants who experience social harms 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.

By-participant listings of all social harms data will be provided as well as summary tables of such occurrences.

DRAFT

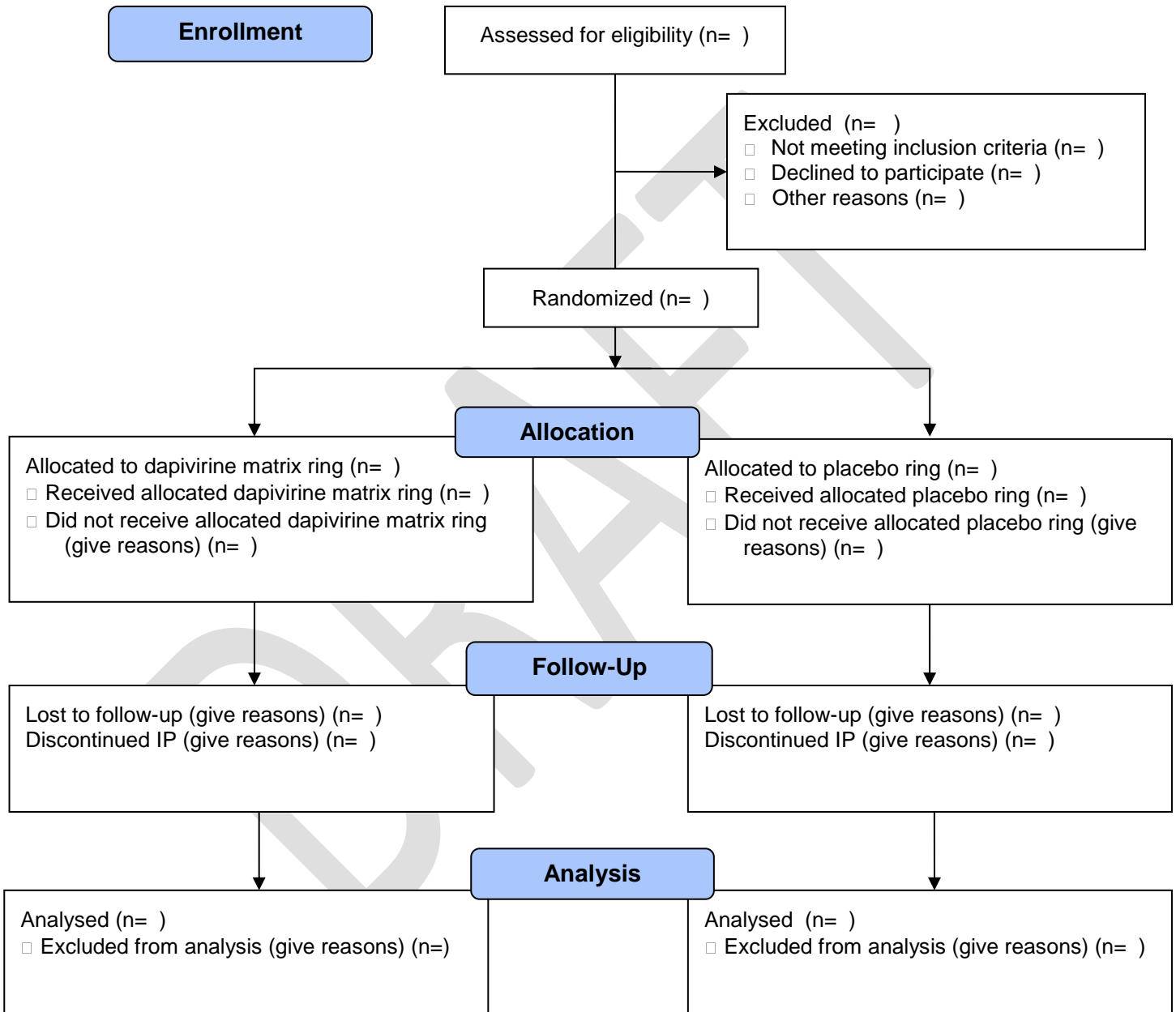
## 11. REFERENCES

1. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 December, 2004; Clarification 1 August 2009.
2. Hosmer DW, Lemeshow S. Applied Survival Analysis: Regression Modeling of Time to Event Data. New York: Wiley; 1999.
3. ICH (1996). International Conference on Harmonisation. Guideline E3 Structure and Content of Clinical Trial Reports.
4. ICH (1998). International Conference on Harmonisation. Guideline E9 Statistical Principles for Clinical Trials.
5. IPM 027 Protocol: *A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED SAFETY AND EFFICACY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-NEGATIVE WOMEN* Version 1.0, Amendment 2.0; 07 November 2012.
6. Loeys T, Goetghebeur E, Vandebosch A. Causal proportional hazards models and time-constant exposure in randomized clinical trials. *Lifetime data analysis*. Dec 2005; 11(4):435-449.
7. Microbicide Trials Network (MTN). Daily HIV Prevention Approaches Didn't Work for African Women in the VOICE Study. <http://www.mtnstopshiv.org/node/4877> March 4, 2013.

## 12. APPENDICES

- 12.1 **Appendix 1 – Consort Flow Diagram**
- 12.2 **Appendix 2 – Table Shells**
- 12.3 **Appendix 3 – Figure Shells**
- 12.4 **Appendix 4 – List of Individual Participant Listings**
- 12.5 **Appendix 5 – IAS-USA Update of the Drug Resistance Mutations in HIV-1: March 2013**

## APPENDIX 1 – CONSORT 2010 Flow Diagram





**INTERNATIONAL PARTNERSHIP *for* MICROBICIDES**

---

# STATISTICAL ANALYSIS PLAN

---

## **A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED SAFETY AND EFFICACY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-NEGATIVE WOMEN**

IPM 027

(Based on: Protocol Version 1.0, Amendment 4.0, dated 21 August 2014)

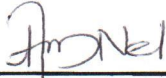
**Version 1.0**

International Partnership for Microbicides  
8401 Colesville Road, Suite 200  
Silver Spring, MD 20910 USA

**APPROVAL SIGNATURE PAGE**  
**IPM 027 – Statistical Analysis Plan**

**A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED SAFETY  
AND EFFICACY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-  
NEGATIVE WOMEN**

I have read the above referenced Statistical Analysis Plan and approve its contents.



Annaléne Nel, MBChB PhD  
Chief Medical Officer  
International Partnership for Microbicides

03 Dec 2015

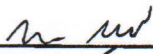
Date



Maarten Borremans, MSc  
Biostatistics Manager  
SGS Life Science Services – Biometrics

03 DEC 2015

Date



Neliëtte van Niekerk, MCom  
Director Biometrics  
International Partnership for Microbicides

03 December 2015

Date



### Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CRF	Case Report Form
CSR	Clinical Study Report
DAIDS	Division of Acquired Immunodeficiency Syndrome
DSMB	Data and Safety Monitoring Board
HIV	Human Immunodeficiency Virus
HSMC	HIV Seroconversion Monitoring Committee
HSV-2	Herpes Simplex Virus-2
ICH	International Conference on Harmonisation
IP	Investigational Product
IPM	International Partnership for Microbicides
IRE	Immediately Reportable Event
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
LOWESS	Locally Weighted Scatterplot Smoothing
MedDRA	Medical Dictionary for Regulatory Activities
m-ITT	Modified Intent-to-Treat
PID	Participant Identification Number
PP	Per-Protocol
PT	Preferred Term
RAM	Resistance Associated Mutation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
STI	Sexually Transmitted Infection
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization

## Table of Contents

1. INTRODUCTION .....	8
2. TRIAL OBJECTIVES .....	8
2.1 Primary Objectives .....	8
2.2 Secondary Objectives .....	8
2.3 Exploratory Objectives .....	9
2.4 Assessment of Objectives .....	9
3 TRIAL DESIGN .....	10
3.1 General Design and Plan .....	10
3.2 Sample Size .....	11
3.3 Randomisation .....	12
3.4 Blinding .....	12
4 SEQUENCE OF PLANNED ANALYSES .....	13
4.1 Safety Monitoring .....	13
4.2 Interim Analyses .....	13
4.3 Final Analysis and Reporting .....	14
5 ANALYSIS POPULATIONS .....	14
5.1 Safety Population .....	14
5.2 Intent-to-treat (ITT) Population .....	14
5.3 Modified Intent-to-treat (m-ITT) Population .....	14
5.4 Per-protocol (PP) Population .....	15
6 GENERAL STATISTICAL CONSIDERATIONS .....	15
6.1 Analysis Software .....	15
6.2 Methods for Handling Missing Data .....	15
6.3 Multiple Comparisons and Multiplicity .....	15
6.4 Multicentre Trials .....	16
6.5 Planned Subgroups, Interactions, and Covariates .....	16
6.6 Data Presentations .....	17
7. TRIAL PARTICIPANTS .....	19
7.1 Disposition of Trial Participants .....	19

7.2	Protocol Deviations and Violations.....	20
7.3	Adherence to Ring Regimen .....	21
7.3.1	Adherence Measures Applying to Both Treatment Arms.....	21
7.3.2	Adherence Measures Applying to Active Arm Only .....	22
7.3.3	Self-reported Adherence by Questionnaire .....	24
8.	EVALUATION OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS.....	25
8.1	Baseline Demographics, and Relationship and Sexual History .....	25
8.2	Baseline Medical and Surgical History .....	25
8.3	Baseline Screening Assessments .....	25
8.4	Obstetrics and Gynaecological History.....	26
9.	EVALUATION OF TRIAL ENDPOINTS.....	26
9.1	Primary Endpoint 1 – Efficacy .....	26
9.1.1	Complementary Analyses on the Primary Efficacy Endpoint .....	28
9.2	Primary Endpoint 2 – Safety .....	29
9.3	Secondary Endpoints.....	30
9.3.1	Secondary Endpoint 1: Seroconversion rate of HIV-2 per 100 person-years of product use at the end of the IP use period .....	30
9.3.2	Secondary Endpoint 2: The incidence of curable STIs, and changes in vaginal flora in each trial arm over the IP use period.....	31
9.3.3	Secondary Endpoint 3: Incidence of pregnancy in each trial arm over the IP use period.....	32
9.3.4	Secondary Endpoint 4: Proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period.....	32
9.3.5	Secondary Endpoint 5: The proportion of women who report the use of the vaginal ring as acceptable.....	33
9.3.6	Secondary Endpoint 6: HIV-1 drug resistance mutations among participants who acquire HIV-1 .....	34
10.	EVALUATION OF SAFETY PARAMETERS .....	34
10.1	Adverse Events.....	34
10.1.1	Treatment Emergent Adverse Events (TEAEs) .....	35
10.1.2	Product-related Adverse Events.....	35
10.1.3	Summary Tables.....	35

10.2	Clinical Laboratory Evaluation.....	38
10.2.1	Assessments .....	38
10.2.2	Summary Tables.....	39
10.3	Pelvic examinations .....	40
10.3.1	Assessments .....	40
10.3.2	Summary Tables.....	40
10.4	Cervical cytology.....	41
10.4.1	Assessments .....	41
10.4.2	Summary Tables.....	41
10.5	Genital infections and other STI assessments .....	41
10.5.1	Assessments .....	41
10.5.2	Summary Tables.....	41
10.6	Immediately Reportable Events .....	43
10.6.1	Assessments .....	43
10.6.2	Summary Tables.....	43
10.7	Concomitant Medications.....	44
10.8	Physical Examination Findings and Vital Signs .....	45
10.9	Social Harms .....	46
11.	CHANGES IN THE PROTOCOL-PLANNED ANALYSES .....	46
12.	REFERENCES .....	47
13.	APPENDICES.....	47
13.1	Appendix 1 – Consort Flow Diagram.....	47
13.2	Appendix 2 – Table Shells .....	47
13.3	Appendix 3 – Figure Shells .....	47
13.4	Appendix 4 – Individual Participant Listing Shells .....	47
13.5	Appendix 5 – IAS-USA Update of the Drug Resistance Mutations in HIV-1: October/November 2015 .....	47
13.6	Appendix 6 – Adverse Events of Special Interest: Grouped Preferred Terms	47
13.7	Appendix 7 – IPM 027 Protocol Deviation Criteria (v3.0, dated 14 September 2015).....	47

13.8 Appendix 8 – Interpretation of Cervical Cytology Results .....47  
13.9 Appendix 9 – IPM 027 Analysis Visit Windows.....47

## 1. INTRODUCTION

This document serves as the Statistical Analysis Plan (SAP) for the protocol pre-specified primary and secondary endpoints for the pivotal Phase III trial, IPM 027. Specifically, this document describes the statistical methods that will be used to analyse the final data from IPM 027 to support the completion of the Clinical Study Report (CSR). The planned analyses described in this SAP will form the basis for the assessment of safety and efficacy of the dapivirine vaginal ring, as determined in the pivotal trial, and will be included in regulatory submissions and/or future manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program.

Table shells, example figures, and listing shells that will accompany the analysis are provided in Appendices 2, 3, and 4, respectively. The appendices are viewed as supporting material of the analysis and will not require signature approval if formatting changes are made.

This document is based on the final version of the IPM 027 trial protocol Version 1.0, Amendment 4.0, which was finalised on 21 August 2014, and refers to Case Report Forms (CRFs) Version 1, dated 07 February 2012, and additional CRFs for capturing ring removal and visual assessment of returned rings (dated 17 July 2013), additional seroconversion data and genotype testing information (dated 30 July 2013), vaginal fluid sampling (dated 28 October 2013), Investigator signature (dated 26 February 2015), and participant transfer to and receipt at other research centres (dated 22 July 2015).

## 2. TRIAL OBJECTIVES

### 2.1 Primary Objectives

The primary objectives of this trial are:

- To determine the efficacy of dapivirine administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks), in preventing HIV-1 infection among healthy, sexually active HIV-negative women
- To assess the safety of dapivirine administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks over a period of approximately 24 months (104 weeks).

### 2.2 Secondary Objectives

The secondary objectives of this trial are:

- To assess and compare the incidence of HIV-2 in the dapivirine and placebo vaginal ring groups

- To assess and compare the incidence of curable sexually transmitted infections (STIs), and changes in vaginal flora in the dapivirine and placebo vaginal ring groups
- To determine the incidence of pregnancy in both trial arms
- To assess reported adherence to the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period
- To assess reported acceptability of the use of either a dapivirine or a placebo vaginal ring inserted once every 4 weeks over the investigational product use period
- To assess the frequency and type of HIV-1 drug resistance in women who acquire HIV-1 infection while using the investigational product.

### **2.3 Exploratory Objectives**

The exploratory objectives of this trial are:

- To evaluate the association between HSV-2 and HIV-1 infection in both trial arms
- To explore the potential relationship between method of contraception, pregnancy incidence and HIV seroconversion in both trial arms
- To explore the relationship between drug concentrations and trial outcomes (HIV-1 seroconversion and viral resistance)
- To explore the correlation of drug concentrations and self-reported adherence measures.

### **2.4 Assessment of Objectives**

Consistent with the primary objectives, the primary endpoints are:

- The incidence rate of HIV-1 seroconversion
- All adverse events (AEs) (full descriptive evaluation).

The primary endpoints will be assessed by:

- Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm (refer to *Appendix C: HIV Testing Algorithms* of the clinical trial protocol).
- Self-reports, physical examination, gynaecological assessments, including pelvic/speculum examination, laboratory tests and other indicated investigations. All AEs will be reported, regardless of grade or relatedness.

Consistent with the secondary objectives, the secondary endpoints are:

- The incidence rate of HIV-2 seroconversion
- The incidence of curable STIs (*i.e. N.gonorrhoeae, C.trachomatis and T.vaginalis*), and changes in vaginal flora in each trial arm over the IP use period
- The incidence of pregnancy in each trial arm over the IP use period

- The proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period
- The proportion of women who report the use of the vaginal ring as acceptable
- The proportion of participants with HIV-1 drug resistance mutations among participants who acquire HIV-1.

The secondary endpoints will be assessed through:

- Rapid and specialised laboratory testing according to the comprehensive HIV testing algorithm in Appendix C of the trial protocol
- STI testing, vaginal flora and vaginal pH testing
- Pregnancy testing
- Questionnaires and qualitative data regarding sexual behaviour and adherence to the use of a vaginal ring inserted once every 4 weeks over the trial period
- Questionnaires and qualitative data regarding the acceptability of the use of a vaginal ring inserted once every 4 weeks over the trial period
- Viral genotyping methods.

Consistent with the exploratory objectives, the exploratory endpoints include:

- The proportion of HSV-2 among analysed samples
- Incidence of pregnancy in correlation with HIV seroconversion rates and method(s) of contraception used by participants
- Steady-state drug concentrations in blood and vaginal fluid
- Steady-state drug concentrations in correlation with self-reported adherence as outlined above for the secondary objective.

The exploratory endpoints will be assessed by:

- HSV-2 testing
- Pregnancy testing and HIV testing as outlined above for the secondary objective, and documentation of participant contraceptive method(s)
- Drug concentrations in blood and vaginal fluid
- Vaginal fluid, plasma and/or ring residual drug levels and self-reported behavioural measures as outlined above for the secondary objective.

### **3 TRIAL DESIGN**

#### **3.1 General Design and Plan**

IPM 027 is a multi-centre, randomised, double-blind, placebo-controlled trial to assess the safety and efficacy of dapivirine in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks, in healthy, sexually active HIV-negative women, when compared to a placebo vaginal ring. Approximately 1950 participants will be



randomised to receive either the 25 mg dapivirine vaginal ring or a placebo vaginal ring.

**Note:** In total, 1959 women have been enrolled in the trial and the study is closed to accrual.

Each participant will engage in the screening process for up to 4 weeks (28 days) prior to enrolment and will use the IP for a period of approximately 24 months (104 weeks).

Each participant will have an additional 6 weeks of follow-up after ring discontinuation, to assess safety (adverse events) and identify HIV seroconversions after product discontinuation.

### 3.2 Sample Size

IPM 027 will be conducted in a sample of approximately 1950 HIV-negative women in a 2:1 ratio, such that 1300 participants will be assigned to the dapivirine ring and 650 participants will be assigned to the placebo ring. The sample size and power calculations for this trial were based on the primary efficacy endpoint, the incidence rate of HIV-1 seroconversion, in the two treatment arms. The statistical assumptions used in determining this sample size include:

- proportional hazards among the two groups
- microbicide efficacy of  $\geq 50\%$  in preventing HIV-1 infection
- randomisation ratio of 2:1 (dapivirine vaginal ring *versus* placebo ring)
- a two-sided log-rank test statistic, with  $\alpha = 0.05$
- $> 4\%$  average annual HIV incidence in the placebo arm (assumes a reduction in incidence in the trial population due to risk reduction counselling)
- $\leq 10\%$  discontinuation rate over the duration of the trial period.

The increased sample size of 1950 (from 1650, as planned in IPM 027 protocol version 1.0 and amendments 1.0 and 2.0) would mitigate the potential negative impact of product non-adherence on the trial outcome and sustain the power of the trial for the primary objectives. (Refer to Section 9.1.1 for a description of the high level of protocol and product non-adherence observed at one research centre in the trial, which prompted the sample size increase and subsequent discontinuation of all enrolled participants at this centre.)

Table 1 below provides the estimated power to detect 40%, 50% and 60% microbicide efficacy with a sample size of 1950 based on the assumptions as stated above.

**Table 1 Estimated Power for Varying Microbicide Efficacy Levels**

<b>Microbicide efficacy</b>	<b># Expected HIV-1 seroconversions</b>	<b>Power</b>
40%	104	61%
50%	96	81%
60%	88	94%

A trial with the proposed design will provide approximately 81% power to detect a 50% reduction in the rate of HIV-1 seroconversions in the active arm, assuming an annual HIV-1 seroconversion rate of 4% in the placebo arm, and a 10% early discontinuation rate.

In a trial with this number of participants assigned to the IP, there is a 95% probability of detecting an AE occurring at a rate of 0.3% or higher.

### **3.3 Randomisation**

Participants who meet all of the trial inclusion criteria and no exclusion criterion at baseline will be randomly assigned in a 2:1 ratio to one of two groups, receiving either the vaginal ring containing dapivirine or the placebo vaginal ring. Randomisation will be stratified by research centre at the time of enrolment, using a pre-specified block size, and will be determined via the use of an automated randomisation system, IXRS (Interactive Voice/Web Response System for trial management and treatment allocation) to ensure balance of the treatment assignments. Both groups will use a ring inserted at 4-weekly intervals on a continuous basis for the duration of trial participation and have a follow-up visit 6 weeks after ring removal.

A master randomisation list, linking each participant identification number to a trial treatment assignment (dapivirine ring or placebo ring) will be generated for the trial. At each research centre, as each new participant enters the trial, a unique participant identification number will be assigned to that participant using the IXRS automated response system.

### **3.4 Blinding**

The Principal Investigator or his/her designee will be able to unblind each enrolled participant, through the automated system, if necessary. If, during the course of the trial a medical emergency requires knowledge of the test agent used by a particular participant, the trial blind or code may be broken for that specific participant, after discussion with IPM's Clinical Trial Physician or designee, whenever possible. Any unblinding of participant treatment assignments will be justified and explained in the source documents and applicable CRF and reporting forms. If the blinding code is broken by the Principal Investigator or his/her designee, the participant will be

withdrawn from the trial and followed up as appropriate. The blinding and unblinding process will be performed by the IXRS automated response system.

An interim analysis is to be conducted when approximately 50% of the expected efficacy endpoints have been observed, as pre-specified in the protocol. This analysis involves breaking the blind to perform treatment comparisons – see Section 4.2 for more details. Only individuals as detailed in the DSMB charter will have access to the results of the interim analysis.

**Note:** The interim efficacy analysis was conducted for the 18 November 2013 DSMB meeting.

## 4 SEQUENCE OF PLANNED ANALYSES

### 4.1 Safety Monitoring

An independent DSMB has been established for IPM 027. The DSMB members meet bi-annually via conference call or face-to-face during the trial. In addition, *ad hoc* calls or face-to-face meetings may be convened if requested by the DSMB Chair or IPM. DSMB members include individuals not associated with this trial, but who have expertise in conducting clinical trials, experience working in developing countries, and/or a history of working in the microbicide arena. Prior to each DSMB meeting, a data package of all available clinical and safety data is prepared for the DSMB for their review; these data packages, containing blinded and unblinded data (by masked treatment groups), are prepared by an independent statistician not otherwise involved in the trial.

The DSMB has the option to recommend pausing or stopping the trial at any point. The DSMB composition and its charges related to the trial are described in a separate DSMB charter.

### 4.2 Interim Analyses

A separate SAP has been compiled for the interim analysis (Version 1.0, dated 09 October 2013). The analysis is to be performed by an independent statistician who is not otherwise involved in the trial and will include all data available in the clinical database at the time point when 50% of the expected number of trial endpoints have occurred. The results of the interim analysis will be reviewed by the DSMB; only individuals as detailed in the DSMB charter will have access to the results of the interim analysis.

Full details of the efficacy analysis to be performed at the interim analysis, including the statistical hypothesis to be tested, and the trial pausing or stopping rules that will be followed for this analysis, are presented in the SAP for the interim analysis.

**Note:** The interim efficacy analysis was conducted for the 18 November 2013 DSMB meeting, and the DSMB recommendation was to continue the trial as planned.

### 4.3 Final Analysis and Reporting

This SAP will be approved before final database lock. All final and planned analyses identified in the protocol and in this SAP will be performed only after the database has been locked. A blinded review of the data will be performed prior to database lock for data quality purposes and for classification of protocol deviations as minor or major. In addition, treatment codes will only be released after database lock, in accordance with IPM-SOP-0012.00.

## 5 ANALYSIS POPULATIONS

Four analysis populations have been defined for this trial: a safety population, an intent-to-treat population, a modified intent-to-treat population, and a per-protocol (protocol-adherent) population. The number of participants valid for each population, and when appropriate, the reasons for excluding trial participants from these populations, will be presented overall, by research centre, and by treatment arm using relevant summary statistics.

### 5.1 Safety Population

The safety population includes all participants who have been randomised to IP and received at least one dapivirine or placebo vaginal ring.

**Note:** In total, 1959 women have been enrolled in the trial, but 1958 women used at least one dapivirine or placebo ring. One woman at Research Centre 01 was randomised and a ring was dispensed; however, the ring was never inserted as she discontinued from the trial.

### 5.2 Intent-to-treat (ITT) Population

As defined in ICH guideline E9 (*Statistical Principles for Clinical Trials*)<sup>4</sup>, the intent-to-treat (ITT) principle states that the effect of a treatment can be best assessed by evaluating the treatment on the planned treatment arm, rather than the actual treatment given. The intent-to-treat population will include all trial participants who were randomised to one of the two treatment arms, dapivirine ring or placebo ring, and analysed as members of that treatment arm, regardless of adherence to the planned course of treatment.

### 5.3 Modified Intent-to-treat (m-ITT) Population

Some participants may not have detectable levels of HIV antibodies at the enrolment visit, and therefore, HIV-positive women who are assumed to be HIV-negative may be enrolled in the trial. To accommodate this situation, a modified intent-to-treat (m-ITT) population will be determined and used for analysis of the primary efficacy endpoint. This population will include all participants who are included in the ITT population but who were never determined to be HIV-seropositive at the enrolment visit. Women who have seroconverted after enrolment will be excluded from the m-

ITT population on the basis of baseline information collected prior to randomisation and which only became available after randomisation.

#### **5.4 Per-protocol (PP) Population**

The per-protocol (or protocol-adherent) population is a subset of the m-ITT population, *i.e.* all trial participants who are HIV-1 negative at the enrolment visit, with no major protocol deviations, as defined in Section 7.2.

## **6 GENERAL STATISTICAL CONSIDERATIONS**

### **6.1 Analysis Software**

Statistical analyses will be conducted by an external statistical service provider (SGS Life Science Services) and reviewed by the International Partnership for Microbicides. The analyses will be performed using SAS<sup>®</sup> for Windows XP or Linux/Unix (version 9.1 or higher, SAS Institute Inc., Cary, North Carolina, USA).

### **6.2 Methods for Handling Missing Data**

All participants in the m-ITT population will be included in the analysis of the primary efficacy endpoint (refer to Sections 9.1 and 9.1.1). While every effort will be made to minimise the amount of missing data, some degree of missing data, primarily associated with missed visits, is expected. For the analysis of adherence to 4-week ring use, patterns of missing data may be informative. As the effect of missed visits is expected to be balanced across the treatment arms, no imputation for missing data is planned prospectively, with the exception of the time-varying product-adherence analysis (complementary analysis of the primary efficacy endpoint; refer to Section 9.1.1). For this analysis, missing ring residual levels and/or plasma concentrations of dapivirine will be imputed using LOCF (Last Observation Carried Forward).

If more than 10% of participants discontinue from the trial early (with the exception of Research Centre 03, where all participants were discontinued from trial participation in 2013 [Sponsor decision]), potential covariates that may be associated with time to discontinuation will be investigated. These results may be useful in identifying factors that influenced trial participation. The time of discontinuation will be defined as the time from the Enrolment visit until the first missed visit after which the participant did not return for any subsequent visits.

### **6.3 Multiple Comparisons and Multiplicity**

Section 4.2 describes the planned interim analysis when approximately 50% of the expected efficacy endpoints are available. The plan for adjusting for multiple reviews of the efficacy data is as follows (also detailed in the SAP for the interim analysis):

At the interim analysis, the null hypothesis that the HIV-1 seroconversion hazard rate of active product relative to placebo equals 0.75 ( $H_0$ : HR = 0.75) will be evaluated at

a nominal, one-sided 2.5% significance level. To avoid inflation of the Type I error rate when evaluating superiority both at the interim and the final analysis, the Lan and De-Met's implementation of the O'Brien-Fleming grouped sequential stopping boundary, with the time scale measured on the cumulative number of HIV-1 seroconversions, will be used. With 40 of the expected efficacy endpoints available, the adjusted one-sided significance levels are equal to 0.0015 at the interim analysis and 0.0245 at the final analysis, with -2.9626 and -1.9686 the respective, corresponding critical values for the test statistic (on the Z-scale). If the actual number of events at the interim analysis is different from 40, the O'Brien-Fleming-adjusted critical values/significance levels corresponding to the actual fraction of information will be used.

**Note:** The actual number of efficacy endpoints at the interim analysis was 52, and hence the O'Brien-Fleming-adjusted significance level corresponding to this fraction of information was used, *i.e.* a one-sided significance level of 0.0054. The adjusted one-sided significance level for the final analysis will be 0.0233 (adjusted two-sided significance level of 0.0466).

The final analysis of the primary efficacy endpoint only involves a single treatment comparison (between the two arms of the trial), which does not require further adjustment.

#### **6.4 Multicentre Trials**

Differences in participant safety and efficacy of the dapivirine vaginal ring across research centres will be explored graphically and descriptively. The key efficacy and safety analysis will be summarised overall and for each research centre separately. For the primary efficacy endpoint and primary safety endpoint, a formal comparison of the data will be performed to evaluate for homogeneity of the treatment effect across research centres.

#### **6.5 Planned Subgroups, Interactions, and Covariates**

As stated in Section 5, the analysis of the primary efficacy endpoint will be based on the m-ITT population, which will include all participants who were confirmed to be HIV-negative at baseline and who were randomised to IP.

As this is a randomised trial in healthy HIV-negative women, it is anticipated that the treatment arms will be comparable at baseline with respect to pre-existing conditions. Furthermore, it is expected that women with pre-existing conditions will be treated and evaluated before being enrolled into the trial. For this reason, no baseline adjustments are planned prospectively; however, all data will be reviewed to assess any potentially relevant baseline imbalances.

Unless specified otherwise, statistical models will include treatment and research centre as main effects, with treatment-by-centre as interaction term. Log rank tests

and Cox regression models will be performed, stratified by research centre. The primary efficacy analysis will be repeated for the following subgroups:

1. participant age at baseline (< 25 *versus*  $\geq$  25 years)
2. participant age at baseline ( $\leq$  21 *versus* > 21 years) (the data of the younger age group will provide insight in the efficacy of the vaginal ring in young women, in lieu of efficacy data in adolescent girls)
3. marital status at baseline (married *versus* not married)
4. number of male sex partners at baseline (0-1 *versus* 2 or more)
5. partner knowledge of ring use at baseline (yes *versus* no)
6. presence of genital symptoms/STIs at baseline (yes *versus* no)
7. use of long-acting progestins as contraceptive method during the period of IP use (yes *versus* no)
8. type of long-acting progestins used as contraceptive method during the period of IP use (depot medroxyprogesterone acetate [DMPA] *versus* norethisterone)
9. self-reporting the use of any vaginal products at  $\geq$  80% of the scheduled trial visits during the period of participation in the trial (yes *versus* no)

In each case, the analysis will be stratified by research centre and will include treatment, the subgroup covariate and the treatment-by-covariate interaction. Kaplan-Meier survival curves will be presented for each subgroup separately.

Furthermore, as a sensitivity analysis, a multivariate analysis will be performed, including the above-mentioned subgroup variables (subgroups 2 to 6) as covariates (only variables that prove to have a significant effect on the primary efficacy endpoint, based on the individual subgroup analyses and at a 5% significance level) will be included in the multivariate model in a stepwise manner. Covariates that prove to be non-significant at the 5% level in the multivariate setting will be excluded from the final model.

The following subgroup analysis will be performed for the primary safety endpoint (adverse events of interest), and for the secondary endpoints STI incidence and incidence of pregnancy, if appropriate:

- Participants in the age group  $\leq$  21 years, and > 21 years, in lieu of safety data in adolescent girls

## 6.6 Data Presentations

Descriptive statistics will be presented overall, by research centre and by treatment arm (dapivirine ring or placebo ring).

For continuous variables, the descriptive statistics will include: mean and standard deviation (when appropriate), quartiles, range, and number of observations. For categorical variables, descriptive statistics may include frequencies, relative frequencies, and the number of observations. Percentages will be presented to one

decimal place. The subsequent sections discuss the planned analyses beyond the listings and simple descriptive analyses.

Baseline is defined as the last available measurement before the first insertion of the IP. This measurement may be made at Screening 1, Screening 2, or at the Enrolment visit (prior to ring insertion).

Missing or partial dates will be imputed for adverse event or concomitant medication start dates. No other date imputations will be performed. For adverse event or concomitant medication start dates, the following conventions will be applied:

- If only the month and the year are known, then the 15th of the month will be used, *i.e.* “15” will be used as the day of the month, unless the month and the year equal the month and the year of the first insertion of the ring; in such cases, the same day as the day of ring insertion will be used (to ensure that the adverse event or concomitant medication is considered as treatment-emergent)
- If only the year is known, then the first day of January will be used, *i.e.* “01JAN” will be used as the day and month, unless the year equals the year of first ring insertion, in which case the date will be imputed with the date of first ring insertion.

For concomitant medication end dates, the following conventions will be applied:

- If only the month and the year are known, then the last day of the month will be used
- If only the year is known, then the last day of December, *i.e.* “31DEC” or the date of trial completion/discontinuation will be used (whichever comes first).

In instances where the date of IP initiation, *i.e.* the start date of ring use, is missing or unknown, the missing date will be imputed with the date of the enrolment visit, *i.e.* the Visit 1 date.

In accordance with the protocol, each scheduled visit while the participant is on IP has a window period of  $\pm 7$  days. However, consecutive visits should be no less than 21 days and no more than 35 days apart. If a participant presents for a visit outside the window for a scheduled trial visit, this will be documented as a protocol deviation (refer to Section 7.2); however, the data recorded at this visit will be analysed as pertaining to the scheduled visit. Unscheduled visits may be performed at any time during the trial. If an unscheduled visit takes place within any given window period and any repeat observations are made within the given window period, the repeat values will be captured as pertaining to the unscheduled visit. Data from scheduled and unscheduled visits will be shown in the participant listings, and listings will be appropriately labelled when data arise from unscheduled visits. For summary tables by trial visit, data from all visits will be assigned to analysis visit windows. Data from scheduled visits will be assigned to their nominal analysis visit window. Data from unscheduled visits will be assigned to an analysis visit window.



based on the relative day in the trial (refer to Appendix 9 for a table of analysis visit windows). Data from scheduled visits will be presented in the summary tables. However, in instances where a result is not available for a scheduled visit but is available from an unscheduled visit in the given analysis visit window, the result from the unscheduled visit will be used. If more than one result is available from unscheduled visits, the one closest to the target day of the analysis visit window will be used. When assessing the “worst case result” during the entire IP use period (*e.g.* for STIs and pelvic examination results), observations at unscheduled visits will be included.

In the calculation of non-adherence events and self-reported adherence, particular rules will be applied to handle data from unscheduled visits (see Sections 7.3.1 and 7.3.3, respectively).

Tables, figures, and listings of trial results will accompany the text of the Clinical Study Report. Listings of all clinical data recorded in the CRFs will be provided, except for those CRFs which are used for administrative purposes, such as the Participant Encounter Form (PEN) and the End of Trial Inventory (ETI). Listings will be sorted by research centre and participant identification number (PID), and key variables such as treatment arm, visit date and/or trial visit number will be presented in each listing.

## 7. TRIAL PARTICIPANTS

All participants who provide informed consent for this trial will be accounted for, in accordance with ICH guideline E3 (*Structure and Content of Clinical Study Reports*)<sup>3</sup>.

### 7.1 Disposition of Trial Participants

The number and percentage of trial participants who were screened, randomised to IP, permanently discontinued IP, permanently discontinued the trial, and who completed the trial will be presented.

For those participants who were prematurely discontinued from the trial, the time to permanent discontinuation of IP and the time to permanent discontinuation from the trial will be calculated, and presented together with Kaplan-Meier curves by treatment, research centre-by-treatment, and baseline covariates (refer to Section 6.5; subgroups 2 to 6).

A listing reflecting each participant’s screening date, enrolment date, and scheduled and unscheduled visit dates, as documented in the PEN CRF, will be provided. The CONSORT flow diagram in Appendix 1 may also be used to depict the disposition of trial participants.

## 7.2 Protocol Deviations and Violations

All recorded protocol deviations will be listed and summarised overall, by research centre, and by treatment arm.

A protocol violation is a major deviation from the protocol which may impact the integrity of the data and/or the safety of the trial participant(s). The IPM Clinical Trial Physician(s) (one or more IPM physicians assigned to continually monitor blinded trial data during the course of the trial) will establish protocol deviation criteria for the trial, in conjunction with the IPM Head of Quality Management and Compliance (QM&C), the Head of Biometrics and other clinical team members, as appropriate. The final list of protocol deviation criteria will be approved by the IPM Chief Medical Officer (refer to Appendix 7 for the final list of protocol deviation criteria). Before database lock and statistical analysis, all reported protocol deviations will be reviewed by the IPM Clinical Trial Physician(s), Head of QM&C and Head of Biometrics, in conjunction with the trial statistician (from SGS Life Science Services), to determine the impact of each deviation on the analysis, and to compile a final list of major protocol deviations for purposes of defining the per-protocol (protocol-adherent) analysis population. The final list will be signed off by the IPM Chief Medical Officer.

Major protocol deviations that will result in either exclusion of a participant from the protocol-adherence analysis or censoring of the participant's data at the date of the last negative HIV-1 test result prior to the occurrence of the major protocol deviation will include:

- Inappropriate enrolment into the trial (e.g. participant met an exclusion criterion, or participant failed to meet all inclusion criteria) as documented in the DL CRF. A major deviation will exclude the participant completely from the population.
- IP-related deviations (e.g. IP was incorrectly withheld from participants, participants incorrectly resumed IP use, or inappropriate IP was dispensed to a participant). The data of such participants will be censored at the date of the last negative HIV-1 test result prior to the occurrence of the deviation.
- The participant demonstrated three "non-adherence" events in a window of one year (12 scheduled visits). A "non-adherence event" can either be a missed visit, a self-report that the ring was out for 12 hours or more, or the non-return of a used vaginal ring. The data of such participants will be censored at the date of the last negative HIV-1 test result prior to the first "non-adherence" event.
- Any other major protocol deviation identified during the blinded review that may impact the integrity of the data. The decision whether the participant should be excluded entirely from the population or whether the data of the

participant should be censored will be made during the blinded review of the protocol deviations.

The number of participants with minor and major protocol deviations will be presented using appropriate summary statistics overall, by research centre, and by treatment arm.

### **7.3 Adherence to Ring Regimen**

The data collected in IPM 027 allow both subjective and objective assessments of adherence to ring use by the participants in this trial. The subjective adherence measures include self-reported ring use as collected by adherence questionnaires, and/or feedback from participants or male partners following qualitative individual interviews or focus group discussions. Missed and/or late clinical trial visits (outside protocol-allowed visit windows – refer to Section 6.6) will also be used as indicator of non-adherence to prescribed product use. Objective, quantitative measures of adherence include plasma and vaginal fluid concentrations of dapivirine in samples collected at the 4-weekly trial visits, as well as the residual levels of dapivirine in all used rings returned to the research centres.

#### **7.3.1 Adherence Measures Applying to Both Treatment Arms**

As described in Section 9.1.1, three complementary analyses on the primary efficacy endpoint will be performed on the m-ITT population. For the analysis where the data of non-adherent participants will be censored (product-adherence analysis), one set of criteria will be applied for all participants to define non-adherence, *i.e.* the same criteria will apply to both the dapivirine ring and placebo arms, so as not to introduce bias in the analysis. The criterion that will be used is the following:

- The participant demonstrated three "non-adherence" events in a window of one year (12 scheduled visits). A "non-adherence event" can either be a missed visit, a self-report that the ring was out for 12 hours or more, or the non-return of a used vaginal ring. The data of such participants will be censored at the date of the last negative HIV-1 test result prior to the first "non-adherence" event.

**Note:**

- Missed visit = no scheduled visit
- Self-report that the ring was out for 12 hours or more = self-report at the scheduled visit or any preceding unscheduled visit between the previous and the current scheduled visit
- Non-return of used vaginal ring = the number of rings returned after the previous and till (including) the current scheduled visit is less than the number of rings dispensed at the previous scheduled visit up till (excluding) the current scheduled visit

- In case more than one ring was dispensed for a pre-planned non-availability of the participant at a scheduled visit, and all rings were returned at the next scheduled visit, this will not be considered as a non-return. Additionally, this visit will also not be considered as a missed scheduled visit.

### **7.3.2 Adherence Measures Applying to Active Arm Only**

Residual levels of dapivirine in used rings, and plasma and vaginal fluid concentrations of dapivirine will be determined for those participants assigned to the active arm, as measure of adherence to ring use. The data will be listed, summarised and presented graphically, as described below.

#### **Dapivirine Ring Residual Levels**

All used vaginal rings that are returned to the research centres at each trial visit are collected and shipped at regular, pre-defined intervals to an analytical laboratory, where the rings of those participants assigned to the active ring are analysed to determine the residual amounts of dapivirine in the rings.

For this trial, a reported ring residual level of > 23.5 mg dapivirine will be used as indication of non-adherence to ring use over the 28-day period ( $\pm 7$  days) that a woman was to keep the ring *in situ*. This value was obtained as the lower limit of the 95% confidence interval of ring residual levels of dapivirine (from a blinded analysis of all available ring residual levels to date) corresponding to plasma dapivirine concentrations below 95 pg/mL, which was determined as the plasma dapivirine concentration below which a participant was most likely not adherent to ring use over the intended 28 days, based on the population PK model for dapivirine (refer to “Plasma and Vaginal Fluid Concentrations of Dapivirine” below).

The following summaries and graphical presentations will be produced for these data:

- A summary of ring residual levels at each trial visit, with standard descriptive statistics – presented overall and by research centre. Corresponding box plots will be prepared.
- A descriptive summary of the ring residual levels by trial visit and by category of residual amount (< 19 mg, 19 – 23.5 mg, and > 23.5 mg). This summary will be prepared overall and by research centre, with corresponding bar charts.
- A summary relating the ring residual amounts to time intervals (in days) between consecutive trial visits (< 21 days, 21-35 days, and > 35 days), to determine whether a trend between residual amounts and visits outside the permitted window periods is apparent. Corresponding box plots will be prepared.

In addition, a listing of those trial participants who HIV seroconverted (confirmed trial endpoints), together with the date of the last negative HIV RNA PCR test, the date of the first positive HIV RNA PCR test, the number of days in-between, and the

corresponding ring residual levels of dapivirine, will be produced. A scatter plot of the residual levels of dapivirine in the last ring returned by these participants prior to HIV seroconversion will be produced and compared visually with the average ring residual levels of those participants who remained HIV-negative over the duration of the trial.

**Plasma and Vaginal Fluid Concentrations of Dapivirine**

All blood and vaginal fluid samples collected at each trial visit are shipped to a bio-analytical laboratory, where the blood samples of all participants assigned to active rings are analysed for plasma concentrations of dapivirine. Vaginal fluid samples collected from all participants up to 28 February 2014 were analysed for dapivirine concentrations.

A population pharmacokinetic model for dapivirine has been developed based on the Phase I trials IPM 013 and IPM 024, and validated with the data from IPM 028<sup>7</sup>. This model has been used to simulate the effect of different ring use/removal scenarios on plasma and/or vaginal fluid concentrations of dapivirine, to assist in defining a range of dapivirine plasma and/or vaginal fluid levels that may be indicative of non-adherence to ring use over the 28-day period ( $\pm 7$  days) that a woman was to keep the ring *in situ*. The following scenarios were simulated:

- Removal of the ring 24 hours after first insertion, and re-insertion of the same ring on Day 27, to predict the plasma and/or vaginal fluid level on Day 28
- Removal of the ring 2 weeks after first insertion, with no re-insertion for the remainder of a 28-day period
- Removal of the ring 3 weeks after first insertion, with no re-insertion for the remainder of a 28-day period.
- Removal of the ring 3 weeks after first insertion, and re-insertion 4 hours before the clinic visit on Day 28
- Removal of the ring 3 weeks after first insertion, and re-insertion 8 hours before the clinic visit on Day 28

Based on these simulations, a range of plasma and vaginal fluid concentrations of dapivirine, respectively, was defined, below and above which the participant was most likely not adherent to ring use over the intended 28 days. The ranges of expected dapivirine concentrations after 28 days, associated with 100% adherence to ring use over this period, are as follows:

	<b>Median concentration</b>	<b>90% confidence interval</b>
Plasma	236 pg/mL	95.4 – 572 pg/mL
Vaginal Fluid (cervix)	18.4 $\mu$ g/g	4.6 – 61.1 $\mu$ g/g

The following summaries and graphical presentations will be produced for the plasma and vaginal fluid data, respectively:

- A summary of the concentration values at each trial visit, with standard descriptive statistics – presented overall and by research centre. Corresponding box plots will be prepared.
- A descriptive summary of the concentration values by trial visit and by concentration interval (< 95 pg/mL, 95 – 572 pg/mL, and > 572 pg/mL for plasma, and < 4.6 µg/g, 4.6 – 61.1 µg/g, and > 61.1 µg/g for vaginal fluids). These summaries will be prepared overall and by research centre, with corresponding bar charts.
- A summary relating the concentration values to time intervals (in days) between consecutive trial visits (< 21 days, 21-35 days, and > 35 days), to determine whether a trend between plasma/vaginal fluid concentrations and visits outside the permitted window periods is apparent. Corresponding box plots will be prepared.

In addition, a listing of those trial participants who HIV seroconverted (confirmed trial endpoints), together with the date of the last negative HIV RNA PCR test, the date of the first positive HIV RNA PCR test, the number of days in-between, and the corresponding plasma and vaginal fluid concentrations of dapivirine, will be produced. Scatter plots of the plasma and vaginal fluid levels of dapivirine measured prior to HIV seroconversion for these participants will be produced and compared visually with the average plasma and vaginal fluid levels of dapivirine for those participants who remained HIV-negative over the duration of the trial.

The correlation between the amount of residual dapivirine in the used rings and the corresponding plasma and vaginal fluid levels of dapivirine will be explored graphically and summarised descriptively.

### **7.3.3 Self-reported Adherence by Questionnaire**

Self-reported adherence to the ring regimen will be calculated per visit and overall, and presented descriptively by research centre and treatment arm. The adherence rate per visit will be calculated as:

- $100 \times (\text{Number of days that the participant reportedly wore the ring} / \text{total number of days that the participant was expected to wear the ring})$ .

The number of days that the participant reportedly wore the ring is calculated cumulatively based on the self-report at the scheduled visit and any preceding unscheduled visit between the current and the previous scheduled visit.

The self-reported adherence rates will be presented in the following categories:

- $\geq 90\%$
- $\geq 80\%$  to  $< 90\%$

- < 80%.

A comprehensive description of the planned analysis of self-reported adherence data is provided in Section 9.3.4.

## 8. EVALUATION OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Unless otherwise specified, demographics (DEM) and other baseline characteristics, including relationship and sexual history (BBQ), medical and surgical history (MED), and obstetrics/gynaecological history (GHX), and the physical examination obtained at the Screening visits and the Enrolment visit, will be summarised descriptively overall, by research centre, and by treatment arm using appropriate summary statistics as described in Section 6.7.

### 8.1 Baseline Demographics, and Relationship and Sexual History

The following baseline demographic characteristics will be listed and summarised: age, race, height, weight and body mass index (BMI), as well as information on education level, and relationship and sexual history. Age and BMI will be derived as described in Table 2.

**Table 2 Derived and Computed Demographic Variables**

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes, or Equation(s)
Age	Age (years)	18 to 45 (inclusive)	INT((date of enrolment – date of birth)/365.25)
BMI	Body Mass Index (kg/m <sup>2</sup> )		(Participant body weight in kg)/ (Participant height in m) <sup>2</sup>

Qualitative demographic characteristics (nominal or ordinal categories) will be summarised using absolute and relative frequencies. Quantitative demographic characteristics (continuous) will be summarised using the appropriate summary statistics, namely number of participants, mean, standard deviation (SD), quartiles, and range. All demographic and baseline characteristics will be presented in participant listings.

### 8.2 Baseline Medical and Surgical History

Medical and surgical history will be collected during the Screening visit and Trial Visit 1 (pre-enrolment). Medical history will be presented in tabular form using appropriate descriptive statistics.

### 8.3 Baseline Screening Assessments

Laboratory assessments conducted at baseline, including cytology, syphilis testing (RPR; confirmatory TPHA/TPPA), haematology, biochemistry, urine pregnancy tests, HSV-2 serology tests, and HIV rapid tests will be presented for all participants.

#### **8.4 Obstetrics and Gynaecological History**

Obstetrics and gynaecological history will be collected during the Screening visit, and gynaecological conditions will be coded using Version 15.0 of the Medical Dictionary for Regulatory Activities (MedDRA). Obstetrics and gynaecological history will be presented in tabular form with absolute and relative frequencies, and gynaecological conditions will be classified using System Organ Class (SOC) and Preferred Term (PT).

#### **8.5 Prior Therapies and Medications**

Prior medication is defined as any medication that started and ended before the first administration of IP. Medications will be coded using the WHO Drug Dictionary (version 01 June 2011). A table summarising the number and percentage of participants using drugs within each Anatomical Therapeutic Chemical (ATC) classification will be presented.

### **9. EVALUATION OF TRIAL ENDPOINTS**

#### **9.1 Primary Endpoint 1 – Efficacy**

According to the sample size calculation and underlying assumptions (refer to Section 3.2), the IPM 027 trial has 81% power to detect a reduction of 50% in the HIV-1 seroconversion rate for the dapivirine ring relative to placebo. The primary null and alternative hypotheses for this trial are:

$H_0$ : HIV-1 seroconversion hazard rate of active product relative to placebo = 1  
(hazard ratio = 1)

$H_1$ : HIV-1 seroconversion hazard rate of active product relative to placebo  $\neq$  1  
(hazard ratio  $\neq$  1)

Trial participants are to be followed on IP for 24 months, and will be tested for HIV-1 infection at 4-weekly visits until the last product use visit, as well as at the exit visit, 6 weeks after ring discontinuation. HIV seroconversion will be determined per the HIV testing algorithm presented in the IPM 027 protocol<sup>5</sup>. However, only HIV-1 seroconversions that have been confirmed by the independent IPM 027 HIV Seroconversion Monitoring Committee (HSMC) as occurring after enrolment into the trial will be regarded as trial endpoints. The point of HIV-1 infection is determined by performing reverse sequential HIV RNA PCR testing (on stored samples collected at each visit) until a negative test result is achieved.

Participants who are not diagnosed with HIV-1 at the end of the trial participation period will be censored at the last HIV-1 test date at or prior to the last product use visit.



If HIV-1 is detected at the exit visit (6 weeks after ring discontinuation), HIV RNA PCR testing will be performed on stored samples in reverse sequential order to estimate the time point of HIV-1 infection. If HIV-1 infection is detected at or prior to the last product use visit, the participant will be included in the analysis as an HIV-1 seroconverter. If the time of infection is determined to be after completion of product use, the participant will be censored on the last HIV-1 test date at or prior to the last product use visit. Refer to Table 3 for calculation methods of derived variables.

**Table 3 Derived and Computed Variables – HIV Seroconversion**

Variable Name	Description	Computation Methods, Notes, or Equation(s)
HIV_TTS	Time to HIV-1 seroconversion	Date_HIV_seroconversion* – Date_enrolment
HIV_TDP	Time to discontinuation of IP	Date_LPUV – Date_enrolment
HIV_TDT	Time to discontinuation of trial	Date_trial completion – Date_enrolment
HIV_C	Censor variable	

\* Date of first trial visit with an HIV-positive test result.  
 LPUV = Last product use visit.

The primary analyses will be performed on the m-ITT population, as well as the PP (protocol-adherent) population. The aggregate of the m-ITT analysis results and the three additional complementary analyses described below (Section 9.1.1) will be used to assess the efficacy of the dapivirine vaginal ring in preventing HIV-1 acquisition as compared to placebo. All of these analyses will be presented in the Clinical Study Report.

The formal statistical test used to evaluate the efficacy of the dapivirine ring will be the two-sided log-rank test, stratified by research centre, and this test will be evaluated at the adjusted two-sided significance level of 0.0466 (to account for the superiority evaluation at the interim analysis; refer to Section 6.3). It will be assumed that censoring is unrelated to HIV-1 acquisition and that survival probabilities are the same for participants recruited early and late in the trial.

The test statistic for the stratified log-rank test with  $m=1, \dots, M$  strata is given by:

$$X_{MH} = \frac{[\sum_{m=1}^M (d_{1m} - \hat{e}_{1m})]^2}{\sum_{m=1}^M \hat{v}_{1m}}$$

where

$d_1 = \sum_{k=1}^K d_{1k}$  is the number of HIV-1 seroconversions (trial endpoints),

$e_1 = \sum_{k=1}^K e_{1k}$  is the conditional expected number of seroconverters, and

$v_1 \sum_{k=1}^K v_{1k}$  is the conditional variance of  $d_{1k}$ , at each  $k$ -th time point.

The log-rank test is a non-parametric, fully efficient test under the assumption of a constant hazard ratio over time. The analysis will include presentation of Kaplan-Meier survival curves, in addition to an evaluation of Schoenfeld residuals, log(-log(survival)) versus log of survival time plots, and the LOWESS smooth for visual inspection of the proportional hazards assumption. In case visual inspection indicates severe violations of the proportional hazards assumption, more appropriate models will be explored, e.g. time-by-treatment interactions in a semi-parametric Cox proportional hazards model.

The log-rank test applies equal weighting to all parts of the survival curve, and it is believed that this will be appropriate for the purpose of evaluating efficacy of the dapivirine ring. The LIFETEST SAS procedure will be used to apply the log-rank test to the data. The output from this procedure will provide a Chi-square value with an associated p-value, as well as a Kaplan-Meier survival curve (representing the estimated proportion of HIV-negative participants at every time point).

The Cox proportional hazards model (using a discrete time scale) will also be used to estimate the effect of the dapivirine ring regimen, and to provide an estimate of the risk ratio, or hazard ratio (using SAS procedure PHREG or TPHREG). This method is selected as it yields estimates closer to those obtained using the exact partial likelihood compared to estimates obtained by using other proposed methods<sup>2</sup>.

The number of HIV-1 seroconversions (confirmed trial endpoints), the incidence density rate of HIV-1 seroconversion, *i.e.* HIV-1 seroconversion rate per 100 person-years of follow-up time, as well as a 95% confidence interval for the HIV-1 seroconversion rate per 100 person-years, will be presented for each treatment arm and research centre.

### **9.1.1 Complementary Analyses on the Primary Efficacy Endpoint**

A blinded review of the data included in the May 2013 DSMB review (data cut-off date: 28 February 2013), confirmed a suspicion of product non-adherence in the trial. Specifically, at Research Centre 03 in KwaZulu-Natal, South Africa, a high incidence of protocol non-adherence (primarily missed and late visits, and early trial discontinuations) was observed in December 2012 – a finding which prompted the Sponsor to analyse all used rings returned to all research centres as of 28 February 2013 for residual dapivirine amounts. This (blinded) analysis revealed that during any given month of ring use, the majority (50-80%) of women assigned to the dapivirine ring at Research Centre 03 had drug residuals in used rings of 24 mg or more (*i.e.* essentially all of the initial drug load) indicating limited ring use.

For this reason, the following complementary analyses of the primary efficacy endpoint will be conducted:

- Analysis on the m-ITT population, excluding participants enrolled at Research Centre 03. All participants enrolled at this centre – both adherent and non-adherent participants in both the active and placebo arms – will be excluded from the analysis.
- Product-adherence analysis: Analysis on the m-ITT population, with censoring of the data of non-adherent participants at the date of the last negative HIV-1 test result prior to the first "non-adherence" event. The same criterion for non-adherence will be applied to both the active and placebo arms, as defined in Section 7.3.1.
- Time-varying product-adherence analysis: Analysis on the m-ITT population, including adherence as a time-varying covariate. Participants will be categorized as either adherent or non-adherent, based on quantitative measures. Non-adherence will be defined as a dapivirine ring residual level > 23.5 mg and a plasma concentration < 95 pg/mL if both are available; otherwise, categorization will be based on the available measure. Time points for which no ring residual levels or plasma concentrations are available (and for which sampling was scheduled) will be imputed using LOCF (Last Observation Carried Forward).

The aggregate of these analysis results (Sections 9.1 and 9.1.1) will be used to determine the efficacy of the dapivirine vaginal ring in preventing HIV-1 acquisition, compared to placebo.

A sensitivity analysis to explore the influence on the effect size of those participants reported as lost-to-follow-up will be performed, by imputing the (missing) data of these participants by the placebo arm hazard rate.

The results of all analyses performed on the primary efficacy endpoint will be presented in the Clinical Study Report.

## **9.2 Primary Endpoint 2 – Safety**

The analysis of adverse events (AEs) will be mainly descriptive in nature. That is, the number and percentage of participants experiencing adverse events will be presented per body system (SOC) and PT, by treatment arm. Summaries of specific AEs will be produced, including the proportion of participants experiencing:

- Grade 2 AEs considered by the Investigator as related to IP
- Grade 3 or 4 AEs
- Serious Adverse Events (SAEs)
- AEs leading to IP discontinuation.

For the most frequently reported AEs, *i.e.* AEs occurring in at least 2% of participants overall, the difference in incidence (“dapivirine – placebo”) and the corresponding

95% confidence interval will be presented. The confidence interval will be determined based on linear regression with robust standard errors, with research centre as covariate. In addition, an AE dot plot will be prepared to graphically display the difference in incidence rates.

Separate tabulations will be created for AEs of special interest, *i.e.* urogenital AEs and STIs. For this purpose, PTs may be grouped into categories of interest (refer to Appendix 6).

As this is a randomised trial in healthy HIV-negative women, it is anticipated that the treatment groups will be comparable at baseline with respect to pre-existing conditions. Furthermore, it is expected that women with pre-existing conditions will be treated and evaluated before being enrolled into the trial. For this reason, no baseline adjustments are planned prospectively.

### **9.3 Secondary Endpoints**

#### **9.3.1 Secondary Endpoint 1: Seroconversion rate of HIV-2 per 100 person-years of product use at the end of the IP use period**

Consistent with secondary objective 1, secondary endpoint 1 is the HIV-2 seroconversion rate per 100 person-years of product use at the end of the investigational product use period.

#### ***Assessments***

Trial participants will be tested for HIV-2 infection at 4-weekly visits until the last product use visit, and at the exit visit, 6 weeks after ring discontinuation. Participants who are not diagnosed with HIV-2 at the end of the trial participation period will be censored at the last HIV-2 test date at or prior to the last product use visit.

If HIV-2 is detected at the exit visit, HIV RNA PCR testing will be performed on stored samples in reverse sequential order to estimate the time point of HIV-2 infection. If HIV-2 infection is detected at or prior to the last product use visit, the participant will be included in the analysis as an HIV-2 seroconverter. If the time of infection is determined to be after product use, the participant will be censored at the last HIV-2 test date at or prior to the last product use visit.

#### ***Statistical hypothesis and methods***

If appropriate, dependent on the number of HIV-2 seroconversions that occur, a log rank test will be performed (two-sided,  $\alpha=0.05$ ), stratified by research centre. Additionally, the hazard ratio will be estimated with corresponding 95% confidence interval to quantify the effect of the dapivirine ring on HIV-2 seroconversion. Kaplan-Meier survival curves will be provided to graphically describe the probability of remaining HIV-2 negative over the trial duration for each treatment arm.

The number of HIV-2 seroconversions, the incidence density rate of HIV-2 seroconversion, *i.e.* HIV-2 seroconversion rate per 100 person-years of follow-up time, as well as a 95% confidence interval for the HIV-2 seroconversion rate per 100 person-years, will be presented for each treatment arm and research centre.

### **9.3.2 Secondary Endpoint 2: The incidence of curable STIs, and changes in vaginal flora in each trial arm over the IP use period**

Consistent with the secondary objective to evaluate the incidence of curable STIs (*i.e.* *N.gonorrhoeae*, *C.trachomatis* and *T.vaginalis*), and changes in vaginal flora in the dapivirine and placebo vaginal ring groups, the second secondary endpoint is the incidence of curable STIs, and changes in vaginal flora in each trial arm over the IP use period.

#### **Assessments**

Laboratory tests for *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* (as recorded on the GTI CRF page) will be performed, and pelvic samples will be collected for assessment of vaginal flora at enrolment and 12-weekly visits until the last product use visit.

#### **Statistical hypothesis and methods**

##### Curable STIs

For each treatment arm, the incidence density rate of STIs will be provided, with a corresponding 95% confidence interval, defined by the number of participants who test positive for a curable STI. The denominator will be the total number of days that each participant contributed to the trial (*i.e.* from enrolment to trial completion/discontinuation).

##### Changes in Vaginal Flora

It will be evaluated whether the changes in vaginal flora over time are the same in the two treatment arms. A generalised estimating equation (GEE) model will be used to evaluate the longitudinal changes in total Nugent score between the trial arms. This model will be used to account for the within-participant correlation structure in Nugent scores over trial visits, and will test for a time-by-treatment interaction. If the p-value for the time-by-treatment interaction is < 0.05, it will be concluded that the changes in vaginal flora during the trial period are different between the dapivirine ring and placebo ring arms.

Additional analyses to assess the change in vaginal flora may be performed. Changes in vaginal flora will be assessed based on the incidence density rate for the first occurrence of vaginal flora changes. A change in vaginal flora is defined as a post-enrolment increase in the total Nugent score category (*i.e.* from *Normal* to *Altered vaginal flora*, from *Altered vaginal flora* to *Abnormal*, or from *Normal* to *Abnormal*). Participants who do not show any post-enrolment increase will be

censored at the date of the last assessment of vaginal flora. In case a participant has an abnormal result at enrolment, she will be censored at Day 1. Kaplan-Meier survival curves will be presented to compare the time to the first occurrence of vaginal flora changes in each treatment arm. The log-rank test (two-sided,  $\alpha=0.05$ ) will be used to evaluate the effect of the dapivirine ring on the first occurrence of a change in vaginal flora, and will be stratified by research centre. Cox proportional hazards will be used to estimate the median time to a change in vaginal flora in the treatment groups.

### **9.3.3 Secondary Endpoint 3: Incidence of pregnancy in each trial arm over the IP use period**

Consistent with the secondary objective to evaluate the incidence of pregnancy between the two arms, secondary endpoint 3 is the incidence of women who have a confirmed positive pregnancy test at any point during the trial.

#### **Assessments**

Urine pregnancy tests will be performed at every trial visit. Confirmatory serum pregnancy tests will be performed at the Investigator's discretion. A participant will be prematurely discontinued from the trial if she is confirmed to be pregnant (but may continue in the trial if she is confirmed to be no longer pregnant).

#### **Statistical hypothesis and methods**

For each treatment arm, the incidence density rate of pregnancy will be determined, with a corresponding 95% confidence interval. The numerator will include the number of participants who had a positive urine or serum pregnancy test during the trial period and the denominator will include the total number of days that each participant contributed to the trial (*i.e.* from enrolment to pregnancy, or trial completion, whichever occurs first).

In addition, a line listing will be produced that shows participants with a confirmed positive pregnancy test, their method(s) of contraception, and whether they HIV seroconverted.

### **9.3.4 Secondary Endpoint 4: Proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period**

Consistent with the secondary objective to evaluate self-reported adherence, secondary endpoint 4 is the proportion of women who report adherence to the use of the vaginal ring inserted once every 4 weeks over the trial period.

#### **Assessments**

Trained staff will administer adherence questionnaires at 4-weekly trial visits, from Week 4 until the last product use visit. Adherence questionnaires include questions

about ring use. The diary cards will serve as a memory aid for the participant during the adherence questionnaire session, and will be collected at each 4-weekly visit.

### ***Statistical hypothesis and methods***

For each participant, the total number of days that the participant reported removing the vaginal ring via the question: “Since your last regularly scheduled visit, how many times was the vaginal ring out of your vagina” will be summed across all trial visits and will be divided by the total number of days that the participant was expected to wear the ring. Categories of “self-reported adherent participants” are defined as < 80%, ≥ 80 - < 90%, and ≥ 90% adherence. The proportion of participants who are adherent to the ring regimen based on self-reports will be estimated and reported using a 95% confidence interval. Additional cut-off values may be useful to describe self-reported adherence and may be explored.

Multiple methods of data collection will be utilised to examine self-reported adherence; comparisons across the different methods will be exploratory. For instance, the ring removal and ring insertion CRFs may be used as an additional way to monitor adherence.

Additional explanatory analyses will utilise the qualitative data from focus group discussions and individual interviews, and discussed in the Clinical Study Report.

#### **9.3.5 Secondary Endpoint 5: The proportion of women who report the use of the vaginal ring as acceptable**

Consistent with the secondary objective to evaluate acceptability of the dapivirine vaginal ring, secondary endpoint 5 is the proportion of women who report a willingness to use the vaginal ring if proven effective against HIV-infection.

### ***Assessments***

Acceptability questionnaires will be administered at the second trial visit (Week 4), and at 24-weekly intervals thereafter, until the last product use visit.

### ***Statistical hypothesis and methods***

The proportion of participants among all trial participants who respond positively (*i.e.* “likely” or “very likely”) to the question: “If in the future a vaginal ring was available that provided some protection against HIV, and it was similar to the one you used in this trial, how likely would you be to keep it inserted in your vagina every day” at the last available assessment will be presented with a 95% confidence interval.

A participant will be classified as having found the vaginal ring acceptable if she responds positively to the above question about willingness to use the ring if in the future it is found to provide protection against HIV (last available response). The difference in the proportion of participants who found the ring acceptable (“dapivirine–placebo”) and the corresponding 95% confidence interval will be calculated and presented.

Summary tables with descriptive statistics will be presented for the socio-demographic variables and psycho-social variables collected in the acceptability questionnaires.

Additional explanatory analyses will utilise the qualitative data from focus group discussions and individual interviews, and discussed in the Clinical Study Report.

### **9.3.6 Secondary Endpoint 6: HIV-1 drug resistance mutations among participants who acquire HIV-1**

Consistent with the secondary objective to evaluate HIV-1 drug resistance mutations among participants who acquire HIV-1 in the trial, secondary endpoint 6 is the proportion of HIV seroconverters with drug resistant mutations.

#### **Assessments**

HIV viral genotyping will be performed on all HIV seroconverters.

#### **Statistical hypothesis and methods**

The analysis of HIV-1 drug resistance will be primarily descriptive in nature, and will depend on the pattern of resistance associated mutations (RAMs) observed in the HIV-1 seroconverters. The latest IAS-USA update of Drug Resistance Mutations in HIV-1 (dated October/November 2015) is provided in Appendix 5.

The number of RAMs observed will be listed by participant, and a frequency tabulation of individual RAMs associated with the various classes of antiretrovirals (Protease Inhibitors (PIs), Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Non-nucleoside Reverse Transcriptase Inhibitor (NNRTIs)) will be produced. The proportion of HIV-1 seroconverters with at least one HIV-1 drug resistant mutation will be presented overall, and by treatment arm, with corresponding 95% confidence intervals. The distribution of the most frequent HIV-1 resistance mutations (*i.e.* present in at least 5% of the participants in the dapivirine arm) will be presented graphically with a bar chart of relative frequencies, overall and by treatment arm.

It is possible that prolonged exposure and adherence to the IP may influence the development of drug resistant mutations. A box plot displaying the distribution of days on IP may be presented for each treatment arm. The number of days of IP use prior to HIV-1 seroconversion as well as adherence to the IP may be evaluated as an independent predictor of acquiring a resistant mutation.

## **10. EVALUATION OF SAFETY PARAMETERS**

### **10.1 Adverse Events**

An adverse event is defined as any untoward medical occurrence in a clinical trial participant. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory assessment finding), symptom or disease



temporally associated with the participation in this trial, whether or not considered related to the IP.

#### **10.1.1 Treatment Emergent Adverse Events (TEAEs)**

TEAEs are defined as those AEs which started on or worsened after the first application of the IP. Only TEAEs are reported in the AE CRF.

#### **10.1.2 Product-related Adverse Events**

Product-relatedness is reported as “Related” or “Not Related”. While every effort is made to ensure that this field is not missing through data reviews and queries, if the relationship with the IP is missing on the CRF, it will be assumed that the AE was “related” to the IP.

#### **10.1.3 Summary Tables**

A summary table of AEs will be presented, indicating the frequency and proportion of participants with:

- At least one TEAE
- At least one serious TEAE
- At least one DAIDS Grade 3 or 4 TEAE
- At least one product-related TEAE
- At least one serious product-related TEAE
- A TEAE leading to death
- A TEAE leading to premature (permanent) IP discontinuation.

The definitions and location of data elements to be used to define each measure are described in Table 4 below.

**Table 4 Definition and Data Sources of AEs**

<b>Measure</b>	<b>Statistic</b>	<b>Data Sources*</b>
Participants with at least one TEAE	Frequency	A participant reported with an AE in the AE CRF Source: AE
Participants with at least one serious TEAE	Frequency	A participant reported as having an SAE per the AE CRF Source: AE
Participants with at least one DAIDS Grade 3 or 4 TEAE	Frequency	A participant reported as having a DAIDS Grade 3 or 4 AE Source: AE
Participants with at least one product-related TEAE	Frequency	A participant reported as having a “related”, “not related” event, per the AE CRF Source: AE
Participants with at least one serious product-related TEAE	Frequency	A participant reported as having a “related”, “not related” SAE, per the AE CRF Source: AE
Participants with a TEAE leading to death	Frequency	A participant reported as having an AE with the reported outcome “death” per the AE CRF Source: AE
Participants with a TEAE leading to premature (permanent) IP discontinuation	Frequency	A participant reported as having an AE for which the IP was discontinued and not reintroduced per the AE CRF Source: AE

\* Percentages will use the total number of enrolled participants as denominator.

Summary tables will include the following variables:

**Table 5 AE Variables**

Variable	Data Type	Data Sources
Serious AE (SAE)	Dichotomous	Yes/No Source: AE
Outcome	Nominal	Death, Worsened, Resolved/recovered w/sequelae, Resolved/recovered, Ongoing at trial end, Unknown Source: AE
Severity	Ordinal	Grade 1 Mild, Grade 2 Moderate, Grade 3 Severe, Grade 4 Life-threatening, Grade 5 Death Source: AE
Relationship	Ordinal	Related, Not related Source: AE
Action	Nominal, DDDMMYY	IP continued, IP interrupted, IP withdrawn, N/A Date discontinued, date reintroduced Source: AE
Other action	Nominal	None, treatment medication, non-drug therapy, hospitalisation, other Source: AE
SOC	Nominal	System Organ Class Source: AE
PT	Nominal	Preferred Term Source: AE

The incidence of the following AEs by severity will be presented by SOC and PT and by treatment arm:

- TEAE
- Serious TEAEs
- Product-related TEAEs
- Serious product-related TEAEs
- Social harms reported as TEAEs (refer to Section 10.8).

A by-participant listing of all deaths, SAEs and premature discontinuations will be presented in Appendix 16 of the Clinical Study Report. These by-participant listings will include variables described in the summary of TEAEs in addition to the following variables:

**Table 6 Additional AE Variables**

Variable	Data Type	Data Sources
AE start date	DDMMYY	Start date Source: AE
Outcome date	DDMMYY	Outcome date Source: AE
Trial day	Continuous	Trial day = (Start Date of AE – Date of First Application of IP) + 1 Source: Calculated from AE ( <i>AESStartDate</i> ) and ENR ( <i>TrialConsentDate</i> )
Duration (days)	Continuous	Duration (days) = <i>AESStopDate</i> – <i>AESStartDate</i> + 1 Source: Calculated from AE Duration will only be calculated if both the start and stop dates are available, or if the start date is known and the AE is ongoing at trial end; in such cases, the duration will be reported as “> (Trial Termination Date – Start Date of AE) +1”

Adverse events and abnormal observations during the gynaecological examinations may be compared to other data collected in the trial, including STI and HIV test results, since detected genital abnormalities may also be caused by medical conditions. This may be done in an exploratory manner via the data provided in participant listings.

## 10.2 Clinical Laboratory Evaluation

### 10.2.1 Assessments

Collection of blood and urine specimens for haematology, biochemistry (including electrolytes, liver function and renal function) and urinalysis tests is conducted at Screening 1, and every 12 weeks. For the South African research centres, clinical laboratory assessments are performed by a central laboratory, and for the Uganda research centre, by the research centre's certified laboratory. In accordance, reference ranges are provided by the central laboratory and local laboratory, respectively.

Listings of all clinical laboratory data for each participant will be provided. Laboratory test results will be categorised by DAIDS Grade, and clinical significance. In addition, urinalysis and microscopy data will be summarised. Specific haematology, biochemistry, urinalysis, and microscopy parameters assessed during the trial are listed below.

**Table 7 Haematology, Biochemistry, Urinalysis and Microscopy Parameters**

<b>Haematology (continuous)<sup>1</sup></b>	<b>Biochemistry (continuous)<sup>1</sup></b>	<b>Urinalysis (continuous)</b>
Erythrocytes Haemoglobin Haematocrit Platelets Leukocytes Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Electrolytes Sodium Potassium Chloride Calcium Phosphate Liver Function Bilirubin Alkaline phosphatase ALT AST Renal Function Urea Creatinine	pH Urobilinogen
		<b>Urinalysis (categorical)</b>
		Specific gravity Blood Leukocytes Protein Glucose Ketones Bilirubin Nitrites
		<b>Microscopy (categorical)</b>
		WBC RBC Casts Squamous epithelial cells Bacteria Yeasts Crystals Parasites

Data sources: Haematology and biochemistry reported in HAE and CHEM CRFs; urinalysis and microscopy reported in UTR CRF.

### 10.2.2 Summary Tables

Routine clinical laboratory findings will be summarised for each of the trial visits during which these data are collected, using appropriate descriptive statistics as described in Section 6.7. A five-number summary will be included by way of box plots, presented overall, by research centre, treatment arm and by trial visit; absolute change from the Screening visit to each trial visit will also be summarised in tabular form. Shift tables will be used to present the percentage of individuals with DAIDS Grades 1 to 4 haematology and biochemistry laboratory findings for each parameter under investigation using the maximum severity at the Screening visit *versus* the worst-case observation of treatment-emergent abnormalities post-baseline. A table of Grade 3 and 4 laboratory abnormalities will also be provided. The frequency and proportion of clinically significant laboratory abnormalities will be displayed by trial visit in tabular form for each parameter, as reported on the LTR-1

<sup>1</sup> Graded according to the DAIDS table<sup>1</sup> (Grades 1-4).

or LTR-2 CRF, data element: *<parameter name>sig*. By-participant listings will be provided and will present findings from each clinical assessment.

### 10.3 Pelvic examinations

#### 10.3.1 Assessments

Pelvic examinations will be performed at Screening 1 and Screening 2, and at every 12-weekly visit until the last product use visit. On-trial examinations will be performed to assess safety, *i.e.* any local vaginal reactions.

#### 10.3.2 Summary Tables

A summary of pelvic examinations will be presented overall, by research centre, treatment arm, and by trial visit in tabular form. By-participant listings will also be provided. The summary tables and listings will include the following variables:

**Table 8 Pelvic Examination Variables**

Variable	Data Type	Data Sources
Presence of Vulvar findings	Categorical	Source: PEL Indicator variable for: Vulvar erythema, vulvar edema, vulvar rash, vulvar tenderness, Bartholin's or Skene's gland abnormality
Presence of Vaginal findings	Categorical	Source: PEL Indicator variable for: Vaginal erythema, vaginal edema, vaginal masses, vaginal abrasions or lacerations, vaginal tenderness, vaginal discharge
Presence of Cervical findings	Categorical	Source: PEL Indicator variable for: Cervical erythema, cervical edema and/or friability, cervical masses, cervical motion tenderness, cervical discharge
General/other findings	Categorical	Source: PEL Indicator variable for: Odour, uterine masses, adnexal masses, uterine tenderness, adnexal tenderness, condyloma, abnormal genital tract bleeding, other
Presence of Vulvar Lesions findings	Categorical	Source: PEL Indicator variable for: Ulcer, blister, pustule, peeling, ecchymosis, other lesions
Presence of Vaginal Lesions findings	Categorical	Source: PEL Indicator variable for: Ulcer, blister, pustule, peeling, ecchymosis, other lesions
Presence of Cervical Lesions findings	Categorical	Source: PEL Indicator variable for: Ulcer, blister, pustule, peeling, ecchymosis, other lesions
Cervical ectopy	Categorical	Source: PEL

## 10.4 Cervical cytology

### 10.4.1 Assessments

A cervical cytology sample will be collected at Screening 1, Week 52 and at the last product use visit.

### 10.4.2 Summary Tables

A summary of the cervical cytology results will be presented overall, by research centre, treatment arm, and by trial visit in tabular form. By-participant listings will also be provided. The summary tables and listings will include the following variables:

**Table 9 Cervical Cytology Variables**

Variable	Data Type	Data Sources
Cervical cytology result	Categorical	Source: CR Indicator variable for: Negative for intraepithelial lesion or cancer (malignancy), ASCUS, SIL-low grade (LSIL), ASC-H, SIL-high grade (HSIL), AGC, AGC-favor neoplastic, cancer, other findings

At one research centre (Research Centre 06 in Uganda), some of the cytology samples that were initially analysed by a local laboratory were re-analysed by the central laboratory, resulting in two cervical cytology CRFs being completed for certain trial visits. The by-participant listings for this research centre will include both sets of results, where applicable. For the summary tables, the more severe of the two findings will be reported per visit, where this finding will be selected based on the flow diagram presented in Appendix 8.

## 10.5 Genital infections and other STI assessments

### 10.5.1 Assessments

Cervicovaginal samples will be collected for genital infection and STI testing (Trichomonas, Gonorrhoea, and Chlamydia) at Screening 1 and every 12 weeks until the last product use visit. Assessments of vaginal flora and vaginal pH will be assessed at the Enrolment visit and every 12 weeks, to assess changes in vaginal flora as measured by the Nugent score for three pathogens, and overall.

### 10.5.2 Summary Tables

In addition to tables provided in support of the safety endpoint, genital infection and STI results will be presented overall, by research centre, by treatment arm and by trial visit. By-participant listings will also be provided. Variables that will be summarised in the tables and listings include:

**Table 10 Genital Infection and STI Variables**

Variable	Data Type	Data Sources
Trichomonas rapid Test	Dichotomous	Source: GTI
Gonorrhoea	Dichotomous	Source: GTI
Chlamydia	Dichotomous	Source: GTI
Syphilis RPR screening test	Dichotomous	Source: GTI
Syphilis RPR titre	Discrete	Source: GTI
Syphilis confirmatory test TPHA/TPPA	Categorical	Source: GTI
Vaginal pH	Discrete	Source: GTI
Whiff test	Dichotomous	Source: GTI
Clue cells (WM)	Dichotomous	Source: GTI
Yeasts (WM)	Dichotomous	Source: GTI
Trichomonas	Dichotomous	Source: GTI
Homogeneous vaginal discharge	Dichotomous	Source: GTI
Bacterial vaginosis	Dichotomous	Source: GTI

In addition to the tables provided in support of this safety endpoint, appropriate statistics will be presented to describe the Nugent score for each type of bacteria (*Lactobacilli*, *Gardnerella* and anaerobic gram negative rods morphotype, and *Mobiluncus Spp.*) overall, by research centre, treatment arm, and trial visit. Participant listings will also be provided. Bar charts will present comparisons between the number of abnormal, normal, and intermediate diagnoses based on Nugent Scores by visit and treatment arm. A five-number summary of Nugent Scores and vaginal pH will be presented by treatment arm, and by trial visit. The average paired difference in vaginal pH at each trial visit from the Enrolment visit will be presented. Variables that will be summarised in the tables and listings include:

**Table 11 Bacteria, Nugent Score and Vaginal pH**

Variable	Data Type	Data Sources
Lactobacilli	Discrete	Source: VF
<i>Gardnerella</i> and anaerobic gram negative rods morphotype	Discrete	Source: VF
<i>Mobiluncus Spp.</i>	Discrete	Source: VF
Total Nugent Score (numeric)	Discrete	Source: VF
Total Nugent Score (categorical)	Categorical	Source: VF
Vaginal pH	Discrete	Source: VF



## **10.6 Immediately Reportable Events**

In addition to SAEs, the following events are considered immediately reportable events:

- 1) Pregnancy
- 2) HIV seroconversion
- 3) Any non-serious adverse event leading to permanent discontinuation of the IP

### **10.6.1 Assessments**

Urine pregnancy tests are conducted at Screening Visits 1 and 2, and at every 4-weekly visit until the last product use visit. Serum pregnancy tests will be performed at the Investigator's discretion. A negative serum test after a positive urine test would overrule the positive urine test.

HIV-1 rapid tests will be conducted at Screening Visits 1 and 2, and every 4 weeks after enrolment until the last product use visit, as well as at the exit visit 6 weeks after ring discontinuation. HIV RNA PCR samples will be collected at the Enrolment visit and every 4 weeks, but will only be analysed if there is reason to believe that the participant is HIV-positive. All adverse events (serious and non-serious) are monitored throughout the trial; analysis of AEs is discussed in Section 10.1.

### **10.6.2 Summary Tables**

Results from pregnancy tests will be presented in tabular form overall, by research centre, treatment arm, and trial visit and will include appropriate statistics. A table summarising the pregnancy incidence rates by treatment arm and contraceptive method (DMPA, norethisterone, oral contraception, etc.) will be produced. By-participant listings will be provided for each participant.

**Table 12 Pregnancy Tests**

Variable	Data Type	Data Sources
Type of test (urine or serum)	Dichotomous	Source: PHTR
Pregnancy Test	Dichotomous	Source: PHTR

Results from HIV tests will be presented in tabular form overall, by research centre, treatment arm, and trial visit and will include appropriate statistics. By-participant listings will be provided for each participant.

**Table 13 HIV Tests**

Variable	Data Type	Data Sources
HIV Test Result (Test #1)	Dichotomous	Source: SER
HIV Test Result (Test #2)	Dichotomous	Source: SER
Repeat Testing (Test #1)	Dichotomous	Source: SER
Repeat Testing (Test #2)	Dichotomous	Source: SER
Western Blot	Nominal	Source: SER
RNA PCR Testing	Nominal	Source: SER *Only tested for HIV seroconverters

### 10.7 Concomitant Medications

Concomitant medication is defined as any medication taken in conjunction with the IP, *i.e.* medication that either:

- 1) Started after the first application of the IP, or
- 2) Started before the first application of the IP, but ended on or after the first application of the IP. This includes medication indicated as “Ongoing” at the end of the trial.

Concomitant medications will be coded using the WHO Drug Dictionary (version 01 June 2011); a table displaying the frequency and proportion of participants using medications during the trial overall, by treatment group, and by ATC categories will be presented. Concomitant medication will also be presented in the form of listings which will contain information for each medication used.

**Table 14 Concomitant Medication Variables**

Variable	Data Type	Data Sources
Drug Name	Text	Verbatim; Source: CM, <i>MedName1-3</i>
ATC category	Text	Verbatim
Indication	Text	Verbatim; Source: CM, <i>MedIndication1-3</i>
Dose/Unit/Route	Text	Verbatim; Source: CM, <i>MedDose1-3</i>
Frequency	Text	Verbatim; Source: CM, <i>MedFreq1-3</i>
Start date	DDMMYY	Source: CM, <i>MedStartDate1-3</i>
Stop date	DDMMYY	Source: CM, <i>MedStopDate1-3</i>
Ongoing at last visit	Dichotomous	Source: CM, <i>MedOngoing1-3</i>

**10.8 Physical Examination Findings and Vital Signs**

A physical examination will be conducted at Screening 1 and at the last product use visit. At these visits, vital signs will be recorded and body systems will be evaluated for abnormal/normal findings. For vital signs, the observed data and the absolute change from baseline (Screening 1) will be summarised overall, by research centre, and treatment arm using appropriate descriptive statistics, as described in Section 6.6. Data from physical examination findings will be listed only.

Listings of all vital signs data will be provided. Variables that will be summarised in the tables and listings include:

**Table 15 Physical Examination and Vital Signs Parameters**

Variable	Data Type	Data Sources
Weight	Continuous	Source: PX
BMI	Continuous	Derived: weight(kg)/height(m) <sup>2</sup> , rounded to 1 decimal
Temperature	Continuous; Dichotomous	Source: PX
Pulse	Continuous; Dichotomous	Source: PX
Respiratory rate	Continuous; Dichotomous	Source: PX
Blood pressure	Continuous; Dichotomous	Source: PX
<i>General Examination of Body Systems:</i> General appearance, skin and mucous membranes, cardiovascular, respiratory, gastrointestinal, and neurological systems, lymph nodes, eyes, ears, nose and throat, musculoskeletal system, and other (1-3).	Nominal	Source: PX

## 10.9 Social Harms

During each HIV counselling session, participants will be asked questions to assess the occurrence of social harms. Participants who experience social harms 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.

By-participant listings of all social harms data will be provided as well as summary tables of such occurrences. Social harms that were reported as AEs, as well as all occurrences of sexual assault (whether associated with physical injury or not), will be summarised by SOC and PT, by severity and treatment arm (refer to Section 10.1).

## 11. CHANGES IN THE PROTOCOL-PLANNED ANALYSES

The Phase III clinical program of the dapivirine vaginal ring includes a second pivotal safety and effectiveness trial, MTN-020 (ASPIRE). To harmonise the statistical analysis of the two trials, some changes in the planned analyses described in the IPM 027 protocol have been made:

- Censoring of data for the primary efficacy analysis: In the IPM 027 protocol it was stated that participants who are not diagnosed with HIV-1 at the end of the trial participation period will be censored at the earliest date of any of the following events: completion of investigational product use, trial drop-out, a positive pregnancy test followed by permanent product discontinuation, or death. This was revised to “Participants who are not diagnosed with HIV-1 at the end of the trial participation period will be censored at the last HIV-1 test date at or prior to the last product use visit” (refer to Section 9.1). This approach ensures that available information is utilised when censoring data.
- The statistical analysis of some of the secondary endpoints (self-reported adherence to ring use, acceptability of the vaginal ring, HIV-1 drug resistance mutations) has been simplified, compared to the methods described in the trial protocol, in that the analyses will be primarily descriptive in nature.

Furthermore, the safety and efficacy results of MTN-020 are expected to be known before the clinical completion of IPM 027, *i.e.* during Q1 2016. The MTN-020 results will be communicated to the relevant local and international regulatory authorities, and should MTN-020 provide compelling evidence of risk reduction in the dapivirine arm and clearly rejects the null hypothesis, IPM would consider an early analysis of IPM 027 and discuss specifics with the regulatory authorities. Should a final data analysis be performed before the natural end of IPM 027 and efficacy and safety of the dapivirine vaginal ring be demonstrated that complement the results of MTN-020, participants who were randomized to the placebo vaginal ring will be

reassigned to the 25 mg dapivirine vaginal ring until an open-label extension trial of the dapivirine vaginal ring is implemented. Data collected after this treatment reassignment until trial completion or termination will be listed and summarised descriptively.

## 12. REFERENCES

1. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 December, 2004; Clarification 1 August 2009.
2. Hosmer DW, Lemeshow S. Applied Survival Analysis: Regression Modeling of Time to Event Data. New York: Wiley; 1999.
3. ICH (1996). International Conference on Harmonisation. Guideline E3 Structure and Content of Clinical Trial Reports.
4. ICH (1998). International Conference on Harmonisation. Guideline E9 Statistical Principles for Clinical Trials.
5. IPM 027 Protocol: *A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED SAFETY AND EFFICACY TRIAL OF A DAPIVIRINE VAGINAL MATRIX RING IN HEALTHY HIV-NEGATIVE WOMEN* Version 1.0, Amendment 4.0; 21 August 2014.
6. Microbicide Trials Network (MTN). Daily HIV Prevention Approaches Didn't Work for African Women in the VOICE Study. <http://www.mtnstopshiv.org/node/4877> March 4, 2013.
7. Population PK Modeling of Dapivirine in Vaginal Fluids and Plasma Released by Vaginal Rings, Version 1.0, 13 February 2015. Internal IPM Report.

## 13. APPENDICES

- 13.1 Appendix 1 – Consort Flow Diagram
- 13.2 Appendix 2 – Table Shells
- 13.3 Appendix 3 – Figure Shells
- 13.4 Appendix 4 – Individual Participant Listing Shells
- 13.5 Appendix 5 – IAS-USA Update of the Drug Resistance Mutations in HIV-1: October/November 2015
- 13.6 Appendix 6 – Adverse Events of Special Interest: Grouped Preferred Terms
- 13.7 Appendix 7 – IPM 027 Protocol Deviation Criteria (v3.0, dated 14 September 2015)
- 13.8 Appendix 8 – Interpretation of Cervical Cytology Results
- 13.9 Appendix 9 – IPM 027 Analysis Visit Windows