

**Title:**

**An international multi-centre, randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of 0.5% and 2% PRO 2000/5 gels for the prevention of vaginally acquired HIV infection**  
**Microbicides Development Programme (MDP) 301 (version 2.1)**

The MDP is funded by the UK Department for International Development (DFID) and the UK Medical Research Council (MRC)  
 Trial products will be supplied by Indevus Pharmaceuticals, Inc.

The UK MRC will act as Sponsor  
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**Signature page**

The signatures below confirm agreement by the individuals authorised by the Sponsor and principal participating institution at the clinical site responsible for signing the clinical trial agreement, that this is the protocol, MDP 301 (2.1) 8th May 2008. The trial will be conducted in accordance with this protocol and ICH GCP. Any amendments to this protocol that have a direct influence on the participants in the trial will be approved by the relevant ethics committees before implementation

_____	_____	_____	_____
Clinical site signature	Printed name	Designation	Date

_____	_____	_____	_____
Sponsor signature	Printed name	Designation	Date

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## **ABBREVIATIONS**

AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Transaminase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
BV	Bacterial Vaginosis
CIOMS	The Council for International Organizations of Medical Sciences
CRFs	Case record forms
CT	<i>Chlamydia trachomatis</i>
CTU	(Medical Research Council) Clinical Trials Unit
CVL	Cervico vaginal lavage

DAIDS	Division of AIDS
DfID	Department for International Development
EC	Ethics Committee
FGD	Focus group discussion
GMP	Good Manufacturing Practice
HCG	Human chorionic gonadotrophin
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
HVS	High vaginal swab
ICH GCP	International Conference of Harmonisation Good Clinical Practice
IDI	In-depth interview
IDMC	Independent Data Monitoring Committee
IMB	Inter-menstrual bleeding
LREC	Local research ethics committee
MDP	Microbicides Development Programme
MIA	Microbicide Initiative in Africa
MRC	Medical Research Council
N-9	Nonoxynol-9
NAAA	Nucleic acid amplification assay
NG	<i>Neisseria gonorrhoeae</i>
PI	Principal Investigator
PLG	Programme Liaison Group
PMB	Programme Management Board
SAE	Serious adverse event
STI	Sexually Transmitted Infection
TMG	Trial Management Group
TSC	Trial Steering Committee
TT	Thrombin Time
TV	<i>Trichomonas vaginalis</i>
VCT	Voluntary Counselling and Testing for HIV

## **GLOSSARY AND DEFINITIONS**

Central Pharmacy Record	Data on amount of study product in central pharmacy at any one time
Clinical Folder	Participant's individual data folder kept in the clinic with all CRFs and any other information pertaining to the individual in the study
Clinical personnel/team	Staff from a clinical background (doctors, nurses and clinical officers)
Clinical site principal investigator	The person responsible for the conduct of the study at a study site. If the study is conducted by a team of individuals at a site, the investigator is the responsible leader of the team.
Clinical Trial Manager	Investigator at CTU responsible for monitoring the progress of the study and for site monitoring
Competent Authority	National Authority responsible for the licensing of medications
Counsellors	Staff that have undergone nationally recognised training in counselling who may be from a clinical or non-clinical background

Database	The programmed software into which the data from the CRFs are entered
Datafiles	Data extracted from the database at a given timepoint
Data Folder	Participant's individual data folder kept in the data management centre with all CRFs and data queries pertaining to the individual in the study
Discontinuation	A permanent cessation of study gel
Dispensing Log	Record of study gel dispensed to individuals
Interruption	A temporary cessation of study gel
Interviewers	Staff from a non-clinical background with research experience that have undergone study specific training in interview techniques
Manual of operating procedures	The manual containing both site specific and trial specific procedures
Medical Expert	Clinician responsible to the Sponsor
Site/Central	Site indicates one of the designated sites listed in the protocol and central is CTU
Site specific operating procedures	Procedures which vary between the sites
Standard operating procedures	Instructions/flow diagrams to be followed when completing study related tasks
Study personnel/team	All staff involved in the study
Trial specific operating procedures	Procedures common to all sites
Withdrawal from study	Discontinuation of study visits and gel

## 1. Summary of trial

### Objective

To determine the efficacy and safety of 0.5% and 2% PRO 2000/5 Gel (P) compared to placebo in preventing vaginally acquired HIV infection.

### Design

A multi-centre, randomised, double-blind, placebo controlled trial.

### Population and sites

Four types of populations will be studied

- a) women from communities with access to primary health care facilities in Durban, Johannesburg and the Africa Centre sites, South Africa, and Mazabuka, Zambia
- b) women who are entitled to primary care either through their employment or their partner's employment on the Nakambala sugar estate, Mazabuka, Zambia
- c) women working in bars, hotels, guesthouses and other food or recreational facilities in or near Mwanza City, northern Tanzania
- d) HIV sero-discordant couples (and some HIV-negative sero-concordant couples for the purposes of confidentiality in the community) recruited in the Masaka district of Uganda from either office based voluntary counselling and testing services or following census and sero-survey

### Sample size

A maximum of 9673 women will be recruited in total, of whom a minimum of 6600 will be allocated to 0.5% PRO 2000/5 Gel (P) or placebo arms. This will enable 5280 woman years to be accumulated for 12 months follow-up in the trial, for the primary endpoint for the comparison of 0.5% PRO 2000/5 Gel (P) versus placebo. This will provide at least 90% power to demonstrate a 40% reduction in an HIV incidence of 4 per 100 woman years at the 5% level and at least 80% power to demonstrate a 35% reduction in an HIV incidence of 4 per 100 woman years. This assumes that 20% woman years of observation are lost by 52 weeks because of women dropping out of the trial.

## Interventions

Participants that are eligible and have provided informed consent will receive pre-filled vaginal applicators containing an inert gel (the placebo gel), 0.5% or 2% PRO 2000/5 Gel (P). Participants will be asked to insert one dose of gel intravaginally within 1 hour before each act of vaginal sexual intercourse during the follow-up period. From February 2008, following a recommendation from the IDMC no additional women will be allocated the 2% PRO 2000/5 Gel (P).

## Procedures

Female participants will undergo the following:

- demographic, sexual behaviour and clinical interview
- general and genital examinations
- HIV and syphilis testing with pre and post test counselling
- Safe sex education and condom distribution
- Urine pregnancy tests
- *Neisseria gonorrhoeae* (NG), Herpes Simplex Virus Type 2 (HSV) and *Chlamydia trachomatis* (CT) testing
- Testing for *Trichomonas Vaginalis* (TV) and Bacterial Vaginosis (BV)
- Routine laboratory parameter testing in a subset of participants in Durban and Johannesburg, and in all participants in Masaka
- Coital diary recording in a subset of participants at each site
- In-depth interview and focus group discussions in a subset

Male participants (a subset of partners) will undergo the following:

- In-depth interview or focus group discussion.

A small group of men and women from the communities but who are not enrolled in the trial, or partners of women enrolled in the trial will undergo the following:

- Focus group discussion

## Outcome measures

### Primary

- Acquisition of HIV infection before or at the 12 month time point, confirmed by a Central Reference Laboratory, in participants confirmed to be HIV negative at enrolment
- Grade 3 (severe) or 4 (life-threatening) clinical events noted through systematically solicited questions, or laboratory adverse events confirmed on examination or repeat testing respectively

### Secondary

- Acquisition of HIV infection before or at the 6, 9 and beyond 12 month time points, confirmed by a Central Reference Laboratory, in participants confirmed to be HIV negative at enrolment
- Acquisition of HSV-2 in women uninfected at enrolment
- The point prevalence of NG or CT after 24 weeks of follow-up, determined by a positive nucleic acid amplification assay
- All systematically solicited genital adverse events
- All clinical and laboratory adverse events

## Duration of study

Enrolment will continue for approximately 30 months. Screening will take place between 1 and 6 weeks prior to randomisation. Follow-up visits will continue for 12 months in the

majority. Participants recruited into the cohort in Masaka will continue in follow-up for a maximum of 24 months.

### **1.1 Rationale for changes to version 0.5 to create version 1.0 23<sup>rd</sup> December 2004**

The pre-clinical data on PRO 2000/5 were reviewed at the 4<sup>th</sup> Investigators' Workshop in 2004 and the investigators agreed that the participant information sheets for women and men did not precisely reflect these data, in that the reduction in fertility of rabbits exposed to PRO 2000/5 meant that it was possible that sex acts protected by active gel may be less likely to result in pregnancy. The text was changed accordingly. The MRC (South Africa) Ethics Committee requested that the text highlighting points to be discussed prior to enrolment include information from clinical trials on genital sores/ulcers and penile irritation (highlighted p.24) and that the sentence containing the words '...did not seem to worry the women' be removed.

As the analysis will focus on weeks 0 and 40 for HIV and HSV2 status, and on weeks 0 and 24 for other sexually transmitted infections for the majority of participants, the schedule for the 52 and 104 week follow-up were amended accordingly. An additional week 78 specimen was added for HIV status to the 104 week schedule in view of the long gap between week 40 and 104.

The investigators requested further distinction between the definitions for probably and definitely related to study product. The phrase 'and reappear when using study product' is now only included in the definition for events that are considered definitely related.

There have been changes to the named investigators, the MDP logo added and an ISRCTN number will be added, with a date, as soon as it becomes available. Contact details for Investigators will be updated as they occur, and the date amended.

Other minor changes to the text have been made for the purposes of clarification, or to correct typographical and formatting errors. These include clarification that unused applicators brought back to clinic by participants will only be returned to pharmacy if they are 5 months beyond the date of first issue or at the final visit, and clarification that the toxicity table may be updated during the course of the trial.

### **1.2 Rationale for changes to version 1.0 to create version 1.1 14<sup>th</sup> January 2005**

It was noticed that on the schedule of visits for the 24 month follow up at the Masaka, Uganda site, there had been some errors made in regard to the week numbers where some of the tests were being performed. These errors were corrected in version 1.1 of the protocol, which was then circulated to the Uganda site. It was only circulated to the Uganda site as the changes did not affect any of the other sites. It became apparent, however, that the protocol would need to be amended following comments by the Food and Drug Administration (FDA), so version 1.1 was not submitted to any regulatory or ethics committees, and was not implemented.

### **1.3 Rationale for changes to version 1.1 to create version 1.2 9<sup>th</sup> May 2005**

In response to the US FDA's recommendations that a larger number of women be followed for longer, and that more women participate in the routine laboratory evaluations, the MDP Investigators have decided to extend the follow-up to 12 months and increase the number that will be monitored for haematology, biochemistry and clotting parameters from 450 to 1490. The 1490 will be composed of the first 500 women enrolled at each of Durban and Johannesburg and all the 490 women enrolled in Masaka. The primary efficacy analysis for HIV will still be undertaken using the 9 month dataset, but a secondary efficacy analysis for this endpoint will be conducted on the 6 month and 12 month datasets. The primary safety analysis will be on the 12 month dataset.

The local and national ethics and regulatory authorities that have reviewed protocol version 0.5 and/or version 1.0 requested various clarifications, and the protocol text has been amended to address these.

The Investigator names and contact details have been updated and clarification of those responsible for clinical decisions added. The sample label has been updated.

#### **1.4 Rationale for changes to version 1.2 to create version 1.3 29<sup>th</sup> June 2006**

A number of the investigator names and contact details have changed since version 1.2 of the protocol was made. These have all been updated, including the addition of two new community representative members of the Trial Steering Committee. The ISRCTN number has also been added to the protocol.

The text in the 'summary of the trial', section 'sample size' has been edited to improve clarity. However, this has not constituted any change in study design or follow-up procedure.

In order to increase recruitment rates in the Masaka site, couples will be recruited from office based voluntary counselling and testing services, in addition to the census and sero-surveys in the area. This will capture sero-discordant couples living in villages not currently covered by the census teams. Sections 1, 3.3 and 4.1 of the protocol have been changed accordingly.

The text in section 4.2 which details the procedures carried out during screening, has been corrected to better reflect the tests shown in 4.7.1 and 4.7.2.

The paragraph on the pilot study (Section 2.3.2) has been updated to reflect the completion of this study in all sites.

The main analysis will censor pregnant women at the time they have to interrupt gel due to pregnancy, although they remain in follow-up and contribute to the secondary analysis. The pregnancy rate at 31<sup>st</sup> March 2006 was 19 per 100 women years, and this will result in a loss of years on gel that could compromise the power to demonstrate effectiveness. Following discussion at the Trial Steering Committee, it was proposed that women resume gel after pregnancy, provided they are willing to do so, and contribute person years to the main analysis provided they are HIV negative on resumption of gel. This will result in extra specimens being taken when the participant resumes gel in order to be able to confirm their HIV status at that time. Sections 6.2.7, 6.7.1, 6.7.2, 7.4, 7.6 and the information sheets have changed accordingly. Text in section 7.4 that implies only 'on treatment' safety analyses will be performed has been deleted. Text in section 7.6 has also been amended as the NG/CT samples are collected at week 24 not the final visit.

In the summary schedule of clinical visits, procedures and assessments for 12 and up to 24 months follow-up (sections 4.7.1 and 4.7.2) a superscript for footnote 5 relating to serum being collected and stored if a woman refused to have a rapid HIV test at certain time points, was omitted in error from weeks 40 and 52 in protocol v1.2 and has now been added for the row "HIV Ab test with counselling, real time, 8.5mls (SST). Store residual for EQA".

Text has been added to section 5.2.4 'Serious Adverse Events' in order to clarify procedures for reporting notifiable adverse events to CTU.

An error was made in the parameters in the laboratory events table in V1.2 as they were not based on the Division of Aids (DAIDS) Table for grading of the severity of adult and pediatric adverse events, publish date December 2004. The table has now been corrected to reflect the DAIDS table.

#### **1.5 Rationale for changes to version 1.3 to create version 2.0**

The IDMC met on 8<sup>th</sup> February to review the HIV incidence data for safety and efficacy collected on 7,735 women enrolled since October 2005. They recommended that the 0.5%

and placebo arms should continue, but that the 2% should not as there was no more than a small chance of demonstrating benefit according to the original statistical plan. They advised that the women allocated to 2% gel be informed and the 2% PRO 2000/5 gel be withdrawn as soon as practically possible.

The TSC met to consider this recommendation and accepted the recommendation of the IDMC. They agreed that it was important to continue with the 0.5% and placebo arms, and indeed to increase the power to detect a reduction in HIV incidence by increasing the numbers originally allocated to these two arms, if possible in the remaining enrolment timeline.

This necessitated changes to sections 1, 3.4, 4.2, 4.3, 4.3.1, 7.1, 7.2, 7.3 and the addition of sections 2.2.3.1, 4.5.6 and 6.2.8, changes to the participant information sheet, and additional participant information sheet (appendix 3).

Contact details were updated on Pages 1 – 4.

Clarifications were added to the following sections:

Clarifications to section 4.5.2, 4.7.1, 4.7.2 were added to further clarify testing procedures for pregnant women, those diagnosed as HSV positive at enrolment and seroconverters.

Section 6.2.7 was amended to include procedures for restarting gel after pregnancy.

The section on ethnography (6.3.4) was changed to allow for increased scope of activities for the social science team in the study communities.

The protocol will no longer be reviewed by the Local Research Ethics Committee at St Mary's hospital as the study falls outside their remit, as there are no patients in the UK. This is now reflected in section 6.8.1.

## **1.6 Rationale for changes to version 2.0 to create version 2.1**

The primary efficacy endpoint was originally set at 40 weeks in order to maximise follow-up and adherence rates. Examination of the accruing trial data indicated that retention and adherence were not decreasing between week 40 and week 52 by such an amount that would offset the gain in power from using all the data up to week 52. It was therefore agreed at the Trial Steering Committee on 8<sup>th</sup> May 2008, that in order to maximise the power of the study, the primary endpoint would be shifted to week 52. The week 40 endpoint would therefore become secondary.

This necessitated changes to sections 1, 3.5, 7.1 and 7.2. In addition the information sheets (Appendix 3) were amended to reference the latest protocol version.

Contact details were updated on Pages 1 – 5.

Safety reporting details were updated in sections 6.6.1 and 6.6.2

## 2. Introduction

### 2.1 Background

The HIV pandemic continues with an estimated 13,000 new infections each day in 2003, the vast majority of which were acquired through heterosexual intercourse [1]. Although consistent and correct use of condoms by men remains the most effective form of protection from heterosexually-acquired HIV, women are not always able to negotiate condom use. An effective prophylactic vaccine remains a key objective, but development is slow because of virus variability and difficulty in determining the immunological correlates of protection. Vaginal microbicides are being developed in response to the urgent need for an HIV prevention method that women can control. Licensed spermicides containing nonoxynol-9 (N-9), which has potent anti-HIV activity *in vitro*, were the first products to be investigated as potential microbicides. However, the association of N-9 and other products belonging to this class (surfactants) with genital epithelial disruption [2-5], histologically-determined genital inflammation [6], and reduction in populations of vaginal lactobacilli [7] led to concerns that their use could enhance the risk of HIV transmission. Early phase III studies of N-9 products yielded conflicting results [2,8-10], but more recently, a multicentre randomised placebo-controlled trial (COL-1492), a low dose N-9 formulation, demonstrated an increased incidence of HIV infection in the N-9 group compared to placebo [11]. These findings have intensified efforts to develop agents with a more favourable toxicity profile. At least four of these have, or will have in the next year, entered trials to assess effectiveness in preventing vaginally acquired HIV infection: Buffer Gel, Carraguard, cellulose sulphate and PRO 2000/5 Gel. This protocol describes a randomised placebo-controlled trial design to explore the safety and efficacy of two concentrations of PRO 2000/5 Gel.

#### 2.1.1 Microbicides Development Programme

The Microbicides Development Programme (MDP) is a partnership set up to develop vaginal microbicides for the prevention of HIV transmission, funded by the UK Department for International Development through the UK Medical Research Council (MRC) and coordinated by the MRC Clinical Trials Unit (CTU) and Imperial College London.

The ultimate goal of the MDP is to develop effective, safe, acceptable and affordable microbicides. The MDP aims to evaluate potential microbicides *in vitro*, to carry out clinical safety studies in the UK and Africa, to conduct social science research into acceptability and barriers to adherence, to conduct clinical efficacy trials and to facilitate marketing and access to a successful microbicide.

#### 2.1.2 MDP partners (as of 10<sup>th</sup> March 2005)

In addition to the MRC CTU and Imperial College, the MDP partners are:

##### Africa

Medical Research Council (South Africa), Durban, South Africa  
Reproductive Health and Research Unit, University of the Witwatersrand, Johannesburg, South Africa

The Africa Centre for Health and Population Studies, Somkhele, KwaZulu Natal, South Africa  
African Medical and Research Foundation (AMREF) and the National Institute for Medical Research (NIMR), Mwanza, Tanzania  
Laboratoire de Sante Hygiene Mobile, Yaounde, Comeroun  
Uganda Virus Research Institute/Medical Research Council, Entebbe, Uganda  
University Teaching Hospital, Lusaka, Zambia

##### UK

London School of Hygiene and Tropical Medicine  
MRC Social and Public Health Sciences Unit, University of Glasgow  
St George's Hospital Medical School  
Southampton University  
Population Services International  
University of York

## 2.2 PRO 2000/5 Gel (P)

PRO 2000/5 Gel (P) is an antimicrobial gel designed to be applied vaginally before each act of sexual intercourse. The active ingredient, PRO 2000/5, is a naphthalene sulphonate polymer with an average molecular weight of 5 kD.

### 2.2.1 Pre-clinical research

*In vitro*, PRO 2000/5 has been shown to protect cell lines and cervical tissue explants from infection by a range of HIV isolates, including strains that utilise the co-receptor R5 [12-14]. The compound appears to disrupt the initial attachment and fusion steps of the HIV infection process. PRO 2000/5 is also active *in vitro* against herpes simplex virus (HSV) [15], *Neisseria gonorrhoeae* (NG) [16] and *Chlamydia trachomatis* (CT). Moreover, vaginally applied PRO 2000/5 Gel (P) at concentrations as low as 0.5% has been found to provide statistically significant protection in a monkey model for vaginal HIV-1 transmission (19/21 animals protected compared to 0/7 controls) [17] and a mouse model for vaginal HSV-2 infection [18]. Though not spermicidal, PRO 2000/5 Gel (P) has been found to inhibit fertilisation and pregnancy in rabbits.

Repeated application of PRO 2000/5 Gel (P) at concentrations up to 4% was well tolerated in rabbit models for vaginal, penile and ocular irritation, and had no effect on embryo-foetal development in rats and rabbits. No adverse effects were associated with repeat intravaginal administration of 0.5% PRO 2000/5 Gel (P) for 6 months in rats and for 9 months in rabbits. Gels containing 2% and 4% PRO 2000/5 were associated with genital irritation in some pre-clinical studies, but the findings tended to be species-specific and their relevance to human safety is unclear. Intravaginal administration of 4% PRO 2000/5 Gel (P) was associated with unscheduled deaths in two rabbit toxicity studies conducted by the same laboratory, but the circumstances suggest that the method of administration was a factor. The 4% gel was not associated with unscheduled deaths in other repeat-dose toxicity studies in rabbits, nor in a 6-month repeat-dose study in rats. Other studies indicate that PRO 2000/5 is non-mutagenic, non-toxic to vaginal lactobacilli, and compatible with latex condoms.

PRO 2000/5 was not detected in rabbit plasma following up to 14 intravaginal doses of 4% PRO 2000/5 Gel (P). Low levels of PRO 2000/5 were reported in plasma samples collected from pregnant rats after twelve intravaginal gel applications. However, PRO 2000/5 was not detected in plasma specimens collected after intravaginal administration of up to 4% PRO 2000/5 Gel (P) for 90 or 180 days in non-pregnant rats, or 260 days in rabbits. Intravenous administration of PRO 2000/5 to laboratory animals and humans produced toxicological effects typical of polyanions, including reversible coagulopathy, leukocytosis, thrombocytopenia and liver and kidney pathology.

### 2.2.2 Clinical research in female and male volunteers

The early and expanded safety trials are summarised in the table below:

Dates of enrolment	Population	Concentration	Period of exposure	n	Ref
Jan 1997- Sept 1997	Sexually abstinent women in Belgium and UK	0.5%	Once daily for 2 weeks	24	19
		4%		24	
		Placebo		25	
Sept 1999- Oct 2000	Sexually active HIV negative women in the US and South Africa	2%	Once daily	12	20-22
		2%	Twice daily	13	
		4%	Once daily	12	
		4%	Twice daily	13	
	Sexually abstinent HIV positive women in the US and South Africa	4%	Twice daily	13	
			For 2 weeks		
Feb 2001 - Apr 2001	Sexually abstinent men at low risk for HIV in US	4%	Every night for 7 nights	24	23
		Placebo		12	
Oct 2001- May 2002	Sexually abstinent HIV positive men in US	4%	Every night for 7 nights	24	23
Aug 2003-	Sexually active HIV	0.5%	Twice daily	42	Unpublished

Apr 2004	negative women at low (n=30) and higher (n=12) risk for HIV in India		for 2 weeks		
Oct 2003- July 2004	Sexually abstinent HIV-positive women with high viral loads in US	0.5% Placebo	One dose	10 10	24
June 2003- Dec 2004	Sexually active HIV negative and HIV positive women in Uganda	0.5% 2% Placebo	Twice daily for 4 weeks	63 61 25	25

The results of these trials are detailed in the Investigator's Brochure. In summary, no serious adverse events (SAEs) were reported, and there was no evidence for significant systemic absorption or toxicity. The most common adverse events reported were vaginal discharge, vaginal bleeding/spotting, and vulvo-vaginal pruritus, burning, and pain. These were generally mild and resolved during or shortly after cessation of dosing. Cervical and vulvo-vaginal ulceration was seen colposcopically in less than five percent of participants during product use, and was usually attributed by the investigators to trauma or HSV infection. Intermenstrual bleeding (IMB, spotting) has been observed in some of the safety studies of PRO 2000/5 Gel (P), as in clinical studies of other vaginal gels, but rates among active gel recipients were comparable to those exposed to placebo and on observation.

Acceptability was good in all studies. In Belgium and the UK, most participants found the consistency, colour and odour of the gel acceptable ("liked a lot" or "like somewhat"). In the US and South Africa, all study participants asked reported that they would use the gel if they perceived themselves to be at risk for HIV infection, and all reported that they would recommend the gel to other women [20, 21].

Phase I studies also have been conducted to assess the safety of 4% PRO 2000/5 Gel (P) on the penile epithelium and urethral mucosa in uncircumcised and circumcised men [23]. In one study, men at low risk for HIV infection applied either 4% PRO 2000/5 Gel (P) (n=24) or a matched vehicle control gel (n=12) to the penis for seven consecutive nights. One in six users of both gels, active and vehicle, reported mild transient symptoms of genital itching, tingling, irritation, or abrasion.

A small Phase I clinical trial to assess the effect of intravaginal PRO 2000/5 Gel (P) on levels of infectious HIV-1 and inflammatory mediators in cervicovaginal secretions from HIV-infected women with high plasma viral loads was recently conducted in the US [24]. Twenty eligible volunteers were randomised 1:1 to receive a single dose of 0.5% PRO 2000/5 Gel (P) or matched vehicle control. Treatment and follow-up are complete. No SAEs or significant safety problems were reported by the investigators. Cervico-vaginal lavage (CVL) fluid obtained after application of 0.5% PRO 2000/5 Gel (P) significantly inhibited both HIV and HSV infectivity compared to CVL collected at screening, whereas the placebo had negligible effect. No increase in inflammatory markers was detected in CVL specimens. Analysis of CVL specimens for viral and immunological markers is underway.

In summary, PRO 2000/5 Gel (P) has been judged to be safe and well-tolerated by the investigators in all human clinical trials conducted to date.

### 2.2.3 Rationale for exploring two concentrations of PRO 2000/5

Polyanions are not virucidal but block viral entry to cells and therefore the aim is to give the highest tolerated dose to optimise the chance of demonstrating efficacy. In view of the results of the COL-1492 trial in which the incidence of HIV infection was higher in women exposed to N9 than those exposed to placebo, the possibility that minor local toxicity might increase the risk of HIV infection must be considered. Although N9 was licensed as a spermicide, additional clinical safety data were collected on low dose N9 prior to COL-1492, and no concerns raised. There was however, evidence from the *in vitro* cytotoxicity studies and from histology specimens from women [6] and rats that N9, a surfactant, had a narrow therapeutic

window and these data are now considered critical in the evaluation of new candidate compounds with N9 being a useful comparator. Although 2% PRO 2000/5 is more cytotoxic in cell lines than 0.5%, it is ~1000fold less so than N9, and the histology collected in clinical studies of PRO 2000/5 is favourable [19]. Thus, whilst 2% PRO 2000/5 is significantly more active *in vitro* than 0.5% and offers the best chance of demonstrating efficacy, there may be an increased risk of toxicity at the higher concentration, and even this low risk could facilitate HIV transmission. Consequently it has been decided to investigate both concentrations and for the Independent Data Monitoring committee (IDMC) to monitor safety, including rates of HIV infection in each arm, every 4-6 months.

### 2.2.3.1 Rationale for discontinuing 2%

The IDMC met on 8<sup>th</sup> February to review the HIV incidence data for safety and efficacy collected on 7,735 women enrolled since October 2005. They recommended that the 0.5% and placebo arms should continue, but that the 2% should not as there was no more than a small chance of demonstrating benefit according to the original statistical plan. They advised that the women allocated to 2% gel be informed and the 2% PRO 2000/5 gel be withdrawn as soon as practically possible.

The TSC accepted the recommendation of the IDMC. They agreed that it was important to continue with the 0.5% and placebo arms, and to increase the power to detect a reduction by increasing the numbers originally allocated to these two arms, if possible in the remaining enrolment timeline.

### 2.2.4 Placebo gel

The placebo formulation showed minimal toxicity toward human vaginal epithelial cell monolayers *in vitro*, and did not enhance susceptibility to HSV-2 when administered 12 hours before vaginal challenge in a mouse model for HSV type 2 infection [26]. Daily intravaginal dosing for 10 days was not irritating to the vaginal mucosa of rabbits (BioSyn, Inc., personal communication). In a phase I clinical trial conducted in the US to assess the safety of the placebo gel, no serious or unexpected adverse events were reported following twice daily intravaginal application for 14 days in healthy sexually abstinent women (preliminary findings, CONRAD Program – personal communication).

The placebo was also found to exhibit negligible activity against HIV *in vitro*, and to afford no protection in a mouse model for vaginal HSV-2 infection [26]. The placebo gel was selected in preference to the PRO 2000/5 Gel (P) vehicle because carbomer has been found to exhibit activity against HIV *in vitro*, and its presence in a placebo formulation might affect the study endpoints. The same placebo gel is to be used in other planned microbicide efficacy trials [27].

## 2.3 Preparatory work

### 2.3.1 Feasibility Studies

Feasibility Studies have been initiated in six sites recruiting from four different populations:

- (a) women from communities with access to primary health care facilities in Durban, Johannesburg and the Africa Centre sites, South Africa, and in Mazabuka, Zambia
- (b) women who are entitled to primary care either through their employment or their partner's employment on the Nakambala sugar estate, Mazabuka, Zambia
- (c) women who work in recreational facilities or who sell food along the main highway in Mwanza, Tanzania
- (d) HIV sero-discordant couples (and some sero-concordant couples to maintain blinding of sero-status) recruited in the Masaka district of Uganda following census and sero-survey

To date 2172 women-years of data have been accumulated, 116 incident cases of HIV infection have been identified with incidence rates ranging from 3.5 to 12.6 per 100 woman years of observation. Retention rates vary between the sites but with the exception of Johannesburg and the small discordant couple series in Masaka shows evidence of decline over time.

	South Africa			Zambia	Tanzania	Uganda
	Durban	Joburg	Africa Centre sites	Mazabuka	Mwanza <sup>+</sup>	Masaka*
Populations	Health clinics and associated communities				Recreational facilities	Sero-discordant couples
Start date	Aug 02	Oct 02	Jul 03	Mar03	Mar 03	Oct 03
N screened	1263	1088	882	1974	1573	1370
% HIV +ve at screen	47%	20%	50%	30%	25%	7%
% pregnant at screen	1%	4%	1%	4%	10%	-
N enrolled	608	757	453	590	716	50
% of enrolled seen at FU or later						
3m	94%	84%	63%	87%	83%	90%
6m	88%	79%	56%	79%	79%	84%
9m	82%	83%	56%	70%	70%	86%
12m	67%	87%	58%	63%	71%	86%
Recruitment period (months)	14	15	12	18	14	2
Person years FU	499.2	531.4	158.1	356.4	717.4	31.2
Sero-conversions	37	21	20	13	25	4
HIV incidence	7.4	3.9	12.6	3.6	3.5	12.6
95%CI	5.4, 10.2	2.6, 6.1	8.2, 19.6	2.1, 6.3	2.4, 5.2	4.8, 34.1

+ based on HIV negative women enrolled, (HIV positive women were also enrolled in Mwanza); follow-up rates based on % of 3 month attendees who returned subsequently

\* sero-discordant couples enrolled

### 2.3.2 Pilot Study

Following Feasibility, a Pilot Study was initiated to assess the trial case record forms (CRF), procedures and database and the acceptability of the placebo gel. In particular, the CRF questions on adherence to gel and accuracy of the answers were assessed through integrated social science, using triangulation with coital diaries and in-depth interviews. Ethical and regulatory approval for the Pilot Study was obtained in all sites. The Pilot Study was completed in all sites before commencing enrolment into the trial.

### 2.3.3 Issues addressed during protocol development

#### Design

The advantages and disadvantages of one control group receiving placebo versus two control groups, the second using condoms only (no gel), have been extensively discussed and there was unanimous support for the single placebo control group on the basis that sexual behaviour would be almost certain to differ between participants allocated to gel and participants allocated to 'no gel'. It would not be possible to reliably measure this component and it was thought likely that adherence to the study schedule would be reduced in participants not receiving gel.

After considerable debate within MDP, the duration of 9 months follow up for the primary efficacy analysis was chosen in order to optimise the chance of demonstrating efficacy considering that adherence and follow up rates are likely to decrease with time. To provide additional and longer term safety and efficacy data all women will be followed for at least 12 months. Secondary efficacy analyses will be undertaken on the 6 month and 12 month datasets.

#### HIV infection

In the majority of Feasibility Study sites, voluntary counselling and testing for HIV was not initially readily accessible to the target populations, and there were limited or no services for care and treatment of asymptomatic HIV infection in the public health system. Consequently there were few, if any, benefits to volunteers in knowing their HIV status and this was balanced against the risk of social harm from stigma, and in the Mwanza cohort, potential loss of income. However, through the lifetime of the MDP so far, ARVs have become increasingly accessible.

Although the investigators have agreed that only volunteers who are HIV negative, and willing to receive their result, will be included in the trial, participants who become infected

during the trial or change their mind about receiving results at later time-points will be allowed to continue gel in order to preserve the confidentiality of their HIV status.

#### **Other eligibility criteria (pregnancy, anal sex)**

The data collected so far suggest that a participant's intention to become pregnant in the next 12 months is not predictive of pregnancy, particularly in the sites in which hormonal contraception is used by the minority. The consensus was not to use 'intention to become pregnant in the next 12 months' as an exclusion criterion for the proposed trial but to test 4 weekly for pregnancy in participants who are not sterile.

During Feasibility Studies, quantitative and qualitative data on sexual practices including anal sex were collected. Both quantitative case record form (CRF) and qualitative focus group discussion (FGD) data suggested that anal sex is unusual (~ 1% of participants in the majority of sites). The investigators are agreed that it would be difficult to exclude women that practice anal sex on the basis of the lack of self-reporting. Due to the infrequency with which it appears to be conducted it is unlikely to be a significant threat to the ability to demonstrate efficacy.

#### **Discontinuation and interruption of gel**

The safety profile of PRO 2000/5 Gel (P) has been thoroughly reviewed and *in vitro* cellular toxicity and clinical data on epithelial disruption suggest that the 0.5% and 2% strengths are unlikely to give rise to the epithelial toxicity seen with N-9. The overall frequency of epithelial disruption in the trial population will be closely monitored by the investigators and reviewed, by treatment group by the IDMC.

#### **2.3.4 Community liaison systems**

Community Liaison Officers have been appointed in the Feasibility Study sites to oversee the information provided to local stakeholders and the target population, and to capture and catalogue feedback. Comments have been obtained at an individual level via suggestion boxes and door-to-door campaigns, and at a group level via formal structures such as the Community Advisory Boards/Groups/Committees, as well as more informal groups brought together to participate in Focus Group Discussions. These systems have facilitated acceptance of the research and allowed investigators to identify and respond rapidly to concerns raised. It is envisaged that they will continue in order to prepare the communities for the trial, to monitor progress of the trial, highlight any misconceptions about the clinical trial objectives and procedures, and act as an 'early warning' system for the investigators.

### **3 Trial Design**

#### **3.1 Objective**

The primary objective of the trial is to determine the efficacy and safety of 0.5% and 2% PRO 2000/5 Gels (P) compared to placebo gel in preventing vaginally acquired HIV infection.

#### **3.2 Design**

MDP 301 is a multi-centre, randomised, double-blind, placebo-controlled trial.

#### **3.3 Populations**

Four types of populations will be studied

- a) women from communities with access to primary health care facilities in Durban, Johannesburg and the Africa Centre sites, South Africa, and in Mazabuka, Zambia
- b) women who are entitled to primary care either through their employment or their partner's employment on the Nakambala sugar estate in Mazabuka, Zambia
- c) women working in bars, hotels, guesthouses and other food or recreational facilities in or near Mwanza City, northern Tanzania
- d) HIV sero-discordant couples (and some sero-concordant couples to maintain blinding of sero-status) recruited in the Masaka district of Uganda from either office based voluntary counselling and testing services or following census and sero-survey

### 3.3.1 Inclusion Criteria

- ◆ Women aged 16 years and above at enrolment in Masaka and Mwanza, or aged 18 years and above at enrolment in the South African and Zambian sites
- ◆ Likely to be sexually active at entry and during follow-up
- ◆ Willing to undergo HIV testing at screening and approximately 12 weekly intervals, and additionally if required to determine HIV status
- ◆ HIV negative at screening according to the local HIV testing algorithm
- ◆ Willing to receive the HIV result before randomisation
- ◆ Willing to use study gel as instructed
- ◆ Willing to undergo regular speculum examinations and genital infection screens
- ◆ Willing to have regular urine pregnancy tests
- ◆ Willing to receive health education about condoms
- ◆ Willing and able to give informed consent

### 3.3.2 Exclusion Criteria

- ◆ Unable or unwilling to provide a reliable method of contact for the field team
- ◆ Likely to move permanently out of the area within the next year
- ◆ Likely to have sex more than 14 times a week on a regular basis during the course of follow-up
- ◆ Using spermicides regularly
- ◆ Pregnant or within 6 weeks postpartum at enrolment
- ◆ Has grade 3 clinical or laboratory abnormalities which are considered by the clinician or the Trial Management Group (see section 8.2) to make enrolment inadvisable
- ◆ Requiring referral for assessment of a clinically suspicious cervical lesion
- ◆ Treatment to the cervix, or to the womb through the cervix, within 30 days of enrolment
- ◆ Known latex allergy
- ◆ Participating, or having participated within 30 days of enrolment, in a clinical trial of an unlicensed product, microbicide, barrier method or any other intervention likely to impact on the outcome of this trial
- ◆ Considered unlikely to be able to comply with the protocol

## 3.4 Interventions

The three study products are 0.5% and 2% PRO 2000/5 Gel (P), and a placebo gel. The 2% PRO 2000/5 gel was withdrawn after February 2008 following recommendations by the IDMC and TSC. Participants will be counselled that consistent use of condoms is the only known way to prevent sexual transmission of HIV, and condoms will be provided free of charge to all participants as needed.

### 3.4.1 PRO 2000/5 Gel (P), 0.5% and 2%

The active pharmaceutical ingredient, PRO 2000/5, is a synthetic polymer prepared by the acid-catalyzed condensation of 2-naphthalene sulphonic acid and formaldehyde, followed by neutralisation and molecular weight fractionation. The material has a weight-average molecular weight of  $5 \pm 1$  kilodaltons and a narrow molecular weight distribution. PRO 2000/5 Gel (P) is an aqueous gel formulation containing PRO 2000/5 (0.5% or 2%), carbomer 1382, lactic acid, trolamine, and the preservatives methylparaben, propylparaben, and sodium benzoate (indicated by the "P" suffix). It is buffered to pH 4.5. Two-gram intra-vaginal doses of 0.5% and 2% PRO 2000/5 Gel (P) contain 10mg and 40mg of PRO 2000/5, respectively. Further details can be found in the PRO 2000/5 Gel (P) Investigator's Brochure.

### 3.4.2 Placebo gel

The placebo gel to be used in the study (HPTN035 Placebo Gel) is a clear, water-based formulation designed to serve as an inert comparator in clinical trials of active vaginal

microbicide candidates [26]. The composition of the formulation is 2.7% hydroxyethyl-cellulose (Natrosol 250 HX Pharm), 0.85% sodium chloride, 0.1% sorbic acid, sodium hydroxide (qs pH 4.4), and 96.3% purified water (all percentages are on a weight-to-weight basis). All ingredients are compendial (United States Pharmacopoeia/National Formulary) and are generally recognised as safe for use in topical pharmaceutical preparations. The gel is similar in composition to marketed over-the-counter lubricants for vaginal use. Further details can be found in the HPTN035 Placebo Gel Investigator's Brochure.

### **3.4.3 Supply, packaging, labelling and monitoring supplies**

The study gels will be identically packaged in opaque, pre-filled vaginal applicators sealed in a foil/paper wrapper. Each applicator is designed to deliver a 2g dose in approximately 2ml. The supplies will be further packaged in identical cartons containing 10 pre-filled applicators each. The cartons will be labeled with the information shown in appendix 1. Indevus Pharmaceuticals, Inc. will oversee the manufacture of the study gels to Good Manufacturing Practice (GMP) standards.

Designated site pharmacists will obtain study products according to trial-specific procedures. On arrival at the site, the site pharmacist or authorised personnel will conduct an inventory of the contents of the shipment and document receipt.

The site pharmacist or authorised personnel will be responsible for labelling individual supplies with the trial identifiers unique to each randomised participant.

A sufficient number of cartons will be dispensed to each randomised participant to last two weeks beyond their next scheduled visit, up to a maximum of 6 cartons per scheduled visit. Within this limit, participants may obtain additional study gel supplies between scheduled visits. Allowances will be made for dispensing up to a three-month supply of study gel in exceptional circumstances in accordance with trial specific procedures. The site pharmacist or authorised personnel will monitor supplies and order additional supplies when needed. Manual and electronic records will be maintained, and these will be monitored during site visits.

### **3.4.4 Storage of products**

The study products will be stored in a secure, limited-access location at controlled room temperature (15-30° C). The temperature of the storage facility will be monitored on a regular basis according to trial-specific procedures. Expiry dates will not be printed on the applicators/cartons. Cartons will be date stamped when leaving the pharmacy and will be collected from participants if returned to the clinic more than 5 months after this date. Stability will be monitored on an ongoing basis.

### **3.4.5 Dispensing records**

The study gel will be dispensed to participants by the site pharmacist or other authorised personnel according to trial-specific procedures. The point of distribution will most often be a clinic setting (or a participant's home in some cases). The site pharmacist will be responsible for maintaining full records of the study products. Returned gel supplies will be counted and disposal will be according to local procedures.

### **3.4.6 Disposal**

Used applicators that are returned by participants will be disposed of with clinical waste or forwarded to the central pharmacy point for disposal at the site according to local pharmacy guidelines and all applicable regulations. Unused applicators brought back to clinic by participants will only be collected if they are beyond 5 months of the first date of dispensing (date stamped on the carton) or at the final visit. Documentation of returns and disposal will be monitored.

### **3.4.7 Concomitant medication records**

Concomitant medications at enrolment and during the trial will be recorded in the CRF, which

will be considered the source data for this information.

### 3.5 Outcomes

#### 3.5.1 Primary

The primary efficacy outcome is acquisition of HIV infection by 52 weeks, confirmed in a central laboratory, in participants confirmed to be HIV negative at enrolment.

The primary safety outcome is a grade 3 (severe) or 4 (life-threatening) clinical or laboratory adverse event confirmed on examination or repeat testing respectively. The characteristics that determine grade are provided in appendix 2.

#### 3.5.2 Secondary

The secondary efficacy outcomes are

- (i) acquisition of HIV infection by the 6 month time point, confirmed in a central laboratory, in participants confirmed to be HIV negative at enrolment.
- (ii) acquisition of HIV infection by the 9 month time point, confirmed in a central laboratory, in participants confirmed to be HIV negative at enrolment.
- (iii) HSV-2 incidence rates by the 9 month time point in participants uninfected at enrolment. Although prevalence rates are high, 75% - 85% in some sites, data from feasibility studies indicate that incidence rates are also likely to be high.
- (iv) HSV-2 incidence rates by the 12 month time point in participants uninfected at enrolment. Although prevalence rates are high, 75% - 85% in some sites, data from feasibility studies indicate that incidence rates are also likely to be high.
- (v) Cross-sectional prevalence of NG at 24 weeks, determined by a positive nucleic acid amplification assay
- (ii) Cross-sectional prevalence of CT at 24 weeks, determined by a positive nucleic acid amplification assay

The secondary safety outcomes are

- (i) all systematically solicited genital adverse events
- (ii) all clinical or laboratory adverse events

## 4 Study Schedule (see 4.7 for summaries)

### 4.1 Recruitment

The trial is anticipated to last for 42 months with enrolment continuing for a maximum of 30 months. This enrolment period may be amended on the recommendation of the Trial Steering Committee (TSC) and IDMC.

Volunteers have been recruited into the Feasibility Studies and Pilot Study from the target communities using a variety of mobilisation strategies such as public meetings, newsletters, posters, drama groups, peer-led education, door-to-door campaigns, and presentations in clinic waiting rooms. The Masaka site recruited a sero-discordant couple cohort following a census and sero-survey of 25 villages. In Mwanza, community-based mobilisation activities have been conducted in hotels, restaurants, bars and other food or recreational facilities. All sites will recruit new individuals to the trial using similar strategies to those described above. In addition, some sites may recruit participants from women who were enrolled in earlier MDP related cohorts, and Masaka may recruit couples through office based VCT services. The recruitment methods are subject to continuous evaluation through the community systems already referred to in section 2.3.4.

Volunteers who are willing to be screened will be provided with general information about microbicides and research, will be informed about the need to have and receive the result of an HIV test in order to participate, and the logistics of attending the clinics for screening.

### 4.2 Screening

A member of the study team will briefly check that the volunteer understands that to participate in the study she must be 16 years or over (or over the age of 18 in South African and Zambian sites), sexually active and not knowingly pregnant.

After discussion has established that the volunteer is eligible to participate on the basis of these 3 criteria they will be provided with information about microbicides, the risks and benefits of participating in clinical trials in general, confidentiality and the right to withdraw, as well as details specific to this trial.

The discussion will focus on ensuring comprehension of four critical points:

- a) that the primary reason for doing the trial is to test whether 0.5% PRO 2000/5 will prevent HIV;
- b) that there is a 50% chance that participants will receive the product that we don't think will prevent HIV (dummy, placebo) and no-one, including the staff, will know which product each participant is using;
- c) that the correct and consistent use of condoms is known to protect against HIV; and,
- d) that screening includes sensitive questions about sexual activity and an HIV test, and that they will need to know their HIV result if they wish to join the trial.

Priority will be given to these key points at screening, after which the following will be addressed:

- a) that agreeing to be screened does not mean that they have to join the trial;
- b) that there are several reasons why a woman might not be eligible to participate in the trial: being HIV positive is only one of the reasons;
- c) that participation in the trial will include regular genital examinations, blood tests, urine pregnancy tests and sensitive questions about their sexual activity at each visit; and,
- d) that any information collected that is entered into the database for the trial, or sent to the laboratory will be identified by a number and not by a name.

Study personnel will use written information (appendix 3) and visual aids to assist in these explanations. If they are satisfied that the volunteer understands the above information about the screening procedures, and she is willing to continue, then the volunteer will be asked to indicate her consent to be screened either by signature or by thumbprint (if the volunteer is illiterate) to part 1 of the informed consent form (appendix 5). If the volunteer is illiterate, she will be encouraged to have an impartial witness present (friend, family or appropriate member of the study team) to witness the discussion and thumb-print consent. If the volunteer is illiterate and declines to have a witness present at screening, this will be recorded on the informed consent form. Once a participant has signed an informed consent form her contact details will be recorded on a screening register. Participants will be given a copy of the signed/thumb-printed consent form and an information sheet to take away if they wish.

They will have an opportunity to have their questions answered by a member of the trial team in private. If they are willing at this point participants will undergo the following:

- demographic interview
- eligibility CRF
- behaviour interview
- pre-HIV test counselling which will include promotion of safe sex practices and a demonstration of how to use a condom
- blood collection for serum storage required for EQA or HIV antibody status determination in the event of HIV seroconversion
- urine collection for urinary pregnancy test if indicated

In addition, the first 500 participants enrolled in each of Durban and Johannesburg, and all the participants enrolled in Masaka, will have

- blood collected for routine laboratory parameters (haematology, biochemistry & coagulation)

HIV results will be provided with post-test counselling the same day, or at the next scheduled appointment if the woman cannot wait on that day.

Contact details of participants who will be invited for an enrolment visit will be collected onto a form which is separate from the case record form and confidential to the study personnel that see participants themselves, or that are responsible for organising field visits. It will be explained to participants that it is not possible to conduct the genital examination if they have their menses and they will then be invited to attend between 1 and 6 weeks later for review and possible randomisation and enrolment into the study. The appointment will be made at a time-point approximately half way in their menstrual cycle and they will be reminded that they will not be reimbursed if they attend during their menses.

#### **4.2.1 Timing of screening procedures and assessments**

The listed assessments should be conducted within 6 weeks of the enrolment date, but they do not have to be conducted on the same day. For example, in clinics providing a Voluntary Counselling and Testing (VCT) service, a volunteer might attend for VCT and have blood collected for HIV and syphilis, have a brief discussion about the trial but prefer to return on a later date to be screened. Informed consent will be collected when she is ready to be screened, and the case record forms completed after informed consent has been collected, but the HIV and syphilis do not need to be repeated if the enrolment date will fall within 6 weeks of the date the specimens were collected.

If there are clinical events or laboratory abnormalities reported at screening which render the participant ineligible but which are expected to resolve, for example requiring referral for further investigation of a suspicious lesion, or bloody diarrhoea due to infection, then participants can be re-screened within a time-frame appropriate to the event. The interviews and investigations should be repeated unless the enrolment date will fall within 6 weeks from the date that these were first completed or collected respectively.

### **4.3 Secondary screening and enrolment**

Contact details will be checked. The results from screening will be reviewed, and participants will be reminded that the genital examination cannot be conducted if they have their menses. A new appointment will be made for menstruating participants.

Participants will be asked to provide a specimen for a urinary pregnancy test and the result will be entered on the case record form (CRF). There will be a further discussion about the trial with more emphasis on gel use, and the potential risks associated with gel and study procedures.

The discussion will focus on ensuring comprehension of the following key points:

- a) that the primary reason for doing the trial is to test whether 0.5% PRO 2000/5 will prevent HIV: at the moment we do not know;
- b) that there is a 50% chance that participants will receive the product that we don't think will prevent HIV (dummy, placebo) and no-one, including the staff, will know which product each participant is using;
- c) that participants are asked to use the gel during all episodes of sexual intercourse during the study, and, because it is not known if the gels prevent HIV transmission, it is best that condoms are used with gel whenever possible;
- d) although unlikely, it is not known with certainty that the products are harmless to an unborn child and they will have to stop using the gel if they become pregnant;
- e) that there may be symptoms as explained in the information sheet such as genital irritation (for men as well as women), unexpected bleeding, and genital sores/ulcers, or others that can't be anticipated, and that we need to collect information on them all so any symptoms should be reported to the study team, regardless of whether or not the participant thinks they are related to the gel (contact details and mechanisms are given on the information sheet); and,

- f) they should provide answers that are as accurate as possible, especially to the questions on gel use and sexual practices (eg to say so if they haven't used gel or condoms).

Priority will be given to these six points after which the following will be covered:

- a) that the visits will be 4 weekly and either short (questions, and gel and condom distribution) or long (questions, examination, blood tests and gel and condom distribution);
- b) that it is important to attend the clinic when asked both for their own safety, and because the study results are threatened if many participants do not attend;
- c) the reimbursements they can expect to receive; and,
- d) that a sample of participants will be randomly selected to fill in coital diaries and participate in in-depth interviews on variety of occasions, or to participate in focus group discussions during the trial.

Any questions that the participant has will be fully answered. If the study staff are satisfied that the participant understands that it is not known if any of the gels prevent HIV and it is known that condoms do prevent HIV if used consistently, and she is willing and eligible to continue, then she will be asked to indicate her consent either by signature or by thumbprint (if she is illiterate) to part 2 of the informed consent form (appendix 4). If the participant is illiterate, an impartial witness of their choice (friend, family or appropriate member of the study team) will be present to witness thumb-print consent. A copy of the informed consent will be provided to the participant for her own use unless she prefers not to take this away with her for reasons of preserving confidentiality.

Participants will then go through the following:

- behavioural interview
- clinical interview of history relevant to eligibility, solicited genital events and general adverse events
- genital examination including collection of endo-cervical swab for NG/CT testing, and high vaginal swab (HVS) for In-Pouch testing for TV, pH and Gram stain
- general examination
- eligibility CRF
- blood collection for syphilis serology
- blood collection for buffy coat and to store serum for possible future testing of HIV and HSV-2.

Syndromic treatment of STIs will be provided on the same day according to national guidelines if necessary.

#### 4.3.1 Randomisation

Preparation and maintenance of the randomisation list will be undertaken by MRC CTU. Details of this are provided in the statistical section 7.3. The ratio is 1:1:1 for 0.5% PRO 2000/5:2% PRO 2000/5:placebo. Following the IDMC recommendation in February 2008 not to continue with the 2% PRO 2000/5 arm, the ratio for 0.5% PRO 2000/5 gel and placebo will be 1:1.

MRC CTU will prepare a register with sequential trial numbers for each site. The trial numbers will be allocated consecutively to participants as they enrol, and this number will determine whether the participant receives 0.5% PRO 2000/5, or placebo gel. The allocation will not be known to any staff at the site including those overseeing gel supplies, and there will be no documentation at the clinical sites that permits unblinding (see section 6.7.5 for unblinding procedure of individual participants).

Trial staff will be unblinded to the 2% allocation from February 2008. However the study blind for the primary comparison of 0.5% PRO 200/5 gel versus placebo, will be maintained.

The trial number should be used at enrolment and thereafter on all documents in the trial, and under no circumstances should it be given to any other participant.

#### 4.3.2 Dispensing instructions

The various positions that can be adopted for insertion of the applicator, and the mechanism for expelling the contents will be illustrated with visual aids. Participants will be advised to take one of the applicators from their dispensed supply and insert it whilst in the clinic, to ensure that they have no difficulty following the instructions. They will be advised to insert gel:

- Within one hour before sex
- A second time, if more than 1 hour has elapsed since they administered the previous dose
- Again, if their partner has ejaculated and they are having sex a second or subsequent time, even if within the hour of the original application

They will be advised NOT to:

- Insert other products into the vagina at all if possible, but definitely not from one hour before a gel application until one hour after sex has occurred
- Wash the gel out (for example by finger-cleansing or using a cloth) for at least one hour after sex has occurred
- Share their gel supplies with anybody else, even if the other person is also in the study.

There will be a discussion about where they will store the gel, and advice to help them note their use and non-use of gel and condoms. The importance of this information to the result of the trial will be emphasised. All participants will be given an aide mémoire, together with their gel, at each clinic visit. The aide mémoire will have space for the participants to record their sex acts, condom and gel use. They will be told that they do not *have* to fill the aide mémoire in or return it, but that it is intended to help them remember the things they are going to be asked about in the CRF. Gel and condoms, as required for the next 6 weeks will be dispensed (a supply expected to last 2 weeks beyond the date of the clinic visit based on sexual frequency data collected during the behavioural interviews at screening and enrolment) up to a maximum of 6 cartons of gel.

Participants will be given an appointment in 4 weeks time, for clinical review and to collect further supplies. They will be advised to contact a member of the trial team earlier if they experience difficulties applying gel, or symptoms that they think might be related to gel.

#### 4.4 First follow-up visit

Contact details and willingness to continue to participate will be checked. The participant will be reminded that the examination cannot be conducted if she has her menses. The following procedures and assessments will take place:

- behavioural interview
- clinical interview for solicited genital events and other general adverse events
- gel dispensing and accountability
- genital examination
- general examination if indicated
- urine collection for  $\beta$ HCG pregnancy test (if indicated)
- blood collection to store serum for possible future testing for HIV

A trial team member will check there have been no problems in applying gel and will dispense additional supplies of gel and condoms. Unused gel supplies will be counted and given back to the participant. Total supplies will be sufficient to last for two weeks beyond the next visit, up to a maximum of 60 doses. An appointment for the next visit, which will be a Short Follow-up visit, will be made, timed so as not to coincide with menses.

## 4.5 Follow-up

The format of subsequent follow-up visits will be 'short' or 'long' and these will continue for 52 weeks in the majority (schedule 4.7.1). The first 500 participants recruited in each of Durban and Johannesburg, and all the participants recruited in Masaka, will also have routine laboratory parameters tested at weeks 12 and 24 (schedules 4.7.1 and 4.7.2). Participants recruited into the HIV sero-discordant couple cohort will continue on gel with clinical monitoring and routine laboratory testing for a maximum of 104 weeks (schedule 4.7.2). If the recruitment phase is extended by the Trial Steering Committee on the recommendation of the Independent Data Monitoring Committee, then those recruited towards the end of the trial are likely to be followed up for shorter periods. Similarly the Trial Steering Committee may recommend that the follow-up be extended or reduced during the trial on the recommendation of the IDMC.

### 4.5.1 Short Follow-up

The following procedures and assessments will take place:

- behavioural interview
- urine collection for urinary pregnancy test (if fertile)
- gel dispensing and accountability

The behavioural CRF will collect information on whether a condom or gel was used during the last sex act.

The participant will be asked if she has experienced inter-menstrual bleeding/spotting symptoms, genital sores or ulcers, or other unusual genital discomfort, and whether she has been admitted to hospital. A clinical assessment will be triggered by a 'yes' answer to any of these clinical questions. If there is no indication for a clinical assessment, staff will dispense additional supplies of gel and condoms. Total supplies provided will be sufficient to last for 2 weeks beyond the next visit, up to a maximum of 60 doses of study gel.

An appointment for the next visit according to the individual schedule for each participant (based on the randomisation date) will be made, and if this is to be a long follow-up appointment it will be timed so as not to coincide with menses.

### 4.5.2 Long Follow-up

Contact details and willingness to continue to participate will be checked. The participant will be reminded that the examination cannot be conducted if she has her menses. Each participant's comprehension of the following will be reviewed:

- a) that no-one knows whether any of the study products will protect against HIV or STI infections and so it is best to use condoms with gel;
- b) that they should contact the study staff before their next appointment if they have a problem such as bleeding or suspect that they might be pregnant;
- c) that they need to try to answer the questions about gel use accurately; and,
- d) that they are free to withdraw at any time, or to stop using gel; that we would like them to continue to attend but that this is also not mandatory.

The study staff will tailor the discussion to address any gaps in the participant's understanding.

Participants will then undergo the following:

- pre-HIV test counselling with promotion of safer sex practices
- behavioural/adherence interview
- clinical interview of solicited genital events and general adverse events
- genital examination which may include collection of endo-cervical swab for NG/CT testing, and high vaginal swab (HVS) for In-Pouch testing for TV, pH and Gram stain (as per the schedule)
- urine collection for urinary pregnancy test (as per schedules)
- blood collection for HIV test and serum and buffy coat store (as per schedules)

- blood collection for syphilis serology (at the visits described in the schedules 4.7.1 and 4.7.2)
- blood collection for HSV2 testing (at the visits described in the schedules 4.7.1 and 4.7.2)

In addition, at weeks 12 and 24, the first 500 participants enrolled in each of Durban and Johannesburg and all the participants in Masaka will have

- blood collected for routine laboratory parameters

The long behavioural CRF will collect information on the number of acts when a condom and/or gel was used either in the last 1 week (if a participant has had sexual intercourse in the last week) or in the last 4 weeks (if she has not had sex in the last week), and the number of unprotected acts with each partner. Partners will be categorised as 'long term/stable partners' and 'other types of partner'.

Trial staff will check that there have been no problems in applying gel, and will prescribe further supplies of gel. Total supplies will be sufficient to last for two weeks beyond the next visit. An appointment for the next visit will be made according to the participant's schedule based on her date of enrolment.

#### **4.5.3 Coital diaries and in-depth interviews**

A subset of participants who are selected to complete coital diaries and in-depth interviews will be contacted by a member of the research team approximately four weeks before their long follow-up visit date. They will be asked to fill in a coital diary until their next scheduled visit and will be instructed in how to fill in the diary. Participants will be requested to return the diaries to the clinic at their next visit.

At the clinic visit they will be asked to participate in a recorded in-depth interview with a member of the social science team within the next 2 weeks. Verbal consent will be obtained at the start of the recording.

Male partners of a subset of these women will also be selected to participate in recorded in-depth interviews to elicit their opinions and preferences regarding the use of gel. They will be provided with a male information sheet about the MDP and trial (Appendix 4).

#### **4.5.4 Focus group discussions (FGDs)**

Two sets of recorded focus group discussions will take place at regular intervals throughout the trial. One set will focus on study participants' and their partners' perceptions of the trial and products, and the other will focus on similar issues in the general community (see section 6.3 on qualitative data collection).

#### **4.5.5 Follow-up of male partners of female participants in Masaka, Uganda**

In Masaka, Uganda, men and women will be recruited as a couple and will be given information about the trial together in the first instance. The men will be allocated an individual trial number after they have signed their consent to participate (appendix 5).

Three groups of men will be followed up systematically. The first will be the male partners of the subgroup of females who are selected for the more intensive qualitative research, the second will be men reporting to the clinic or a member of the trial team with adverse events, and the third will be the partners of women found to have a serious adverse event whilst using the gel. CRFs based on sexual behaviour, acceptability of the study product and issues surrounding the trial will be completed with the men.

The men will not be allocated scheduled clinic visits but will be encouraged to report any complaints or medical events whilst their partner is using the gel to the trial team. Those who present at the clinic or to a member of the trial team with a medical complaint will be invited to undergo general and genital examinations, clinical and sexual behaviour interviews. The female case records forms will be modified to allow collection of similar information in the

men and women. If undergoing clinical interview for any reason, blood and other specimens will be collected as necessary as part of standard medical investigations. After treatment or referral, the male participant will be followed up until resolution of the complaint.

#### 4.5.6 Follow-up of participants randomised to 2% PRO 2000/5 gel

Following the recommendation of the IDMC to discontinue 2% PRO 2000/5 gel, participants who had been randomised to that gel will be seen as soon as practically possible. The new information will be shared, supported by the Additional Participant Information Sheet (Appendix 3a). The discussion will focus on the following points:

- a) that the reason for discontinuing 2% PRO 2000/5 is that there is very little chance of it preventing HIV infection
- b) that provided they are willing, they will continue to be followed for the long visits, at weeks 4, 12, 24, 40, and 52/104 (questions, examination, blood tests and other tests for sexually transmitted infections and vaginal infections)

Final visit procedures will be conducted at the visit that gel is discontinued, including a genital examination and collection of buffy coat sample. The participant will then continue to attend long follow-up visits up for the remainder of her schedule.

#### 4.6 Final visit

This is planned to take place at 52 weeks from randomisation for the majority of participants. There will be a window period of 6 weeks beyond the scheduled final visit for each participant within which the following procedures and assessments can acceptably fall:

- pre-HIV test counselling with promotion of safer sex practices
- long behavioural interview
- clinical interview of solicited genital events and other adverse events
- genital examination
- general examination if indicated
- blood collection for syphilis serology
- blood collection for HIV test and serum and buffy coat store (as per schedules 4.7.1 and 4.7.2) for possible future testing of HSV-2
- HVS for pH and gram stain
- urine collection for urinary pregnancy test
- returns of ALL used and unused gel

In addition, the first 500 participants enrolled in each of Durban and Johannesburg, and all the participants enrolled in Masaka, will have

- blood collected for routine laboratory parameters (haematology, biochemistry & coagulation)
- plasma collection for determination of PRO2000/5 levels

Contact details will be checked, and consent to contact participants at a later date, when the results of the trial are available for dissemination, and to share information about future microbicide trials, confirmed. Every attempt will be made to retrieve all unused gel supplies, including visiting the participant's home (providing they have given their consent for this to happen). Counsellors or clinical personnel will make arrangements for letting participants know the results of assessments that they are responsible for at the final visit according to site-specific procedures.



**4.7.1 Summary schedule of clinical visits, procedures and assessments for 12 month (52 weeks) follow-up** (Brackets indicate that a procedure is done at the discretion of the clinic staff)

	Screen	Enrol	1 <sup>st</sup> Clinical Follow-up (FU)	Gel collection Follow-up (FU)	Clinical FU	Clinical FU	Clinical FU	Final FU
Wk related to enrolment (+/- wk)	-6	0	4 (+/-2)	8,16,20,28,32,36,44,48 (+/-2)	12 (+/-2)	24 (+/-2)	40, (+/-2)	52 (-1/+6)
Contact details	X	X	X		X	X	X	X
Demographics	X							
Eligibility	X	X						
Study gel and condom dispensing		X	X	X	X	X	X	X
Behaviour/adherence interviews Short <sup>1</sup>	X	X		X <sup>2</sup>	X			
Long <sup>1</sup>			X			X	X	X
Clinical interview								
History relevant to eligibility		X						
Solicited genital events		X	X	(X) <sup>2</sup>	X	X	X	X
Other adverse events		X	X	(X) <sup>2</sup>	X	X	X	X
Examinations General		X	(X)		(X) <sup>3</sup>	(X) <sup>3</sup>	(X) <sup>3</sup>	(X) <sup>3</sup>
Genital		X	X	(X) <sup>2</sup>	X	X	X	X
βHCG pregnancy test <sup>4</sup> urine	X <sup>4</sup>	X	X <sup>4</sup>	X <sup>4</sup>	X	X	X	X
HIV Ab test with counselling, real time, 8.5mls (SST) <sup>5</sup> Store residual for EQA	X				X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>
Serum Storage 5ml (SST)		X	X					
BC storage 4ml (EDTA)		X				X	X	X
Syphilis ~4ml (SST)		X				X		X
HSV2 ~4ml (SST)		X					X <sup>7</sup>	X <sup>7</sup>
Routine lab parameters <sup>6</sup>	X				X	X		X
Plasma for PRO2000/5 assay								X
TV In-Pouch/PCR		X				X		
NG/CT endocervical swab		X				X		
HVS for pH (if indicated) and Gram stain including Ison Hay score		X			X	X	X	X

<sup>1</sup> The screening and enrolment interview adherence data will be limited to use of condoms and will not include clinical questions; there will be additional questions asked at the final visit

<sup>2</sup> The 'short' interview at these visits will include clinical questions and women may be referred for clinical assessment according to trial-specific procedures documented in the site manual of procedures

<sup>3</sup> Examinations will be conducted if indicated according to the site manual of procedures

<sup>4</sup> Women who are sterile and those who have been confirmed to be pregnant will be exempt

<sup>5</sup> If a woman declines to have a rapid test at these timepoints, serum will be collected and stored, if seroconversion has been confirmed, these specimens are not required

<sup>6</sup> Haematology (FBC, differential, platelets), biochemistry (ALT, AST, bilirubin, creatinine, urea) and coagulation (INR and APTT) specimens, and a plasma specimen at the final visit, will be collected on the first 500 women in each of Durban and Joburg.

<sup>7</sup> If HSV2 was diagnosed at enrolment, further HSV2 samples are not required



**4.7.2 Summary schedule of clinical visits, procedures and assessments for up to 24 months (104 weeks) follow-up** (Brackets indicate that a procedure is done at the discretion of the clinic staff)

	Screen	Enrol	1 <sup>st</sup> Clinical Follow-up (FU)	Gel collection Follow-up (FU)	Clinical Follow-up(FU)	Clinical Follow-up(FU)	Clinical Follow-up(FU)	Final
<b>Wk related to enrolment (+/- wk)</b>	<b>-6</b>	<b>0</b>	<b>4 (+/-2)</b>	<b>8,16,20,28,32,36, + 4 wkly between clinical FU (+/-2)</b>	<b>12, 52, 64, 88, 100<sup>6</sup> (+/-2)</b>	<b>24 (+/-2)</b>	<b>40, 76 (+/-2)</b>	<b>Up to 104 wks after enrol<sup>6</sup> (-1/+6)</b>
Contact details	X	X	X		X	X	X	X
Demographics	X							
Eligibility	X	X						
Dispensing		X	X	X	X	X	X	X
Behaviour/adherence interviews								
Short <sup>1</sup>	X	X		X <sup>2</sup>	X			
Long <sup>1</sup>			X			X	X	X
Clinical interview								
History relevant to eligibility		X						
Solicited genital events		X	X	(X) <sup>2</sup>	X	X	X	X
Other adverse events		X	X	(X)	X	X	X	X
Examinations								
General		X	(X)		(X) <sup>3</sup>	(X) <sup>3</sup>	(X) <sup>3</sup>	(X) <sup>3</sup>
Genital		X	X	(X) <sup>3</sup>	X	X	X	X
βHCG pregnancy test <sup>4</sup> urine	X <sup>4</sup>	X	X <sup>4</sup>	X <sup>4</sup>	X	X	X	X
HIV Ab test with counselling, real time, 8.5mls (SST) <sup>5</sup> Store residual for EQA	X				X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>
Serum storage 5ml (SST)		X	X					
BC Storage 4ml (EDTA)		X				X	Wk40	X
Syphilis 4ml (SST)		X				X	X	X
HSV2 4ml (SST)		X					X <sup>8</sup>	X <sup>8</sup>
Routine laboratory parameters <sup>7</sup>	X				Wks 12 & 52	X		X
Plasma for PRO2000/5 assay								X
TV In-Pouch/PCR		X				X		
NG/CT endocervical swab		X				X		
HVS for pH (if indicated) and Gram stain including Ison Hay score		X			X	X	X	X

<sup>1</sup> The screening and enrolment interview adherence data will be limited to use of condoms and will not include clinical questions; there will be additional questions asked at the final visit

<sup>2</sup> The 'short' interview at these visits will include clinical questions and women may be referred for clinical assessment according to trial-specific procedures documented in the site manual of procedures

<sup>3</sup> Examinations will be conducted if indicated according to the site manual of procedures

<sup>4</sup> Women who are sterile and those who have been confirmed to be pregnant will be exempt

<sup>5</sup> If a woman declines to have a rapid test at these timepoints, serum will be collected and stored, if seroconversion has been confirmed, these specimens are not required

<sup>6</sup> Follow-up will be a minimum of 12m (52 weeks) and a maximum of 24m (104 weeks); all follow-up will end in the same 3 month period approximately 3 years after the start of the trial same 3 month period

<sup>7</sup> Haematology (FBC, differential, platelets), biochemistry (ALT, AST, bilirubin, creatinine, urea) and coagulation (INR and APTT)

<sup>8</sup> If HSV2 was diagnosed at enrolment, further HSV2 samples are not required

## 5. Assessment of outcome measures

### 5.1 Efficacy

#### 5.1.1 HIV

Testing will be performed according to site specific operating procedures, and HIV status will be determined by the algorithms using FDA and WHO approved assays in use locally at each site. All positive and discordant results at and beyond enrolment, 5% of all sero-negatives and 10% of screened and excluded sero-positives will be retested in the central laboratory. During the trial, MRC CTU will inform the central reference laboratory and the site laboratory which samples should be selected. This will be determined randomly in the case of the 5% sero-negatives and 10% excluded sero-positives.

Only those who are confirmed to be negative locally at screening will be enrolled. All results that are negative at screening and positive/discordant at 12 weeks will be reviewed by the central reference laboratory. Further tests will be performed on the stored specimens collected at enrolment and week 4 as required, to determine HIV status at enrolment.

All rapid results that are positive or discordant locally thereafter, including at the final visit will be reviewed by the central reference laboratory, and further specimens, stored from previous visits may need to be collected and tested according to CLS algorithms, before a decision about status at the final visit can be made.

Participants who are lost to follow-up may reappear at a later date beyond the time of their scheduled final visit. Provided they are willing, they should be tested for HIV (see section 7.6 subsidiary analysis).

#### 5.1.2 *Chlamydia trachomatis* and *Neisseria gonorrhoea*

These will be assessed on endo-cervical material collected during the genital examination by nucleic acid amplification assays (NAAs) in the laboratories local to the sites, subject to internal and external quality assurance systems.

Specimens will be collected on all participants at enrolment and week 24. Only laboratory confirmed infections will be considered an outcome in the analyses.

#### 5.1.3 HSV2

Laboratories will use either the FOCUS HerpSelect 2 IgG or the Kalon Biologicals HSV 2IgG kit depending on the performance of the assay in their environment. Sites to the north of South Africa will be using the Kalon as it has been scientifically proven that the Kalon assay is more specific in those geographical locations.

Detection of HSV 2 seroconversion will be based on demonstration of conversion of HSV 2 Ig G negative at enrolment to positive at a later visit.

HSV 2 seroconversions will be confirmed at CLS using the same assay that is used at the site. Both enrolment and follow-up samples will be tested.

Only samples showing clear evidence of seronegative to seropositive status will be regarded as true HSV 2 seroconversions. Any equivocal results will be regarded as “indeterminate HSV 2 status”.

### 5.2 Safety

An adverse event (AE) is defined as any untoward medical occurrence in a clinical research participant administered an investigational product, and which does not necessarily have a causal relationship with the investigational product (ICH GCP definition). The definition will be applied to all three study gel groups from the time of randomisation and information on AEs will be captured at every visit after enrolment. Pre-existing conditions will not be reported as AEs unless the condition worsens.

### 5.2.1 Solicited genital events

Symptoms that will be assessed systematically in all participants at every clinical visit including enrolment and the final visit are: genital discomfort, non-menstrual bleeding and sores/ulcers. These will be assessed by clinical personnel and graded for severity according to the toxicity table in appendix 2 and recorded on the appropriate CRF. At the non-clinical visits after enrolment, participants will be asked a series of clinical questions which will trigger a clinical assessment if the answer is 'yes'.

Clinical signs that will be systematically recorded in all participants following genital examination at every clinical visit (and if indicated at short follow up visits) are: the presence of blood in the vagina, erythema, oedema and genital epithelial disruption (sores and ulcers) of the vulval and cervico-vaginal tissues. Events will be graded for severity according to the toxicity table in appendix 2 and recorded on the appropriate CRF.

### 5.2.2 Solicited systemic events (Durban, Johannesburg and Masaka only)

Systemic events will be assessed in 500 participants at each of the Durban and Johannesburg sites, and in all participants in Masaka, by collection of blood for haematology (haemoglobin, white blood cell count, neutrophils, lymphocytes, eosinophils, basophils, monocytes and platelets), biochemistry (AST, ALT, total bilirubin, creatinine and urea) and coagulation parameters (INR, APTT) at screening, week 12, week 24, and week 52. These measurements will also be taken in Masaka at the final visit. These events will be graded according to appendix 2. In addition, a plasma specimen will be collected for determination of PRO2000/5 levels at the final visit.

### 5.2.3 Other clinical events

At the long follow-up and the final follow-up visits, participants will be assessed systematically by clinical personnel asking three questions: whether they have experienced any other genital symptoms, whether they have experienced any other illnesses, and whether they have taken any medication. Events reported by participants will be graded for severity according to the toxicity table in appendix 2 and recorded on the appropriate CRF.

Participants will be asked systematically at every clinical visit after enrolment about their general health, and at gel collection follow up visits about whether they have been admitted to hospital for any reason since their last visit. All participants will be clinically assessed at enrolment, long-follow up and final follow-up, and any participant answering 'yes' to any of the trigger question at short-follow up visits will also be referred for clinical assessment.

### 5.2.4 Serious adverse events

Some, but not all of the adverse events that are graded 3 (severe) or 4 (life-threatening) according to appendix 2 will meet the International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) criteria for defining a 'Serious Adverse Event' (SAE), namely one that results in:

- ◆ Death,
- ◆ An immediate threat to life,
- ◆ Requires in-patient hospitalisation or prolongs existing hospitalisation (hospitalisation for elective treatment of a pre-existing condition is not included),
- ◆ Results in persistent or significant disability or incapacity,
- ◆ Is a congenital abnormality (i.e. the outcome of pregnancy involving a participant), or
- ◆ Is any other important medical condition\*

\*Examples of conditions regarded as 'any other important medical condition' that qualify as 'serious' for the purposes of this study include but are not limited to:

- ◆ Hospitalisation, attempted suicide or homicide resulting from social harm linked to gel or participation in this study
- ◆ Vaginal oedema with sloughing of the epithelia

- ◆ Non-menstrual bleeding that is profuse (haemorrhage requiring bed rest or transfusion) of any duration
- ◆ Cervical or other gynaecological cancers

The following conditions, which whilst not considered 'serious' by the definitions above, are considered sufficiently important to be reported to MRC CTU for review by the Medical Experts on an expedited basis using the notifiable adverse event case record form if they are possibly, probably or definitely related to gel:

- ◆ Non-menstrual bleeding that is heavy (like menses) lasting for more than 4 days
- ◆ Genital epithelial disruption that exceeds the size of 4 cotton-tipped swabs (each swab 10x5mm)
- ◆ Marked genital erythema (redness) that is diffuse with symptoms that the participant is aware of at most times
- ◆ Cervical lesions that are suggestive of cervical cancer that have resulted in referral
- ◆ Any event resulting in a clinical decision to discontinue gel
- ◆ Miscarriages

Events that meet the above definitions but are considered unlikely to be, or unrelated to gel, will be prioritised for data entry so they are notified at CTU with the electronic data transfer on the 1<sup>st</sup> and 15<sup>th</sup> of the month.

There are no expected SAEs with reference to the existing available information on 0.5% and 2% PRO 2000/5 Gel (P).

### 5.2.5 Relationship of Adverse Event to study product

Events should be classified for relationship to study product as:

<b>Unrelated</b>	adverse events that can be clearly explained by extraneous causes and for which there is no plausible association with study product, or adverse events for which there is no temporal relationship
<b>Unlikely to be</b>	adverse events that may be temporally linked, but which are more likely to be due to other causes than study product and which do not get worse with continuing use of product
<b>Possibly</b>	adverse events that are temporally linked but could be explained by study product or other causes, which may improve when not using study product but do not reappear when using study product
<b>Probably</b>	adverse events that are temporally linked and for which the study product is more likely to be the explanation than other causes, which may improve when not using study product
<b>Definitely</b>	adverse events that are temporally linked and for which the study product is the most likely explanation, which disappear or decrease when not using study product and reappear when using study product

Decisions about relationship will rest initially with the clinical personnel that reviews the event at the site. For events that are current at the time of the visit, this decision will be made after examination. The final decision on relationship will rest with the TSC.

### 5.3 Adherence to gel

This will be assessed by systematic direct questioning of participants at each visit that gel is dispensed, in conjunction with the short or long behaviour/adherence case record form. Study personnel will ask participants how many times since the last visit they have used gel, and how much gel they have left. Any discrepancies with amounts dispensed will be clarified.

## 6. Procedures

### 6.1 Counselling procedures

Study personnel that are designated counsellors have completed nationally recognised training courses and have experience in VCT. All counselling procedures will take place in a room where privacy can be guaranteed, and the interview will begin by establishing rapport and explaining/reviewing the mechanisms in place to ensure that confidentiality is preserved.

### 6.1.1 HIV voluntary counselling and testing

Women will see a counsellor prior to having blood collected for an HIV test to ensure that they have sufficient knowledge about HIV infection to understand what the test is for, the implications of a positive and negative result, and the fact that the result may be indeterminate. They will also be informed how and when they can receive the result, the standard of care available locally and how the study team will assist them to access this, if necessary, according to the policy at the clinical site detailed in the site specific procedures.

Post-test counselling will also be undertaken by the counsellors, to ensure that women understand the result and the implications for themselves, their partner(s) and children. Women will have the opportunity to express their emotions in a supportive atmosphere.

### 6.1.2 Safe sex counselling

Counsellors, clinical personnel and interviewers will provide advice to participants on how HIV and STIs are transmitted, how participants may protect themselves and to demonstrate the use of a condom using a model.

At each visit, participants will be counselled by study personnel about the importance of using condoms. This will be undertaken by an experienced counsellor at screening, enrolment and the clinical follow-up visits, and reinforced when gel is dispensed by those authorised to do so by the Principal Investigator (PI) at each site.

## 6.2 Clinical procedures

### 6.2.1 Solicited and other adverse event and medication data

These data will be collected during a structured interview directly onto the case record form.

Prior to enrolment women will be asked additional questions related to the eligibility criteria, including details of gynaecological conditions.

### 6.2.2 General examination

Weight, height and temperature will be recorded. Participants will be clinically screened for anaemia and jaundice, and the skin, lymph nodes, respiratory and abdominal systems will be examined for signs of infectious diseases including HIV infection.

### 6.2.3 Genital examination and collection of genital swabs

The examination performed is based on published guidelines [28] in the following sequence:

- inspection of the vulva and perineum
- insertion of a speculum into the vagina, using a small amount of lubricant if necessary
- visual inspection of the vagina and cervix to assess bleeding, discharge and epithelial surfaces
- collection of vaginal discharge sample (if indicated) from the lateral vaginal wall or posterior fornix (away from any apparent abnormal areas) for pH testing, and spreading the contents of the swab onto a glass slide for later microscopy by Gram stain/wet mount
- if the epithelium of the ectocervix or vagina is obscured, a large saline-moistened cotton swab may be used to gently wipe away any excess discharge or debris, minimising the contact with the endocervix
- collection of endocervical swab for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* testing

If indicated following the clinical interview and according to site-specific procedures

- bimanual examination

#### **6.2.4 Collection of blood and urine**

Blood will be collected from the ante-cubital fossa and in some sites by finger-prick.

Urine will be collected prior to genital examination for a pregnancy test to be performed on site by the clinical staff. Pregnancy tests, according to site specific procedures, will be conducted at 4 weekly intervals if the participant is not known to be sterile.

#### **6.2.5 Clinical management following an adverse event**

Events will be reviewed by clinical personnel who will assess, treat and follow-up the event as appropriate, ideally to resolution, or refer if appropriate, for specialist opinion. Additional assessments to those in the schedule may be performed if clinically indicated following an adverse event, and for solicited events such as genital discomfort. Referral and treatment will be determined by the standard of care available in the local Public Health System and these will be detailed in the site specific operating procedures.

Events may occur in the male partners that are reported to the clinical team. A clinical service will be provided to triage these events. Events will be managed either by the clinic team or by appropriate referral. A description of the event will be recorded.

#### **6.2.6 Following an HIV positive result**

Participants who are HIV positive at screening will be counselled by an experienced counsellor, and informed about local care and support services that are available, and how to contact these services. The counsellor will offer to facilitate the referral. Participants may return for further counselling should they wish to do so.

Participants who become infected during the study, including those who are determined to be HIV positive at enrolment by the central reference laboratory, will be provided with the same counselling and advice. They will be allowed to continue with gel and study visits if necessary to protect their HIV status becoming known to the community, and to allow the further collection of safety data in these participants.

#### **6.2.7 Following pregnancy**

Participants who are found to be pregnant at gel follow-up visits will be referred for clinical examination and HIV testing. They will be advised to interrupt gel whilst they remain pregnant, and no further gel supplies will be dispensed until a negative pregnancy test has been obtained and 6 weeks has elapsed after vaginal delivery or 3 weeks after induced/spontaneous abortion or at clinician's discretion after an ectopic pregnancy. They will also have a speculum examination to exclude grade 3 epithelial lesions. Closure of the os cannot be reliably determined by digital or speculum examination in a multiparous woman, and the aforementioned criteria are in place to provide confidence that the cervical os is physiologically closed. They will be asked to continue to attend for the clinical follow-up visits whilst pregnant and every effort will be made by the study staff to find out and record the outcome of pregnancy. Pregnant participants will be referred for local ante-natal care according to site specific procedures.

If a subsequent negative pregnancy test is obtained during the follow-up period participants will be referred for clinical examination and have buffy coat and serum specimens taken and stored in order to ascertain their HIV status according to the MDP algorithm should this be necessary.

#### **6.2.8 Follow up for participants randomised to 2% PRO 2000/5 gel**

Participants who discontinue 2% PRO 2000/5 gel will be asked to continue to attend for the long (clinical) follow-up visits until the end of their visit schedule.

### **6.3 Qualitative data collection procedures**

Accurate data on the frequency of sex, gel and condom use, anal sex, douching and the insertion of various products into the vagina are critical to the interpretation of the result of the trial. These will be even more essential if the gel is shown to work in some sites, and not others, as occurred in the recent COL1492 trial of N-9 [11]. The data gathered by the social science team may also be needed to inform subgroup analyses.

It is well known that data on sensitive topics based on self-reporting are often inaccurate. In order to increase accuracy, a multi-method data collection strategy, involving triangulation of sexual behaviour data from case record forms (which will be collected in all participants), in-depth interviews and coital diaries (which will be collected in a sub-set of participants), will be used. Although these instruments all rely on self-reporting, they can provide reliable estimates if they are carried out and triangulated appropriately.

### **6.3.1 Coital diaries**

A random sub-sample of participants from each site will be selected and asked to keep coital diaries for four weeks prior to each long clinic visit. The intention is to do this in a minimum of 100 participants at each site. The diaries were piloted during the Feasibility Studies and Pilot Study. They will be pictorial and will include spaces for the participant to record daily whether she had vaginal or anal sex, whether she used a condom and/or gel, and whether she inserted any other vaginal products.

### **6.3.2 In-depth interviews**

Once the diaries are completed the same sub sample of female participants (and a smaller number of male partners who are aware of their participation in the trial) will be asked to participate in a recorded in-depth interview. Verbal consent will be obtained at the start of the interview. The interview is aimed at gaining more detailed information on sexual behaviour, assessing patterns of disclosure to their partner(s), and assessing the informed consent process. These interviews will contribute to:

- ◆ assessing the reliability and validity of the data in the CRF on the frequency of sex, gel and condom use, anal sex, douching and the insertion of various products into the vagina. At the end of the interviews the diary entries will be discussed and any discrepancies with the interview examined. Data from the CRF, coital diaries and in-depth interviews will be triangulated;
- ◆ understanding patterns of disclosure: why participants inform or do not inform their partners that they are using gel, and the process in which they negotiate gel use with their partners. This will also be explored from the men's perspective in the interviews with men; and
- ◆ assessing the informed consent procedure and checking whether the participants have understood key aspects of the trial.

In addition, attempts will be made to trace participants who default in order to interview them to find out the reasons for default. This will contribute to improving follow up.

### **6.3.3 Focus group discussions (FGDs)**

Two sets of FGDs will be carried out regularly throughout the trial at each site. One set will be with community members not involved in the trial and will examine community perceptions and perspectives of the trial and the products, opinions circulated in the community about the trial, the products or the procedures that may negatively impact on adherence or acceptability etc. The second set of FGDs will focus on similar issues among the participants. This more general data will complement the individual in-depth interviews and coital diaries.

### **6.3.4 Ethnography**

The social science team will also carry out ethnographic research in the study communities. This will enable them to collect more informal and observational data on the wider social context in which the trial is situated.

## 6.4 Laboratory procedures

### 6.4.1 Site laboratories

Testing for HIV, NG, CT, syphilis, HSV and TV will be performed at Site Laboratories according to procedures that have been, and continue to be, subject to internal quality control. Routine laboratory parameters will be tested at local laboratories in Durban, Johannesburg and Masaka.

### 6.4.2 Central laboratory

The appointed Central Reference Laboratory, Contract Laboratory Services (CLS), will evaluate the HIV testing assays, procedures, algorithms and quality control mechanisms in place in the Site Laboratories; provide training in Good Laboratory Practice where required; and organise proficiency testing exercises. The Central Reference Laboratory will also confirm all HIV sero-conversion specimens, and will re-test a random 5% subset of negative specimens and 10% subset of screened excluded positive specimens from all Site Laboratories. All participants demonstrating HSV2 seroconversion during the study will have this confirmed at CLS.

### 6.4.3 Quality Control and Quality Assurance

SOPs for internal quality control for NG, CT, Syphilis, HSV and TV and external quality control for NG, CT and syphilis will be implemented at all Site Laboratories. In addition, there will be similar protocols for the haematology, biochemistry and coagulation assessments conducted in Durban, Johannesburg and Masaka.

## 6.5 Data management procedures

### 6.5.1 CRFs and Clinical Folders

CRFs will be printed local to the sites (wherever possible) in duplicate (or triplicate if necessary). The CRF will provide the majority of source data for the trial. Study personnel authorised to do so by the PI will enter information directly onto the CRFs, sign and date the form on completion, and separate the copies. Clinical Folders will be stored in the location most likely to guarantee security, confidentiality and ability to retrieve individual records. This need not be the clinical area, but only staff that see participants, or organise the clinics, will be able to access the Clinical Folders.

Documentation of AEs that present to the study clinic will be reported on the CRF, which is designed to capture all the necessary source information. If study personnel make additional notes, these will be written on MDP headed paper and will be kept in the Clinical Folder. Documentation of AEs that present outside the study clinic in the public health system is recognised to be sparse but study personnel will make every effort to obtain confirmatory evidence for events that have resulted in investigations and/or treatment being dispensed, or that are the outcome of a pregnancy following conception during gel administration. This information will be filed in the clinical folders. Confirmatory evidence of cause of death will be considered essential in the event of a death.

The following data should be verifiable from source documents other than the CRF:

- signed or thumbprint consent
- dates that gel was dispensed
- reported laboratory results

In order to maintain participant confidentiality, a file with the HIV results in it may be kept separately from the clinic folders.

In-depth interviews will be transcribed, translated and entered as appropriate into a separate database to the CRF data, for analysis using an appropriate qualitative statistical software package. In-depth interview and focus group discussion recordings will be kept securely by the lead social scientist at each site. A copy may be sent to the MDP social science co-ordinator and copies will be made available for monitoring if necessary.

### **6.5.2 Data entry and checking at sites**

A common database will be in place at each site that will incorporate a process to validate data entry. Changes to the database that are made as a result of the validation process will be tracked using electronic systems. Once the validation process is complete, the CRF will be stored in the Data Folder unique to each participant. Consistency and range checks including flagging of eligibility queries will be part of the data entry/verification process at all sites to assist in the data being entered accurately and in the generation of queries for the study personnel that collected the data. These processes will be the responsibility of a site data manager.

Reports of eligibility, adverse events, laboratory events and compliance with gel will be generated from the database for the attention of study personnel as part of the internal quality control systems by the site data manager.

The aim will be to enter data into the database, together with verification, within 2 weeks of the visit, or within 2 weeks of receipt of laboratory results if these are transcribed onto the CRF.

### **6.5.3 Data management and monitoring at CTU**

CTU will receive the CRF data from the sites electronically twice a month. Copies of these site data-files will be kept as a dated record of the site database until the next copy is sent. Data will be reviewed by site for consistency and to ensure that eligibility criteria are satisfied. A review of adverse events and sexual behaviour data including adherence will be conducted. If there are queries, these will be communicated to the site concerned by email, fax or telephone and changes made to the central data-files created by CTU if indicated.

Queries raised by CTU will be handled at the sites by the Data Management personnel.

An electronic record of the central data-files will be kept, together with copies of the programmes used to manipulate the data and create tables. Copies of queries raised and the responses will act as documentation of any differences between the central data-files and the site data-files.

Typed and translated transcripts of in-depth interviews and focus group discussions will also be sent to the social science co-ordinator, along with the databases where the qualitative data is stored.

All electronic files held at CTU are backed-up daily in the network, and weekly off site according to CTU procedures.

Staff at CTU will be responsible for the preparation of the tables for the monthly Clinical Trial Management Group (see 8.2) conference calls, as well as tables for the IDMC and TSC, and the final analysis. These tables will be prepared under the supervision of the Trial Statistician.

### **6.5.4 Monitoring at site visits**

Staff authorised and trained by CTU will visit the sites before, during and after the trial in order to monitor compliance with ICH GCP. This will involve ensuring that all AEs are reported on the CRF, and checking that the site data management systems are functioning satisfactorily. The clinical investigators and participants, by giving consent, agree that the CTU staff, or personnel authorised by CTU to do so for the purposes of monitoring, may consult and/or copy source records (clinical notes and laboratory values) within the limitations of the host country's Data Protection Law. Such information will be treated as strictly confidential and will not be identifiable by name. The monitoring will adhere to ICH GCP guidelines.

The site file containing the essential documents, gel dispensing logs, central pharmacy records and returns and temperature logs in the gel storage facilities will also be monitored at

visits to the clinical sites.

## 6.6 Expedited reporting procedures

### 6.6.1 Expedited reporting to the competent authorities

The MDP Clinical Trial Managers, or their deputy, at the MRC CTU will confirm receipt of the notification with the site, and arrange for urgent review of the case by one of the medical experts, Charles Lacey or Sheena McCormack and an independent clinician who is a member of the Trial Steering Committee within 2 working days. Should the case be considered reportable, a template report will be prepared by Charles Lacey, Sheena McCormack or their deputies and filed with the relevant Regulatory Authorities, and with Indevus Pharmaceuticals, Inc. on the day the decision is taken.

Staff at CTU will be responsible for informing the IDMC and TSC as well as the clinical investigators at the other sites of the event. Responsibility for forwarding reports to the Research Ethics Committees that have reviewed the protocol will lie with the named investigators who prepared the submission, and will be in accordance with the requirements of each committee.

### 6.6.2 Expedited reporting by site to CTU (see also section 5.2.4 and 5.2.5)

Serious adverse events will be defined according to ICH GCP guidelines as those resulting in:

- death,
- an immediate threat to life,
- in-patient hospitalisation or prolonging existing hospitalisation (hospitalisation for elective treatment of a pre-existing condition is not included),
- results in persistent or significant disability or incapacity,
- is a congenital anomaly (ie, the outcome of pregnancy involving a participant), or
- is any other important medical condition (see section 5.2.4).

For PRO 2000/5 Gel (P) and the placebo gel there are no expected SAEs with reference to the existing pre-clinical and clinical information available.

SAEs considered by clinical personnel to be possibly, probably or definitely related should be discussed with the site PI, or their deputy, and reported to the MRC CTU within two working days of the site becoming aware of the event fulfilling the criteria above. This can be done by telephone, fax or email. The minimum criteria required in reporting a SAE are the participant identifiers (trial number and second identifier), reporting source (name of Investigator and site), and why the adverse event is identifiable as serious. Receipt of the report will be acknowledged by email. Further information should be submitted to CTU as and when it becomes available.

## The adverse event reporting fax number is 00 44 207 670 4689

Examples of important medical conditions and SAEs that would require expedited reporting include but are not limited to:

- Hospitalisation, suicide or homicide resulting from social harm linked to gel or participation in the trial
- Severe vaginal oedema with sloughing of the epithelia
- Non-menstrual bleeding that is either profuse or is heavy for more than 4 days
- Cervical or other gynaecological cancers
- Miscarriages

Examples of SAEs that do **NOT** require expedited reporting include but are not limited to:

- Hospitalisation for scheduled surgery unrelated to gel
- Hospitalisation planned for pre-existing conditions which would be considered 'unlikely to be' or 'unrelated' to gel

- Orthopaedic or traumatic injuries, or accidents requiring hospitalisation, suicide or homicide
- Non-genital infectious diseases requiring hospitalisation other than HIV sero-conversion
- SAEs occurring more than 30 days after gel was last administered or having appeared before randomisation without any aggravation after gel

## 6.7 Interruption and discontinuation of gel, and withdrawal from the trial

Interruption describes a temporary cessation of gel, and discontinuation a permanent cessation.

### 6.7.1 Interruption and Discontinuation of gel

Study gel use by a participant will be interrupted in the presence of any of the following:

- Profuse, non-menstrual vaginal bleeding requiring transfusion, hospitalisation or bed rest for more than 24 hours for which there is no reasonable alternative explanation
- a grade 3 or 4 clinical or laboratory event confirmed on examination or repeat testing respectively and thought to be **probably or definitely related** to gel

Interruption of the study gel due to other adverse events considered possibly, probably or definitely related to study product is at the discretion of clinical personnel, but would be advisable in the event of a grade 3 or 4 clinical or laboratory event confirmed on examination or repeat testing respectively and thought to be **possibly** related to gel.

Study gel may be recommenced after interruption following an adverse event at the discretion of the clinical investigator. If the event recurs, and is grade 3 or 4, then study gel should be discontinued.

Other reasons for interruption or discontinuation of gel include:

- participant's desire to stop gel
- pregnancy (see 6.7.2) below

### 6.7.2 Interruption of gel due to pregnancy

Gel must be interrupted in participants who are pregnant. At the time of interruption, participants will be referred for a clinical examination, and for collection of all parameters listed at the final visit. Study gel may be resumed following interruption for pregnancy once a negative pregnancy test has been obtained and closure of the os confirmed during a genital examination.

Every effort will be made to obtain documentary evidence of the outcome of pregnancy.

### 6.7.3 Follow-up after discontinuation of gel

Participants who discontinue product either by choice or following advice from clinical personnel will be referred for a clinical examination, and for collection of all parameters listed at the final visit and NG and CT at the time of discontinuation. Participants should continue to attend the 12 weekly visits up to and including the final visit, when HIV and syphilis will be repeated.

### 6.7.4 Withdrawal from the trial

Withdrawal means discontinuation of study visits and gel, and the reasons for this should be recorded in the CRF. Examples for study withdrawal include:

- participant desire to stop participating in the trial
- investigator concerns that continuing visits is not in the best interest of the participant
- Trial Steering Committee decision to discontinue the trial in all participants

### 6.7.5 Unblinding individual participants

Whilst it is not anticipated that unblinding will be necessary, a procedure will be in place for unblinding through the MRC CTU. If a clinical investigator associated with the study or

responsible for the care of a participant considers that knowing the allocation is essential for medical management then they should contact the Physician at CTU or her deputy (details provided on the answer phone message out of office hours) by calling:

**+44 207 670 4793/4896**

The Physician or deputy will discuss the case with the Clinical Investigator and if it is agreed to be essential contact the Trial Statistician or their deputy who will access the copy of the randomisation list, unblind the allocation and contact a clinician at the site who is not involved in the day to day running of the study, and not a member of the research team. A CRF should be completed with the reasons for unblinding and stored in the Clinical Folder, but the allocation information should not be recorded in any of the trial documentation at the site. A record of the event will be kept at CTU but MDP staff at CTU will remain blind to the allocation. The IDMC and TSCs will be informed at their next scheduled meetings.

The details for unblinding the trial data are described in section 7.3.

## **6.8 Administrative procedures**

### **6.8.1 Regulatory and ethical approval and requirements**

This protocol will be reviewed by the national competent or equivalent authority, and research ethics committee appropriate to each site. MRC CTU will co-ordinate the trial sites' activities to obtain all regulatory and ethics committee approvals, with the assistance of Indevus Pharmaceuticals, Inc. The site PI, or their deputy, will be primarily responsible for the appropriate ethics committee (EC) application. Indevus Pharmaceuticals, Inc. will submit the protocol to the FDA (IND 56, 962).

A copy of the dated approval letter from the competent or equivalent authority and local/national EC stating the name of the protocol and date of the version must be provided to Indevus Pharmaceuticals, Inc. before study materials can be shipped to that centre.

MRC CTU will coordinate safety reports, including expedited reporting, to the competent or equivalent authority in accordance with each authority's requirements. Reports will be filed with Indevus Pharmaceuticals, Inc. for onward notification to the US Food and Drug Administration, as appropriate.

The PI, or their authorised deputy, is responsible for reporting progress of the trial and safety issues to their ECs in accordance with local requirements and practices. MRC CTU will assist in the preparation of these reports.

CRFs, clinical notes and administrative documentation should be kept by each trial site in a secure location (for example, locked filing cabinets) and held for 15 years after the end of the trial. All data should be accessible for audit during this period to the competent or equivalent authorities, Indevus Pharmaceuticals, Inc. and MRC CTU with suitable notice, and may be subject to an audit by the competent authorities as part of the licensing process if a marketing authorisation is applied for.

### **6.8.2 Finance**

The trial funds are administered through the UK MRC to participating institutions on a quarterly basis. Each trial site will permit MRC to visit (on reasonable notice) and inspect for financial audit/monitoring purposes.

Projected estimates and cost statements will be submitted to the MRC CTU on a quarterly basis. The finances are overseen by the PMB, (see section 8.5) of the Microbicides Development Programme, and a budget for each trial site for the duration of the trial will be set by the PMB before the trial commences. The procedures for virement of funds and for exceeding budget limits are detailed in the agreements between MRC and the sites. Any changes beyond these limits in institutional funding must be approved by PMB.

### **6.8.3 Publication**

It is intended that the trial results will be published in the appropriate scientific literature. The Programme Management Board (PMB) has responsibility for any publication of trial data and no trial site (or Indevus Pharmaceuticals, Inc.) will be permitted to publish, or present publicly, any of the trial data without the advance written permission of the PMB. The procedure for obtaining such permission will be to submit draft abstracts/papers to the PMB for advance approval not less than 30 days prior to submission. Drafts originating from the trial sites will be circulated by the PMB to Indevus Pharmaceuticals, Inc. for comments (such comments are to be submitted within 2 weeks to the PMB). The PMB retains the right to require amendment to any draft abstract/paper, to refuse permission for publication, or to require delay in submission for publication. The PMB will communicate its decision on publication within 30 days of receipt of the draft abstract/paper.

#### 6.8.4 Data Ownership

The data generated in this study will belong to the UK MRC. At the end of the study, once the central data-files and programmes are finalised and the report agreed by the TSC, the data will be made available to Indevus Pharmaceuticals, Inc. in an agreed format. Should data be required by Indevus Pharmaceuticals, Inc. at an earlier point for submission to the regulatory authorities, then a request should be made to the MRC CTU, such a request to be passed on to the TSC. Further detail on the ownership of trial data and agreed provisions for access to data by Indevus Pharmaceuticals, Inc. and the trial sites is contained in the written agreements between each of them and MRC.

### 7.0 Statistical considerations

#### 7.1 Sample size for efficacy endpoint

The primary efficacy endpoint was originally set at 40 weeks in order to maximise follow-up and adherence rates. Examination of the accruing trial data indicated that retention and adherence were not decreasing between week 40 and week 52 by such an amount that would offset the gain in power from using all the data up to week 52. It was therefore agreed at the Trial Steering Committee on 8<sup>th</sup> May 2008, that in order to maximise the power of the study, the primary endpoint would be shifted to week 52. The week 40 endpoint would therefore become secondary.

For the comparison between 0.5% PRO 2000/5 gel versus placebo, it is estimated that there would be an accumulated 2640 woman years of data at 52 weeks. This assumes a total of 3300 women will be enrolled to each group with 20% loss for follow-up.

Data on expected incidence per 100 woman years within the study populations were limited prior to the start of the study. Available estimates indicated that in the proposed study sites it ranged from 3.5 to 12.6 per 100 woman years. At the time of the decision to shift the primary endpoint to week 52, the overall HIV incidence estimate was 4.6 per 100 women years.

The table below gives the power of the study to demonstrate a significant difference in HIV-incidence rates after 52 weeks of follow-up, with an estimated 2640 woman years of data, at the 5% level between the 0.5% PRO 2000/5 arm and the placebo arm for a range of HIV-incidence rates and treatment effect sizes.

Incidence per 100 woman years	Percentage power for different effect sizes		
	0.45	0.4	0.35
4.0	96	90	80
4.5	98	93	85
5.0	99	95	88
5.5	99	97	91

Thus, given an HIV-incidence of 4.5 per 100 women years in the placebo arm the power to detect a significant benefit ranges from 85% to 98% depending on the effect size (percentage

reduction in HIV-infection rate). For a higher incidence of, say 5 per 100 woman years, the power ranges from 88% to 99%.

## 7.2 Sample size for secondary and safety endpoints

After 40 weeks follow-up based on an expected 2030 woman years of data per group the study has 86% power to detect a 40% reduction if the HIV incidence in the placebo arm is 4.5 per 100 woman years.

After 24 weeks follow-up based on an expected 1523 woman years of data per group the study has 75% power to detect a 40% reduction if the HIV incidence in the placebo arm is 4.5 per 100 woman years.

Data from the feasibility studies indicate levels of prevalence of HSV-2 varying from 50% to 85% in the trial populations. Incidence estimates are limited but data from two sites suggest this may be approximately 10 per 100 woman years, although this is likely to be age dependent. Assuming that 75% of the study population are already infected at enrolment and that the incidence is 10 per 100 woman years then given approximately 660 per group of evaluable women years of observation at 52 weeks, the trial would have 90% power to demonstrate a 50% reduction in HSV-2 incidence, 71% power for a 40% reduction and 58% for a 35% reduction.

To test the hypothesis that one or other of the gels is effective against CT or NG it is proposed to test endo-cervical material collected during the genital examination by NAAs on all participants at week 24 when a total of approximately 5000 women (80% of those randomised to the 0.5% and placebo arms, could be expected to be seen.)

The following table gives the power to detect a decrease in prevalence of CT infection from 6% to 3% or 4% (a 50% or 33% reduction) and of NG infection from 3% to 1.5% or 2% (a 50% or 33% reduction) based on sample sizes from 2000 to 3000 per arm, given a Type I error of 5%.

Number of participants per arm	Power to detect decrease in prevalence from:			
	6% to 3%	6% to 4%	3% to 1.5%	3% to 2%
3000	>99%	93%	97%	67%
2500	>99%	89%	94%	59%
2000	>99%	80%	88%	49%

Assuming over 3000 participants are randomised to receive gel in each arm of the study there will be considerable power to detect small increases in rare adverse events, for example 97% power to detect an increase from 1.5% to 3%. There would be 80% power to detect an increase from 0.5% to 1.2% or 0.1% to 0.55%.

The routine laboratory parameter safety data on 1490 women (496 per arm) will enable detection of an increase in abnormalities reported from 5->10%, or 2->6% in abnormalities with 80% power. Power will be greater to detect differences in the distribution of continuous variables such as liver transaminase (LFTs).

## 7.3 Randomisation scheme and maintenance of blinding

Randomisation will be in the ratio of 1:1:1 for active 0.5%:active 2%:placebo. This will be stratified only by site, with the possible exception of the sero-discordant couple cohort in Masaka, which may be stratified by other factors such as age and condom use.

The randomisation code will be prepared at the MRC CTU, under the supervision of the Trial Statistician, by an individual that is not involved in the day to day running of MDP. The randomisation list which links the trial number unique to each participant to one of the three

trial products will also be prepared by this individual at the MRC CTU under the supervision of the Trial Statistician.

A file of the randomisation list in which the study products are identified by 1, 2 or 3 instead of product name will be kept in an electronically secure location at CTU, with off site back-up. A hard copy of the link between this number and the product name will be put in two sealed envelopes, signed and dated by the individual that prepared the randomisation list. One of these will be kept in a secure location at CTU and one off-site. No MDP staff other than the Trial Statistician, no personnel from Indevus, and no member of the TSC will have access to the list or code until the analyses are complete and all decisions about relationship of events to study product final. The duty programmer/statistician for CTU will be able to access the list and code for the purposes of unblinding in the unlikely event that this is required (see section 6) according to CTU trial specific procedures. The opened envelope will be signed and dated and retained and the code put into a fresh envelope, signed and dated across the seal.

Separate lists linking the trial number to the gel allocation will be provided to the authorised personnel at the sites responsible for monitoring gel supplies.

Following the IDMC recommendation in February 2008 to halt recruitment in the 2% PRO 2000/5 arm, trial staff will be unblinded to this allocation from this time. However the study blind for the primary comparison 0.5% PRO 2000/5 versus placebo, will be maintained and randomisation to these groups will continue in the ratio of 1:1.

#### **7.4 Main analysis**

The main efficacy analysis will include all participants that were randomised, except those determined to be HIV infected at enrolment. An algorithm will be in place to identify participants who were enrolled, but are then found to be infected at the enrolment visit. Participants who discontinue gel due to an adverse event, or because they wanted to, will contribute person-years to this main 'intention to treat' analysis for the duration of their follow-up, up to and including the final visit, provided that this occurs within 6 weeks of their individual schedule according to the date of randomisation. Participants who interrupt gel because of pregnancy and who never resume gel use will contribute person-years up to and including the visit at which pregnancy was diagnosed. Participants who are found to be pregnant and who subsequently have a negative pregnancy test and resume gel, will contribute person-years up to and including the visit at which the pregnancy was diagnosed, and from the time of the negative pregnancy test to the end of their follow up period provided they are confirmed to be HIV negative at the time they resume gel use. Participants who are lost to follow-up will contribute person-years up to their last clinical follow-up. HIV incidence rates will be calculated for each allocation and the effect on HIV incidence will be determined using Cox Proportional Hazards models stratified by site. Product efficacy will be expressed as 1 minus the hazard ratio for 0.5% and 2% PRO 2000/5 when compared to placebo.

All participants that were randomised will be included in the main safety analysis, including those who are determined to be HIV infected at enrolment, those who become HIV infected during the trial, although these two groups will be analysed separately. A secondary safety analysis will exclude the time when pregnant women were taken off gel. Participants lost to follow-up will contribute up to the last point that the data to be analysed were collected, for example the last clinical follow-up visit for examination data. Cross-tabulations of the primary and secondary safety outcome measures by allocation will be prepared.

A dummy run of the analysis tables for the IDMC will be prepared by a statistician familiar with the day to day running of the trial under the supervision of the Trial Statistician, with participants grouped according to a random number in the statistical programmes. In preparation for the IDMC meetings, the Trial Statistician will re-run the programmes linking the participant number to the gel identifier. The Trial Statistician will take the sealed envelope containing the code when presenting the tables to the IDMC, in order to unblind the data at the committee's request.

## 7.5 Interim analysis

There will be one planned interim analysis, which will take place after accrual of half the expected person-years of follow-up or earlier if rates in the control arm are higher than expected.

## 7.6 Subsidiary analyses

There will be an efficacy analysis for the primary outcome measure, HIV, that includes participants who discontinued gel due to pregnancy beyond the date they discontinued, as well as participants considered lost to follow-up at the final visit who reappear beyond the window period (6 weeks) who have agreed to be tested for HIV.

All participants will be included in the analyses of NG and CT. For all these secondary outcome measures, the 'intention to treat' analysis will include participants that discontinue due to an adverse event or because they wish to, up to and including week 24. Participants that interrupt due to pregnancy will contribute if the interruption is not coincident with week 24 procedures. 'On treatment' analyses will be up to the point of discontinuation of gel for whatever reason.

Although it will have very limited power, a separate exploratory analysis will be performed of the effect of the gel in preventing HIV-infection in uninfected men in Masaka whose spouse or main partner is infected.

An analytical plan will be finalised and approved by the TSC and IDMC before the data are unblinded to the Investigators. The plan will detail any subgroup analyses of the primary endpoints to be performed. Examples of variables that will be considered to define subgroups include, but are not limited to, site, age, behavioural and adherence characteristics.

## 8.0 Management of the trial

### 8.1 Site Operational Group

The day to day management of the trial at each site will be overseen by this group which will meet on a regular basis (at least once a fortnight) to review progress, eligibility, clinical, follow-up, data management and logistic queries. CTU staff will join these meetings by telephone at the request of the site coordinator. Notes of these meetings will be kept, and any issues that are relevant to all sites brought to the attention of the Clinical Trial Management Group by the site coordinator (see below).

### 8.2 Trial Management Group

The Trial Working Group (see introduction) will become the Trial Management Group, which will communicate by teleconference every 4 weeks. These calls may be held more or less frequently as determined by the Group. The remit of this group will be to review the tables of accrual and follow-up as well as all grade 3 and 4 adverse events by site, and to discuss any issues that have arisen related to eligibility, clinical management, follow-up and data management.

### 8.3 Trial Steering Committee

This committee will provide oversight of the trial and will include independent members including the chair. The TSC will meet approximately twice a year to review the progress of the trial, eligibility issues, all grade 3 and 4 adverse events, and HIV sero-conversions, and to consider any recommendations from the IDMC. Any amendments to the protocol which have a scientific implication should first be submitted to this committee. The trial may be terminated by the TSC for any reason, including the recommendation of the IDMC. CTU will coordinate these meetings.

## 8.4 Independent Data Monitoring Committee

### 8.4.1 Safety reviews

The IDMC will review the safety data every 4-6 months, including the possibility that one of the active gels may be enhancing rather than reducing HIV sero-incidence. The IDMC will also review incidence rates in the different study arms and advise the Trial Steering Committee on any revision of the sample size required during the course of the trial. Meetings will be coordinated by CTU, and the Trial Statistician will supervise and prepare the tables in the format approved by the IDMC.

#### **8.4.2 Interim analysis review**

The IDMC will advise the TSC that the trial should be stopped if in their view:

- the randomised comparison has provided proof beyond reasonable doubt that one of the trial interventions is clearly indicated or clearly contra-indicated in terms of a net difference in sero-incidence or adverse events or
- there is proof beyond reasonable doubt from other studies to influence clinicians in their management of participants that is incompatible with continuing with this placebo-controlled comparison.

### **8.5 Programme Management Board and Programme Liaison Group (PLG)**

The PMB will meet at least twice a year to review progress of the scientific programme including administrative and financial aspects. The PLG is the operational sub-group of the PMB, and this will have contact through conference calls every two months with the site and project PIs. The TSC will report progress of the trial to the PMB by circulating the minutes of the TSC meetings.

## **9.0 Participant considerations**

### **9.1 Confidentiality**

Medical confidentiality will be preserved according to the relevant national data protection laws, or in the absence of these according to ICH GCP. Any notes with personal identifiers will only be accessible to staff that see participants (counsellors, clinical personnel and interviewers), those responsible for coordinating visits, and study personnel authorised by the PI.

### **9.2 Standard of clinical care to be offered to participants**

#### **9.2.1 Framework of clinical care**

A framework for the standard of clinical care to be offered to participants in an HIV prevention trial should include the following:

- Diagnosis and treatment of sexually transmitted infections
- Counselling prior to and after HIV testing
- Counselling support of those infected
- Clinical assessment of HIV status and for medical conditions requiring treatment/referral
- Prophylaxis for opportunistic infections
- CD4 count
- Anti-retroviral therapy
- Cervical cytology and/or clinical screening for lesions requiring referral for gynaecological opinion

Using this framework, MDP Investigators have reviewed what is available within the public health system local to each site, and considered which services should be mandatory and which services MDP might aspire to provide for:

- Women that are screened for the study
- Women that enrol in the study, both during their participation and after their individual participation but during the period that the research services are still available in the site

#### **9.2.2 Principles**

Advances in the treatment of HIV have been considerable over the last decade and yet coverage in less economically developed countries (LEDCs) remains very low. As stated in

the introduction to this protocol, services for care and treatment of asymptomatic HIV infection has become increasingly accessible in the public health system in the majority of study sites. National and international efforts to improve this situation are increasing, but inevitably services will develop at different rates in each country participating in this multi-centre study. Services for other conditions for which detection and treatment have been established for several decades in more developed countries, such as cervical cancer, remain variable in LEDCs, and frequently treatment is still only available in large urban centres. In view of this, the MDP Investigators have reached consensus on the principles which underlie the processes to be followed in developing standard of care documentation for each country. These principles are derived from the UK MRC guidelines of 17<sup>th</sup> July 2002 which are available on the website ([www.mrc.ac.uk](http://www.mrc.ac.uk)). Principles relevant to this trial include:

### **9.2.3 Appropriateness**

There is an inevitable disparity between what is in government policy and what is readily accessible, as has already been highlighted with regard to VCT services. The standard of care should be appropriate to the local population from which the trial participants are drawn.

### **9.2.4 Flexibility**

It is impossible to adopt a uniform approach for the study and indeed there are likely to be challenges within South Africa in implementing the same standard of care in all three sites, given the differences between the urban and rural settings. The MDP investigators respect these differences and recognise the need for site-specific policies and procedures. Further detail is available in the standard operating procedures at each site.

## **9.3 Reimbursements**

Participants will be reimbursed for their time, travel and inconvenience according to site specific operating procedures. The amount will be specified in the local information sheets.

## **9.4 Responsibility for harm**

### **9.4.1 Due to product**

Indevus Pharmaceuticals, Inc. will assume liability for product-related harm in accordance with written agreements between MRC and Indevus Pharmaceuticals, Inc.

### **9.4.2 Due to clinical negligence**

Each site PI shall be responsible for ensuring that all clinical staff engaged in the trial at that trial site are insured in respect of negligent harm to a trial participant, either under insurance taken out by the trial site or the trial site's parent institution in respect of employee negligence; or through a personal insurance scheme. Each trial site or its parent institution shall provide an indemnity to the MRC in respect of such liability for clinical negligence.

### **9.4.3 Due to participation in the trial not related to product or clinical negligence**

The UK MRC, as the sponsor and party responsible for the clinical trial agreement, will be the first point of contact for resolving any issues of responsibility for harm not related to the product or clinical negligence.

## 10.0 References

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2. J. Kreiss, E. Ngugi, K. Holmes, et al. Efficacy of nonoxynol 9 contraceptive sponge use in preventing heterosexual acquisition of HIV in Nairobi prostitutes. *JAMA* 268 (4):477-482, 1992.
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## APPENDIX 1 Product details

### Sample Carton Label

**MDP 301**

**Contents:** 10 x 2-gram Prefilled Applicators  
of MDP 301 Study Gel.

For Vaginal Use Only.  
Use as directed – Refer to information sheet provided.

Store at Room Temperature (15° - 30° C)  
Keep out of reach of children.

May contain sorbic acid, sodium benzoate  
and/or parabens as preservatives.

**CAUTION:** New Drug – Limited by United States law to  
investigational use. Not for sale.

Indevus Pharmaceuticals, Inc., 33 Hayden Avenue, Lexington, MA 02421-7918,  
USA  
Manufactured by DPT Laboratories, Ltd., San Antonio, Texas 78215, USA



**Appendix 2: Grading of solicited clinical, laboratory and other adverse events (23<sup>rd</sup> Dec 2004)**

This is a guide and subject to modifications during the trial to accommodate updates, which will be noted in the site and master files.

<b>GRADE</b>	<b>1</b>	<b>2</b>	<b>3*</b>	<b>4</b>
	<b>Mild</b>	<b>Moderate</b>	<b>Severe*</b>	<b>Life-threatening</b>
<b>Genital discomfort</b>	Easily tolerated	Aware at most times of symptoms, but not preventing daily activities. Able to control symptoms with medication from pharmacies or traditional remedies.	Unable to control symptoms such that cannot undertake essential daily activities.	Hospitalisation for pain control
<b>Non-menstrual bleeding</b>	Light (spotting or brown discharge) $\leq 7$ days	Light (spotting or brown discharge) $> 7$ days Or Heavy (bleeding like menses) $\leq 4$ days	Heavy (bleeding like menses) $> 4$ days Or Profuse of any duration	Hospitalisation for transfusion
<b>Epithelial disruption (sores or ulcers)</b>	$\leq 1$ swab-tip*	$> 1 \leq 4$ swab-tips*	$> 4$ swab-tips*	Hospitalisation
<b>Erythema (redness)</b>	Local/diffuse mild redness Or Local marked redness	Diffuse marked redness with symptoms that are easily tolerated	Diffuse marked redness with Grade 2 or above discomfort	Hospitalisation
<b>Oedema</b>		Oedema without sloughing of the epithelial cells	Oedema with sloughing of the epithelial cells	

\*swab-tip is 5 x 10mm

<b>LABORATORY EVENTS</b>				
<b>PARAMETER</b>	<b>GRADE 1 MILD</b>	<b>GRADE 2 MODERATE</b>	<b>GRADE 3 SEVERE</b>	<b>GRADE 4 POTENTIALLY LIFE-THREATENING</b>
<b>HEMATOLOGY</b>				
**Units for absolute counts will be measured X 10 <sup>9</sup> /L in Durban and Johannesburg, and X 10 <sup>3</sup> /ul in Uganda.				
ULN = Upper Limits of Normal				
Hemoglobin (HIV negative)	10.0 g/dL – 10.9 g/dL <b>OR</b> any decrease 2.5 – 3.4 g/dL	9.0 g/dL – 9.9 g/dL <b>OR</b> any decrease 3.5 – 4.4 g/dL	7.0 g/dL – 8.9 g/dL <b>OR</b> any decrease ≥ 4.5 g/dL	< 7.0 g/dL
WBC elevated**	13.0 – 14.99 X 10 <sup>9</sup> /L <i>13.0 – 14.99 X 10<sup>3</sup>/ul</i>	15.0 – 19.99 X 10 <sup>9</sup> /L <i>15.0 – 19.99 X 10<sup>3</sup>/ul</i>	20.0 – 24.99 X 10 <sup>9</sup> /L <i>20.0 – 24.99 X 10<sup>3</sup>/ul</i>	>25 X 10 <sup>9</sup> /L >25 X 10 <sup>3</sup> /ul
WBC decreased**	2.00 – 2.50 X 10 <sup>9</sup> /L <i>2.00 – 2.50 X 10<sup>3</sup>/ul</i>	1.50 – 1.99 X 10 <sup>9</sup> /L <i>1.50 – 1.99 X 10<sup>3</sup>/ul</i>	1.00 – 1.49 X 10 <sup>9</sup> /L <i>1.00 – 1.49 X 10<sup>3</sup>/ul</i>	< 1.00 X 10 <sup>9</sup> /L < 100 X 10 <sup>3</sup> /ul
Absolute Neutrophil Count**	1.00 – 1.30 X 10 <sup>9</sup> /L <i>1.00 – 1.30 X 10<sup>3</sup>/ul</i>	0.75 – 0.99 X 10 <sup>9</sup> /L <i>0.75 – 0.99 X 10<sup>3</sup>/ul</i>	0.5 – 0.749 X 10 <sup>9</sup> /L <i>0.5 – 0.749 X 10<sup>3</sup>/ul</i>	< 0.5 X 10 <sup>9</sup> /L < 0.5 X 10 <sup>3</sup> /ul
Absolute Lymphocyte Count**	0.60 – 0.65 X 10 <sup>9</sup> /L <i>0.60 – 0.65 X 10<sup>3</sup>/ul</i>	0.50 – 0.59 X 10 <sup>9</sup> /L <i>0.50 – 0.59 X 10<sup>3</sup>/ul</i>	0.35 – 0.49 X 10 <sup>9</sup> /L <i>0.35 – 0.49 X 10<sup>3</sup>/ul</i>	< 0.35 X 10 <sup>9</sup> /L < 0.35 X 10 <sup>3</sup> /ul
Platelets -Decreased**	100.0 – 124.99 X 10 <sup>9</sup> /L <i>100.0 – 124.99 X 10<sup>3</sup>/ul</i>	50.00 – 99.99 X 10 <sup>9</sup> /L <i>50.00 – 99.99 X 10<sup>3</sup>/ul</i>	25.00 – 49.99 X 10 <sup>9</sup> /L <i>25.00 – 49.99 X 10<sup>3</sup>/ul</i>	< 25.00 X 10 <sup>9</sup> /L < 25.00 X 10 <sup>3</sup> /ul
Platelets - Elevated**		555 – 600 X 10 <sup>9</sup> /L <i>555 – 600 X 10<sup>3</sup>/ul</i>	> 600 X 10 <sup>9</sup> /L > 600 X 10 <sup>3</sup> /ul	
APTT (seconds)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3 x ULN
INR	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
<b>CHEMISTRIES</b>				
Creatinine	1.1 – 1.3 x ULN	1.4 – 1.8 x ULN	1.9 – 3.4 x ULN	> 3.5 x ULN
<b>LIVER TRANSAMINASES</b>				
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bilirubin (total)	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
GLUCOSE				
Hypoglycemia	3.05 – 3.55 mmol / L	2.2 – 3.06 mmol / L	1.67 – 2.23 mmol / L	< 1.67 mmol / L
Hyperglycemia (nonfasting)	6.44 – 8.88 mmol / L	8.89 – 13.88 mmol / L	13.9 – 27.8 mmol / L	> 27.8 mmol / L

## Notes:

Highlights indicate changes from the previous table; Values in Italics are for Uganda; APTT, INR provided as standardised reference (x ULN); Glucose not strictly required per protocol; WCC and Platelets elevation and urea grading not found in DAIDS but have been added for use with this trial protocol

<b>OTHER EVENTS (23<sup>RD</sup> DEC 2004)</b>				
<b>PARAMETER</b>	<b>GRADE 1 MILD</b>	<b>GRADE 2 MODERATE</b>	<b>GRADE 3 SEVERE</b>	<b>GRADE 4 POTENTIALLY LIFE-THREATENING</b>
<b>CARDIOVASCULAR</b>				
Hypertension	NA	> 150/100 mmHg (either or both values)	> 170/110 mmHg (either or both values)	Malignant hypertension
Cardiac Arrhythmia	Asymptomatic with transient dysrhythmia causing no interference with ADLs	Notable symptoms causing interference with ADLs	Causing significant incapacity*	Unstable dysrhythmia requiring hospitalization and treatment
Pericarditis	NA	Minimal asymptomatic effusion requiring no treatment	Symptomatic effusion	Tamponade <b>OR</b> Pericardiocentesis/surgery required
Hemorrhage, blood loss	Asymptomatic and requiring no therapy	Mildly symptomatic	Gross blood loss <b>AND/OR</b> 1 – 2 units transfused	Massive blood loss <b>AND/OR</b> > 2 units transfused
<b>GASTROINTESTINAL</b>				
Constipation	NA	Significant abdominal pain with impaction requiring prescription	Requiring disimpaction <b>AND/OR</b> Hospital treatment	Distention with vomiting <b>AND/OR</b> Obstipation
Diarrhoea	Transient or intermittent episodes of unformed stools resulting in minimal or no interference with ADLs	Persistent episodes of unformed-to-watery stools resulting in greater than minimal interference with ADLs	Orthostatic hypotension requiring IV fluid/therapy <b>AND/OR</b> Bloody diarrhea	Hypotensive shock
<b>NEUROLOGIC</b>				
Neuro-psych/mood	NA	Depression or anxiety symptoms causing individual to seek attention and be treated with counseling and/or pharmacotherapy	Severe mood changes requiring additional medical intervention <b>AND/OR</b> Suicidal ideation/gesture	Suicidal attempt
Paresthesia (burning, tingling, etc.)	Minimal discomfort resulting in minimal or no interference with ADLs	Notable symptoms resulting in greater than minimal changes in ADLs	Marked and persistent discomfort resulting in significant incapacity* <b>AND/OR</b> Narcotic analgesia required for symptomatic improvement	NA
Neuro-motor	Mild weakness resulting in minimal or no interference with ADLs	Moderate weakness resulting in greater than minimal interference with ADLs	Significant incapacity*	Paralysis <b>AND/OR</b> Respiratory muscle weakness resulting in ventilator dependence
Neuro-sensory	Mild impairment (decreased sensation) resulting in minimal or no interference with ADLs	Moderate impairment resulting in greater than minimal interference with ADLs	Significant incapacity*	NA
<b>RESPIRATORY</b>				

Bronchospasm Acute	Transient; no Rx; FEV1 or peak flow reduced to 70 - 80%	Rx required; normalizes with bronchodilator; FEV1 or peak flow 50 - 69%	No normalization with bronchodilator; FEV1 or peak flow < 49%; retractions	Cyanosis or other symptoms requiring intubation and ICU hospitalization
Dyspnea	Dyspnea on exertion (such as stairs)	Dyspnea with normal activity (such as walking)	Dyspnea at rest	Dyspnea requiring oxygen therapy
<b>INFECTIONS</b>				
Tuberculosis	-	Outpatient management only required	Requiring Inpatient management	Immediate threat to life
Malaria	Asymptomatic parasitaemia	Uncomplicated clinical malaria	Use WHO definitions	Use WHO definitions
<b>MISCELLANEOUS</b>				
Arthritis	NA	Any pain with inflammation, erythema, or joint swelling that interferes with ADLs	Severe pain with inflammation, erythema, or joint swelling causing significant incapacity*	Associated with clinical diagnosis of a systemic autoimmune disease
Eye	Symptoms resulting in minimal or no interference with ADLs	Notable symptoms resulting in greater than minimal interference with ADLs	Symptoms (such as loss of vision, clinically diagnosed uveitis, or glaucoma) resulting in significant incapacity*	NA
Clinical adverse experience NOT identified elsewhere in this DAIDS Table for grading severity of adverse experiences	Awareness of sign or symptom but tolerated with minimal or no interference with ADLs	Notable symptoms resulting in greater than minimal interference with ADLs	Symptoms causing significant incapacity*	Significant intervention/therapy required; hospitalization required to prevent permanent impairment or death

**Appendix 3  
Sample Female Participant Information Sheet  
Hospital/Clinic headed notepaper**

**Microbicides Development Programme (MDP) Trial 301 Female Participant Information Sheet**

**You have been given an explanation of the trial, but we would like you to read this, or ask a friend to read it to you, so that you fully understand what is involved before you agree to take part in this research. If you decide you want to take part, it is important for you to understand why the research is being done and what it will involve. Agreeing to be screened, does not mean that you have to take part in the trial. If you do enrol in the trial, you will be free to stop product or to stop attending at any time. Please ask if there is anything that is not clear or if you would like more information.**

**MDP 301 (2.1) May 2008**

**Why is this trial being done?**

Throughout the world the most common way in which the Human Immunodeficiency Virus (HIV) is spread is through sexual contact between men and women. Although **condoms are a very effective form of prevention**, it is not always possible for a woman to get her partner to agree to use them. Therefore there is an urgent need for other methods of protection that can be used by women. For this reason, we are studying the safety and effectiveness of gels that are microbicides. **0.5% PRO 2000/5** is the active experimental agent that we are studying. **0.5% PRO 2000/5 may prevent HIV infection** if put in the vagina using an applicator before sexual intercourse. Another gel which has been specially matched is a dummy gel known as a 'placebo'. This **dummy gel has no activity against HIV**.

**WE DON'T KNOW FOR SURE IF 0.5% PRO 2000/5 DOES OR DOES NOT WORK** and that is **WHY** the trial is being done.

**What do we know about PRO 2000/5?**

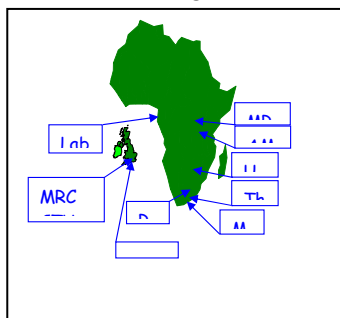
Nearly 300 women in Europe, the United States, South Africa, Uganda and India have used PRO 2000/5 for short periods up to a maximum of twice daily for 28 days to see if it was safe. Some of these women used strengths higher than the ones to be tested in this trial. In these studies women were examined weekly or fortnightly. The gels were safe and caused few side effects. Some women complained of mild itching or other discomfort, but this is common in women not using gel. Some women noticed more discharge than usual. Other symptoms that may be linked to using the gels include light bleeding from the vagina (spotting).

**We do not know if 0.5% PRO 2000/5 is safe to use in pregnancy** and it is important that women stop using gel if they are pregnant. We do not know if you will be prevented from getting pregnant during the sex act when you use the gel. There is no reason to think the gel will affect your chance of becoming pregnant later. You should use a reliable method of contraception every time you have sex.

We were also studying 2% PRO 2000/5 from October 2005 to February 2008. Every 4-6 months a committee of experts that are independent of the trial review the information on safety and effectiveness. They met on 8<sup>th</sup> February 2008 and advised that 0.5% and placebo arms should continue. They also advised that 2% gel should not continue as there was very little chance of showing that 2% gel would prevent HIV. Thus we are now only studying 0.5% PRO 2000/5 and placebo gel for the remainder of the trial, as this has a better chance of preventing HIV infection.

### **What does the MDP 301 trial involve?**

The trial is taking place in several sites in Africa shown in the map. Your site is:



NAME \_\_\_\_\_

0.5% PRO 2000/5 gel will be studied at each site. A second gel which has been specially matched is a dummy gel known as a 'placebo'. This dummy gel has no activity against HIV. Both gels will be packaged in the same applicator and cartons and will look identical so neither you nor the study staff can tell the difference. Chance will determine whether you receive active gel or the dummy gel. You will receive the same type of gel throughout the trial. **NO-ONE KNOWS WHICH GEL THEY ARE ON**, including the study staff. This is the best and only way to test the gels to see if they prevent HIV infection.

### **What will happen to me if I agree to be screened?**

After you have had all your questions answered and feel you understand what you will have to do, you will be asked to sign, or put your thumbprint on a consent form. If you cannot read then we recommend that you have a witness present for the discussion and to see your thumbprint. You will then be given a number which is unique to you, and which will help us to ensure that all your test results and answers to our questions remain private. There will be some screening tests, so the whole visit will take about one and a half hours. The tests will be:

- A blood test for HIV, after you have received private counselling, to help you decide whether or not you wish to have the HIV test
- A urine test for pregnancy
- General questions including health questions
- Sensitive questions about your partners and your sexual practices.

Not all women will be able to take part in the study and if this is the case for you, the research staff will explain why. If you can take part, and you want to, we will ask you to go away, and to think carefully about the trial. You will be asked to come back again to enrol in the study within 1- 6 weeks.

### **What will happen to me if I agree to enrol in the trial?**

You will be asked to sign or put your thumbprint on a second consent form (with a witness, if you cannot read and write), and after this there will be:

- Some more general and sensitive questions
- A general examination of your body, an examination of your genital area and collection of genital specimens
- Blood will be collected to store until the end of the study and urine will be collected to test if you are pregnant

If you are eligible, you will be invited to join and providing you are still willing you will be given another number which is unique to you and which determines by chance the gel that you use throughout the trial. We recommend that you use condoms as well because we know that condoms protect against HIV and other sexually transmitted infections, as well as pregnancy, if used properly every time you have sexual intercourse. An applicator will be used to insert the gel and the staff will explain to you how it should be used. This should be done within one hour before sex. Once the gel has been inserted you should not wash inside your vagina, or put anything else in your vagina, for at least one hour after sex. If you do take part in the study and are given some of the gel you must only use it yourself and not share it with anyone else, even if they are also in the study.

We want you to keep the empty applicators and bring them back to the clinic, as well as unused gel, each time you collect new supplies and at your final visit. This will help you and the staff to work out how much gel you have used and how much more you need. This information will be very important to the result of the trial and so we want you to try to be as accurate as possible.

You will be asked to come to the clinic every 4 weeks for pregnancy tests, to answer some questions and to collect more gel and condoms. At approximately every third visit (every 12-16 weeks), the visit will take longer as there will be more questions about your health and sexual behaviour, as well as a genital examination, swabs and blood tests. One of these tests will be an HIV test, and the staff will explain how you can receive the result. Once the blood has been tested some of it will be kept frozen in the laboratory. This is because the test may have to be repeated and also because new and better tests may become available in the future. This blood will not be given to anyone except appropriate staff involved in medical research, and this trial.

If you become pregnant, you will have to stop using the gel, but we would like you to continue to attend every 12 weeks.

Most women will be followed for 52 weeks (approximately 12 months). 500 women participating in Durban and Johannesburg (South Africa), and 490 women participating in Masaka (Uganda), will be asked to have extra blood tests to check the safety of the gels. These general checks are required for drugs that are not licensed.

We might also ask you to keep a diary and take part in a longer recorded interview with another member of the study team during the study. Verbal consent will be recorded at the beginning of the interview.

You will be asked if we can contact your partner to ask him some questions about the gel. We will not contact your partner if you do not want us to.

You will receive compensation for any costs involved with coming to the clinic and this will be: XXXX per visit or XXXX in total.

### **What if something new is learned about the gel whilst I am in the trial?**

You will be told of any new information learned during the course of the trial that might cause you to change your mind about staying in it.

### **Do I have to take part?**

No. It is up to you to decide, when you feel ready, whether you would like to take part. Once you enrol you are free to stop using the gel and continue attending the clinic, or to stop attending the clinic if you wish to. This will not affect any care you receive now or in the future.

### **Can I stop taking part?**

Yes, you can decide to stop taking part whenever you choose. This would mean that you do not need to explain why you want to stop taking part to anyone, just that you want to stop.

### **What are the risks and benefits?**

#### **The risks are:**

- Taking blood and having genital examinations may be uncomfortable
- The questions might be embarrassing
- It is possible that the gel will not protect you against HIV. If you believe that it will, you may put yourself at risk. Condoms will protect you from HIV if used properly.
- You may experience genital, or other problems that you think are related to the gel. Vaginal gels containing PRO 2000/5 were considered to be safe in previous studies, but these involved less than 300 women and none used the gel for longer than 4 weeks. You should contact the research staff immediately if you have a genital or other problem that you think is related to the gel.

Contact name: \_\_\_\_\_ Contact number: \_\_\_\_\_

Physical address: \_\_\_\_\_

If you feel that you have suffered harm as a result of taking part in the study then you should discuss this with the staff at the clinic. If you would like to speak to someone outside the research team you should contact:

Contact name: \_\_\_\_\_ Contact number: \_\_\_\_\_

**The benefits are:**

- You will receive a general health check and examination
  - You will receive treatment for vaginal and sexually transmitted infections free of charge
  - Staff will refer you to a government health clinic if they find other conditions that need treatment
- You will receive free condoms and advice to help you to use them with your partners

**Can I be withdrawn from the study even if I want to continue?**

Yes. The staff can end your participation in the study without your consent if they feel it is in your best interest. Your participation will also be ended if the study is stopped by the authorities responsible for running the trial.

**Will the information from the trial be confidential?**

Yes. Your contact details will only be available to the staff that run the clinics. Staff that monitor the study have to check the consent forms, and they will see your names briefly when this is being done. All the other information that is collected for the trial will not be identified by your name, only by your trial number, including the tests sent to the laboratory.

**What will happen to the results?**

After the study has been completed the results will be analysed. This can take between 3-6 months, and after this you will be told the results of the study. You will also be told which product you received. The results of the study will be written up and submitted for review by a medical journal. They may also be presented at scientific conferences. If the products are shown to work, then we will try to get a license so that they can become widely available.

**This trial is conducted in accordance with international guidelines for Good Clinical Practice in Clinical Trials and with the approval of:**

*Insert name of local research ethics committee*

*date*

*Insert name of national competent authority*

*date*

# Thank-you for taking the time to read this!

If you have questions about this study you should discuss them with a member of the study team (contact details as provided under 'What are the risks and benefits?' on this form), or the ethics committee (contact details provided above). If they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

The Registrar, SA Medicines Control Council, Department of Health, Private Bag X828, PRETORIA 0001 Fax: (012) 312 3105 Email: labusa@health.goc.za

**Appendix 3a**  
**Sample Female Participant Information Sheet for women in follow-up for MDP301 from 14<sup>th</sup>**  
**February 2008**

**Hospital/Clinic headed notepaper**  
**Microbicides Development Programme (MDP) Trial 301 Female Participant Information**  
**Sheet for women in follow-up for MDP301 from 14<sup>th</sup> February 2008**

Thank you for taking part in the trial. We really appreciate the time you have given up to come to the clinic for the frequent visits.

We have some very important information to share with you.

You will have been told this by the clinic staff, but we would like you to read this, or ask a friend to read it to you, so that you fully understand what has happened. Please ask if there is anything that is not clear or if you would like more information.

MDP 301 Additional Information Leaflet 13 February 2008

**A reminder about the purpose of this trial**

The question we are trying to answer is 'does 0.5% or 2% PRO 2000/5 gel prevent HIV infection?'

The best way to answer this question is in a clinical trial, where women are **allocated by chance** to 0.5%, 2% or placebo (dummy gel with no activity against HIV). This way, the risk factors that are linked to HIV, such as not using condoms, are evenly balanced across the three groups.

**What is the new information?**

You may or may not be aware that the trial is monitored by an independent group of experts, called the Independent Data Monitoring Committee, or IDMC for short. The IDMC has been regularly checking the safety and efficacy of the active gels containing PRO 2000/5. They do this by seeing how often problems arise in the 0.5% and 2% PRO 2000/5 groups compared to the placebo (dummy) gel group. They check the genital problems that women complain of, and anything unusual that staff find on examination. They also check the number of HIV infections in each group. If they are satisfied, then they recommend that the trial should continue.

The IDMC met on the 8<sup>th</sup> of February 2008, and recommended that the **0.5% and placebo gel arms should continue.**

**However** they recommended that the **2% PRO 2000/5 arm should not continue** because there is only a very small chance that MDP301 could show that 2% protects women against HIV infection.

**What does this mean?**

This means that the answer to the question 'does 2% PRO 2000/5 prevent HIV infection' is very likely to be 'no' and therefore there is no point in continuing to test the 2% gel.

The answer to the question 'does 0.5% PRO 2000/5 prevent HIV infection' could still be 'yes' and therefore it is important that we continue the trial in women using the 0.5% PRO 2000/5 and placebo gels so that we can find out.

**Could 0.5% PRO 2000/5 work, when 2% does not appear to?**

Yes. Although 2% PRO 2000/5 is four times stronger than 0.5%, and therefore has more activity against HIV, it's possible that 0.5% works better because it is 'kinder' to the vagina. 0.5% PRO 2000/5 is still very active against HIV in the laboratory and effective in animal experiments.

**What will happen to me now?**

All participants will be seen as soon as possible to share the new information.

At this visit, women using 2% gel will go through the same procedures that a woman with a positive pregnancy test would. As would happen with pregnant participants, they will be asked to continue to attend for the long clinical visits at which the genital examinations and HIV testing are performed. Tests for other sexually transmitted infections and vaginal infections will also be collected. They will be asked to return their gel supplies and no more gel will be dispensed.

**It is up to you whether you agree to carry on coming to clinic.**

Participants using 0.5% or placebo will be provided with this new information at their next visit. We will ask if you are willing to continue in light of this new information. We will not be able to tell you which gel you are on, as we will not know. **It is up to you to decide whether you want to carry on with gel.**

Everyone will be asked to sign, or put their thumbprint below to verify that the information has been discussed and/or if you agree to continue participating in the trial. For participants that cannot read, we recommend that a witness is present for the discussion and to see your thumbprint.

Thank you again for your participation this far. Please think carefully about whether or not you want to continue. Remember that **condoms, if used consistently, do prevent HIV infection.**

**PLEASE CIRCLE THE CORRECT ANSWER**

Have you read or had read to you this participant information sheet YES / NO  
(MDP301 Additional Information leaflet 14 February 2008)?

Do you consent to continue participating in the trial? YES / NO

Signature/Thumbprint of volunteer

Signature or thumb-print		Date of signature	
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Signature of witness (if volunteer illiterate)

Signature		Date of signature	
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Tick box if participant is illiterate and refuses to have witness present

Signature of study staff taking consent

Signature		Date of signature	
Print name			

**Please store one copy of this form in the clinical records**

## Sample Male Participant Information Sheet Hospital/Clinic headed notepaper

### Microbicides Development Programme (MDP) Trial 301 Male Participant Information Sheet

You have been told about the research but we would like you to read this, or ask a friend to read it to you before you decide to take part. Please ask if there is anything that is not clear.  
MDP 301 (2.1) May 2008

#### **Why is this trial being done?**

This trial is being done to test 0.5% PRO 2000/5 which is called a microbicide. **This gel may prevent HIV infection** if put in the vagina using an applicator before sexual intercourse.

However, **WE DON'T KNOW FOR SURE IF IT DOES OR DOES NOT WORK** and that is **WHY** the trial is being done. We know that condoms, when used properly, do protect against HIV, sexually transmitted infections and pregnancy. So it is important that you and your partner try to use condoms to protect yourselves.

#### **What do we know about PRO 2000/5?**

Nearly 300 women in Europe, the United States, South Africa, Uganda and India have used PRO 2000/5 for short periods up to a maximum of twice daily for 28 days to see if it was safe. Some of these women used strengths higher than the ones to be tested in this trial. In these studies women were examined weekly or fortnightly. The gels were found to be safe. Some women complained of mild itching or other discomfort, but this symptom is common in women not using gel. Some women using gel twice a day noticed more discharge than usual. Other symptoms that may be linked to using the gels include light bleeding from the vagina (spotting).

We do not know if the gels are safe to use in pregnancy and it is important that women stop using them if they are pregnant, although they can start using the gel again when they are no longer pregnant if they want to. We do not know if pregnancy will be prevented during sex acts when gel is used. There is no reason to think the gel will affect the chance of women becoming pregnant later.

We were also studying 2% PRO 2000/5 from October 2005 to February 2008. Every 4-6 months a committee of experts that are independent of the trial review the information on safety and effectiveness. They met on 8<sup>th</sup> February 2008 and advised that the 0.5% and placebo arms should continue but they advised that 2% gel should not continue as there was very little chance of showing that 2% gel would prevent HIV. Thus we are now only studying 0.5% PRO 2000/5 and placebo gel for the remainder of the trial, as this has a better chance of preventing HIV infection.

#### **What will happen to the women who are taking part?**

Women who participate will be asked to sign a consent form and will undergo some tests for pregnancy and sexually transmitted infections. They will be given general and genital examinations and will be asked some questions about their sexual behaviour. If they are able and willing to take part in the study they will be given some gel to insert before each time they have sex. They will be asked to come back to the clinic on a regular basis and study team members may contact them at other times to see how they are getting on using the gel. **We strongly recommend that couples use condoms as well because we know that condoms protect against HIV and other sexually transmitted infections, as well as pregnancy, if used correctly every time they have sexual intercourse.**

#### **What will happen to me if I agree to take part?**

After you have had all your questions answered and feel you understand what you will have to do, you will be asked to sign, or put your thumbprint on a consent form. If your current sexual partner has been using the gel before sex you will be asked to take part in an in-depth interview. This means that a study member will ask you some questions about how you felt about your partner using the gel and if you felt it made a difference to your sexual pleasure. They will ask you if you mind if the discussion is recorded. The interview will be casual and you will be encouraged to talk freely about anything you feel is related to your partner using the gel. If your current sexual partner has not been using the gel you will be asked to participate in a focus group discussion. This means that we will show you and 6 to 8 other men like you the gel and the applicator that the women in the trial have been using. We will ask you to discuss the gel and applicator with the other men. Again this will be quite casual and the study team member who is present will start the discussion, ask for your consent and ask you to think of certain situations where the gel might be used.

You will receive XXXX as a contribution towards the cost of your travel and time.

### **What are the risks and benefits?**

We do not think there are any risks involved in you taking part in this study. However, if you do feel that you have suffered harm as a result of taking part in the study then you should discuss this with:

Contact name: \_\_\_\_\_ Contact number: \_\_\_\_\_

The benefits are:

- You will receive free condoms and advice to help you to use them with your partners

### **Do I have to take part?**

No. Your participation is completely voluntary. If you choose not to take part it will not affect any care you receive now or in the future.

### **Will the information that is collected be confidential?**

Yes. Your contact details will only be available to the staff involved in the study. The information you provide will not be available to your partner.

### **What will happen to the results of the study?**

All the information will be closely looked at, at the end of the study. You will be told the result, which may also be published in medical journals and presented at meetings.

# Thank-you for taking the time to read this!

**This study is conducted in accordance with international guidelines for Good Clinical Practice in Clinical Trials and with the approval of:**

*Insert name of local research ethics committee* \_\_\_\_\_ *Date* \_\_\_\_\_  
*Contact number* \_\_\_\_\_

*Insert name of national competent authority* \_\_\_\_\_ *Date* \_\_\_\_\_

**If you have questions about this study you should discuss them with a member of the study team (contact details as provided under 'What are the risks and benefits?' on this form), or the ethics committee (contact details provided above). If they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:**

**The Registrar, SA Medicines Control Council, Department of Health, Private Bag X828, PRETORIA 0001 Fax: (012) 312 3105 Email: labusa@health.goc.za**



**Appendix 4  
Sample Female Informed Consent Part 1  
Hospital/Clinic headed notepaper**

**Microbicides Development Programme Trial 301 (MDP 301) Female Informed Consent  
Protocol version (2.1) May 2008**

Screening Number	<input type="text"/>	Identifier 1	<input type="text"/>	Identifier 2	<input type="text"/>
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Part 1 of the Informed Consent

**PLEASE CIRCLE THE CORRECT ANSWER**

Has the MDP 301 trial been explained to you and have you been given a Participant Information sheet dated **February 2008**? YES / NO

Have you had an opportunity to ask questions and discuss this study? YES / NO

Have you received satisfactory answers to all of your questions? YES / NO

Do you understand that we do not know if the gels prevent HIV? YES / NO

Do you understand that the correct and consistent use of condoms will prevent HIV?  
YES / NO

Do you agree to your blood being tested for HIV? YES / NO

Do you agree to appropriate members of trial staff and the authorities responsible for licensing the gels having access to your medical records? YES / NO

Which member of the study staff have you spoken to about this study?  
..... (please print his or her name)

Do you understand that agreeing to be screened does not mean you have to join the trial?  
YES ? NO

Do you agree to be screened for this study? YES / NO

**If 'NO' to any of the above the volunteer is ineligible for the study**

Signature/Thumbprint of volunteer

Signature or thumb-print	<input type="text"/>	Date of signature	<input type="text"/>
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Signature of witness (if volunteer illiterate)

Signature	<input type="text"/>	Date of signature	<input type="text"/>
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**Tick box if participant is illiterate and refuses to have witness present**

Signature of study staff taking consent

Signature	<input type="text"/>	Date of signature	<input type="text"/>
Print name	<input type="text"/>		

**Please store one copy of this form in the clinical records**

**Sample Female Informed Consent Part 2**  
**Hospital/Clinic headed notepaper**  
**Microbicides Development Programme Trial 301 (MDP 301) Female Informed Consent**  
**Protocol version (2.1) May 2008**

Screening Number  Identifier 1  Identifier 2

Part 2 of the Informed Consent

**PLEASE CIRCLE THE CORRECT ANSWER**

Have you read or had read to you the MDP 301 Participant Information sheet dated **February 2008**? YES / NO

Have you received enough information about the trial? YES / NO

Have you received your HIV result? YES / NO

Do you understand that we do not know if the gels prevent HIV and that you may receive a gel that is unlikely to prevent HIV? YES / NO

Do you agree to use condoms and gel as much as possible when having sexual intercourse during this study? YES / NO

Do you understand that you will have to stop using gel if you become pregnant? YES / NO

Do you understand that you must report any new symptoms to the study team, even if you think they are not related to the gel? YES / NO

Will you give accurate answers to the questions you are asked by the study team? YES / NO

Do you understand that you are free to withdraw from the study:  
 - at any time  
 - without having to give a reason for withdrawing  
 - and without affecting future medical care? YES / NO

Do you agree to take part in this study? YES / NO

**If 'NO' to any of the above the volunteer is ineligible for the study**

Signature/Thumbprint of volunteer

Signature or thumbprint	<input type="text"/>	Date of signature	<input type="text"/>
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Signature of witness

Signature	<input type="text"/>	Date of signature	<input type="text"/>
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Signature of study staff taking consent

Signature	<input type="text"/>	Date of signature	<input type="text"/>
Print name	<input type="text"/>		

**Please store one copy of this form in the clinical records**

**Sample Male Informed Consent  
Hospital/Clinic headed notepaper  
Microbicides Development Programme Trial 301 (MDP 301) Male Informed Consent  
Protocol version (2.1) May 2008**

Date of visit:	Initials:	Partner's screening #:	Partner's trial #:
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**PLEASE CIRCLE THE CORRECT ANSWER**

Have you read or had read to you the MDP 301 Male Participant Information sheet dated **February 2008?** YES / NO

Have you received enough information about the trial? YES / NO

Do you agree to being interviewed or to participate in a focus group discussion about your experiences with your partner participating in this study, or to discuss the use of the gels?

YES / NO

**If 'NO' to any of the above the volunteer is ineligible for the study**

Signature/Thumbprint of volunteer

Signature or thumbprint		Date of signature	
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Signature of witness

Signature		Date of signature	
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**Tick box if participant is illiterate and refuses to have witness present**

**INVESTIGATOR'S DETAILS:**

Signature		Date of signature	
Print name			