

**Phase III Study of the Efficacy and Safety of the Microbicide Carraguard in
Preventing HIV Seroconversion in Women – Protocol Synopsis**

Population Council, Protocol 322

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A collaboration of the Population Council, the South African Medical Research Council, the
University of Limpopo-Medunsa Campus, and the University of Cape Town

**Phase III Study of the Efficacy and Safety of the Microbicide Carraguard in Preventing HIV Seroconversion in Women,
Population Council Protocol No. 322 -- Protocol Synopsis**

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I. INTRODUCTION

In response to the urgent need for widely available and easy-to-use protection against the sexual transmission of human immunodeficiency virus (HIV), Population Council investigators have developed a topical microbicide called Carraguard (formerly known as PC-515). Carraguard is a water-based gel containing the active pharmaceutical ingredient (API) PDR98-15 carrageenan, a mixture of *lambda*- and *kappa*-carrageenans derived from red seaweed.

PDR98-15 has been shown to be effective in preventing the mucosal transmission of HIV at concentrations 100 to 1000 times lower than those associated with significant cellular toxicity *in vitro*. The results of nonclinical studies show that PDR98-15 may also offer protection against a range of other sexually transmitted infections (STIs) including herpes simplex type-2 (HSV-2), gonorrhea, and human papillomavirus (HPV). PDR98-15 has even demonstrated effectiveness against HIV-2 *in vitro*.

While all of the ways in which the formulation offers protection against the mucosal transmission of HIV are still being determined, it is believed that PDR98-15 works by 1) binding to the positively charged regions of the viral envelope of free-virus (carrageenan has a very high negative charge density) and 2) by inhibiting cell-to-cell transmission of the virus by acting as a barrier between infected and non-infected cells.

In addition to effectively blocking the sexual transmission of HIV and other STIs, carrageenans have a long and safe history that is supported by numerous toxicological studies in a variety of animal species. Carrageenan is a US Food and Drug Administration (FDA) approved “GRAS” (Generally Recognized As Safe) compound, deemed safe for human consumption, topical application, and for use as a pharmaceutical excipient¹. Additionally, the Joint Expert Committee on Food Additives has once again granted a “not specified” Acceptable Daily Intake recommendation².

Both nonclinical and clinical tests of PDR98-15-containing formulations conducted by the Population Council show that this carrageenan mixture is safe when vaginally administered. *In vitro* toxicological studies have shown that PDR98-15 carrageenan does not have a proliferative effect on cervical cells (unpublished data), and that it neither inhibits nor enhances *lactobacillus acidophilus*, the most commonly found vaginal flora³. It has also been shown that Carraguard does not cause vaginal irritation or vaginal toxicity *in vivo*.

Clinical trial findings are consistent with laboratory observations regarding the safety of Carraguard. Phase I safety and acceptability studies demonstrated that carrageenan formulations caused no observable irritation to the lower reproductive tract^{4,5}. The impact of carrageenan gel on vaginal flora was assessed and no significant relationship was found between gel and bacterial vaginosis⁵.

II. OBJECTIVE

The *primary objective* of this trial was to determine *the efficacy* of Carraguard gel in preventing HIV transmission when applied vaginally prior to sexual intercourse. In addition, *the safety* of Carraguard gel when applied vaginally prior to intercourse was evaluated. Safety parameters included abnormal genital findings, reproductive tract infections, adverse events, and serious adverse events.

III. RATIONALE

The need for a topical microbicide to protect women from HIV infection during vaginal coitus is well known. *In vitro* (laboratory) experiments conducted at the Population Council, Center for Biomedical Research, demonstrated that Carraguard successfully blocked the HIV virus. Results from Phase I and II clinical trials showed that Carraguard was safe for and acceptable to women in those trials. Specifically, during two large-scale expanded safety and acceptability trials in Thailand (n=165) and South Africa (n=400), where HIV-negative women were randomized to either placebo (methylcellulose) gel or Carraguard gel, there were no statistically significant differences between study groups for most safety endpoints. Almost all findings were mild. These encouraging safety results coupled with the need for a prophylactic HIV prevention method which offers women an option during vaginal intercourse was the rationale for this trial. This Phase III trial was conducted with sufficient power to differentiate efficacy between a placebo and Carraguard.

IV. NUMBER OF PARTICIPANTS AND DURATION OF TREATMENT

The sample size was calculated based on the assumption that the seroconversion rate for the placebo arm would be 3.5% per annum, an expected difference of 33% between the placebo and Carraguard arms, with power of at least 80% and an alpha of 0.05 for a two-sided log-rank survival analysis. Assuming a 20% discontinuation rate, it was estimated that approximately 6,639 participants would need to be enrolled, or as many as possible by June 30, 2006. Recruitment was expected to take approximately 27 months for a total trial duration of 36 months. Data collection ended 9 months after the last participant's enrolment visit.

V. STUDY DESIGN

This was a Phase III, two-arm, randomized, parallel group, placebo controlled, double-blind, efficacy trial of the Council's lead microbicide, Carraguard gel, at three sites in South Africa. The University of Cape Town (UCT) managed one site in the Gugulethu/Nyanga district, the Medical University of Southern Africa (MEDUNSA) managed another in Soshanguve, near Pretoria, and the Medical Research Council-Durban (MRC) managed one in Isipingo, near Durban. (See Appendix for site details). Participants had a screening visit where they were evaluated against the inclusion/exclusion criteria. At the enrolment visit, each consenting eligible participant was randomly assigned to one of two study arms: Carraguard gel plus

condom or its placebo, methylcellulose gel plus condom. A double-blinded randomization scheme, stratified by site (ensuring equal distribution to Carraguard and placebo groups at each site), was used for the trial.

Participants in both study arms received the same HIV prevention package, including condoms, periodic testing for STI and treatment of infections found, and ongoing individualized risk reduction counseling. They were asked to use condoms and insert gel in the vagina every time they had vaginal sex within an hour prior to each sex act. Participants were requested to attend the following visits: screening, enrolment, and months 1, 3, 6, 9, 12, 15, 18, 21, and 24 for clinical evaluations, pelvic exam, HIV counseling and testing, and after enrolment gel supply, applicator return, and other compliance measures. Samples were collected at screening, months 3, 6, 12, 18, and 24, and when clinically indicated for STI testing.

VI. ELIGIBILITY

Inclusion Criteria:

Women who met all the following criteria were eligible for enrolment in the trial:

- HIV-uninfected and agreed to be tested for HIV and told their results at all visits during the study
- Aged 16 to 40 inclusive (at the start of the trial, there was no maximum age limit)
- Have had at least one vaginal intercourse within the last three months
- Willing and able to give written informed consent (or if desired, consent provided by parent or guardian with written assent from the minor participant)
- Provide locator information to study staff throughout the trial
- Comply with all aspects of the study protocol, including random assignment to the Carraguard plus condom or placebo plus condom arm, clinical evaluations, specimen collection and testing, and study drug regimen
- Citizen or permanent resident of South Africa
- Resident for the past year and intended to reside in the catchment area of the site for the next two years
- During the study, did not use any vaginal products except tampons or those prescribed or approved by the study clinician.

Exclusion Criteria:

Women were excluded from the trial if any of the following exclusion criteria applied:

- Currently pregnant, or indicated a desire to become pregnant in the next two years at the time of screening
- Within four weeks of last pregnancy outcome at the time of enrolment
- Pap smear at screening was graded as carcinoma.
- Injected illicit drugs in the 12 months prior to screening
- Participating in any other clinical trial/HIV prevention study

Participant Withdrawal:

Any of the following required withdrawal of a participant from the study:

- The participant seroconverted during the trial. Seroconverters were withdrawn from the study and referred to counseling and medical services in the community
 - Pregnancy
 - Judgment by the investigator at any point during the study that the participant's safety was jeopardized or potentially compromised
 - Withdrawal of participant consent or assent or parent/guardian consent
- Every effort was made by the sites to ensure participants completed all protocol-specified visits and procedures. If a participant was withdrawn from the study due to an adverse event (AE), the AE was followed until the participant returned to baseline conditions or stabilized.

VII. USE OF OTHER PRODUCTS AND MEDICATIONS

Condoms

Study staff provided all potential participants with ongoing, individualized, quality controlled counseling to reduce behaviors that place participants at risk of HIV exposure. Women were provided, at no cost, latex male condoms, non-lubricated or lubricated with a non-spermicidal lubricant. Participants with latex allergy were offered polyurethane condoms.

Concomitant Medications, including Contraceptives

The use of contraceptive was encouraged and all use of medication (including prescribed medicines and contraception, traditional medicines, and vitamins) was recorded. The use of vaginal products other than those prescribed or approved by the Site Physician was prohibited under this protocol.

VIII. STUDY PRODUCT

Packaging

Fifteen single-use applicators containing Carraguard or placebo were packaged into a study product box. Each applicator was labeled with a bar code that identified the production batch number and the expiration date was embossed into the bottom seal of the applicator. Each solid white box was sealed with a two-part sticker with each part of the sticker printed with the corresponding bar code of the applicators inside. One part of the sticker was adhered across the top opening to seal the box and the second part was a perforated portion that was torn off and attached to the study participant's case record form.

Product Dispensation

Each site designated a product dispensary manager who was responsible for all dispensing and tracking. Participants were given an appropriate supply of applicators at enrolment and each study visit. They were instructed to return all used and unused applicators at every visit, at which time they were given a new supply. If additional applicators were needed the participant was instructed to return to the site.

Product Storage and Disposal

Upon receipt of study product from the manufacturer, Clean Chemical Sweden AB (Börlänge Sweden), boxes of gel were inventoried by use of the bar code system and stored in a secure, limited-access Product Dispensary where the temperature was maintained at or below 25° C. The barcode on each box was used for inventory, expiration date, and to avoid any mix-up in dispensing the wrong product than that to which a study participant had been assigned. Site specific SOP's defined storage procedures.

Returned study applicators were treated as biohazards and stored and handled appropriately. Both opened and unopened applicators were counted and reported for each participant. Opened applicators were further tested for usage. Once all testing and counting took place, the applicators were placed in biohazard disposal bins. On a routine basis, a biohazard disposal company collected and subsequently destroyed all returned applicators. Records of destruction activities were maintained by each site, and study monitors ensured all returned applicators were accounted for and destroyed appropriately.

Study Product Administration Instructions

Participants were instructed on the use of the study product at each visit, emphasizing the following:

- Insert one dose of gel within one hour prior to each intercourse. When multiple rounds of sex take place, a new dose of gel should be inserted prior to each act.
- To firmly squeeze as much gel as possible out of each applicator according to instructions, every time they use gel, but to be aware of the fact that some gel is expected to stay behind in the applicator.
- Not to use gel that is more than 4 months old.
- To take all used and unused applicators to the study site at each visit.
- To obtain new applicators at each visit.
- To return to the site between visits if they need more gel.
- Not to use other vaginal products or cleanse the vagina between gel insertion and intercourse, because such practices may remove some or all of the gel before sex has taken place.
- Not to cleanse inside the vagina for at least one hour after intercourse.
- To use the gel only vaginally, not rectally or orally.

IX. STUDY PROCEDURES

Randomization

Using a pseudo-random number generator, available as part of the SAS software package, a statistician not connected with the trial or subsequent analysis produced a randomization scheme (stratified by site) assigning participants to Carraguard or placebo.

Laboratory Evaluations

Laboratory evaluations were performed as follows at the visits indicated:

- Urine pregnancy test: all visits
 - Pap smear: screening, months 12 and 24.
- HIV testing:
 - At all visits (except enrolment), two rapid tests were done (Oraquick and Abbott Determine). If either of the two tests became unavailable, UniGold was a backup.
 - Plasma samples and a dried blood specimen (on filter paper) were collected at enrolment (to be tested if a participant was HIV positive at month 1) and any visit where a participant seroconverted. These were stored at BARC, SA, until the end of the trial. The filter paper was stored at room temperature and the plasma was stored at -70°C as per a standard operating procedure (SOP). Samples were also stored until the end of the trial and may be used for scientific purposes to determine HPV and HSV seropositivity in the study population.
 - Any additional blood sampling for HIV confirmation by Enzyme-Linked ImmunoSorbent assay was conducted if rapid tests were inconclusive, discordant, or positive (test by Abbott Diagnostics).
 - Appendix B outlines the HIV testing procedures that used in this trial.
- Gonorrhoeae and chlamydia (Roche COBAS PCR): screening, months 3, 6, 12, 18 and 24 and other visits if clinically indicated.
- Sampling for trichomoniasis (TV In-Pouch): screening and months 3, 6, 12, 18 and 24 and other visits if clinically indicated.
- Blood sampling for syphilis testing (Rapid Plasma Reagin (RPR) test and *Treponema pallidum* IgG ELISA test): at screening and months 3, 6, 12, 18 and 24 and other visits if clinically indicated.
- Wet mount, pH, Whiff test for BV, trichomoniasis, and yeasts when clinically indicated.

Laboratory Standardization and Quality Control

BARC, SA was responsible for training and standardization of laboratory tests and quality assurance (QA) of all on-site laboratory tests: wet mounts, rapid HIV tests, pregnancy tests, syphilis serological tests, and culture for *T. vaginalis* (InPouch). They determined discrepancy rates between readings for different sites and microscopists. Further training, and/or additional QC readings were performed throughout the trial as needed.

Specimen Tracking and Storage

A bar code system was used to keep track of specimens collected at the study sites and distributed to the various laboratories. The system was implemented according to a site specific

Specimen Tracking SOP. Storage of plasma at -70°C and dried blood filter samples occurred at BARC, SA.

Summary of Visit Schedule and Procedures

Table 1 shows study procedures carried out at each scheduled site visit. ICH's Good Clinical Practice guidelines were followed. All visits, starting with the screening visit, were scheduled for a time when the participant was not menstruating.

Table 1. Procedures–Carraguard Phase III Trial

Activity	Procedure	Screening	Enrolment	Month 1	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24 /Early Termination	Interim and Post-Trial ¹
Administrative	Obtain informed consent and assign ID number	x											
	Administer/confirm inclusion/exclusion criteria	x	x										
	Collect/update locator information	x	x	x	x	x	x	x	x	x	x	x	x
	Obtain random assignment		x										
	Obtain demographic information ²	x											
	Provide HIV counseling, administer questionnaires, & distribute condoms	x	x	x	x	x	x	x	x	x	x	x	[x]
Clinical	Medical History	x											
	Concomitant Medications information	x	x	x	x	x	x	x	x	x	x	x	x
	Adverse Event/Baseline Condition collection	x	x	x	x	x	x	x	x	x	x	x	x
	Physical including breast exam and Vitals	x						x				x	x
Pelvic Exam	Pelvic exam	x	x	x	x	x	x	x	x	x	x	x	[x]
	pH, Wet mount, Whiff test		[x]	[x]	[x]	[x]	[x]	[x]	[x]	[x]	[x]	[x]	[x]
Laboratory Evaluations	Perform urine pregnancy test	x	x	x	x	x	x	x	x	x	x	x	[x]
	Perform rapid HIV testing	x		x	x	x	x	x	x	x	x	x	X
	Collect blood specimens for HIV	x ³	x	x	[x]	[x]	[x]	[x]	[x]	[x]	[x]	[x]	[X]
	Pap smear	x						x				X ²	
Tests for STI	Collect blood specimen for syphilis	x	[x]	[x]	x	x	[x]	x	[x]	x	[x]	x	
	Sampling for trichomoniasis (swab)	x	[x]	[x]	x	x	[x]	x	[x]	x	[x]	x	
	Sampling for NG and CT (swabs)	x	[x]	[x]	x	x	[x]	x	[x]	x	[x]	x	
Product Accountability	Testing of applicator for drug use			x	x	x	x	x	x	x	x	x	
	Product dispensing, instructions and accountability		x	x	x	x	x	x	x	x	x	x	
	Application of study drug in site		x										
	Schedule next study visit	x	x	x	x	x	x	x	x	x	x	[x]	x

[x] If indicated (clinically or otherwise)

1. Interim and post-trial visits occurred to evaluate adverse events, resupply product and condoms etc. 3. Validation of HIV rapid test results for first 100 participants at each site (50 negative and 50 positive)
2. Only at Month 24, not at termination

X. STUDY COMPLIANCE

Compliance to study gel use was assessed through behavioural interviews and the use of a test to determine vaginal use of applicators. However, no participants were withdrawn based on these test results.

XIII. DATA ANALYSIS

Evaluation of Efficacy

The primary endpoint, time to HIV seroconversions, was analyzed using data from all randomized participants who returned at least one opened applicator and who had at least one post-enrolment HIV test result. The primary efficacy analysis was carried out using the Kaplan-Meier method using PROC LIFETEST in SAS which was used for the analysis of the survival data. The null hypotheses [$S_{\text{Carraguard}}(t) = S_{\text{placebo}}(t)$] about differences in survival was tested using the log rank test, stratified by clinic. The Cox Regression method using PROC PHREG in SAS was used to model the survival experience of the treatment and placebo groups adjusting for the possible confounding and/or interaction effects of specific covariates (site, age, baseline condom use, etc.). Secondary efficacy analyses included the comparison of treatment groups using a restricted sample of those participants who were adherent to the visit schedule and gel usage as defined in the Statistical Analysis Plan (SAP), which was finalized prior to the DSMB efficacy review.

Evaluation of Safety

Safety was assessed by recording adverse events (clinical and laboratory) and the change from baseline in clinical laboratory test parameters, STI infections, and physical examination findings. STI infections were also evaluated using incidence rates overall and by visit. Univariate and repeated measures analyses were used.

Reasons for early withdrawal from the study and serious adverse events plus treatment of emergent adverse experiences were tabulated for the total study and for each treatment group. Exploratory analysis of potential covariates, such as HSV-2 infection, were introduced in models investigating their influence or relationship to HIV seroconversion. Information on the possible exploratory models were described within the SAP.

XV. DATA SAFETY MONITORING BOARD (DSMB)

An independent DSMB was convened three times to review interim analyses for safety, and the last review included efficacy as well. The stopping rules, based on NIH guidelines, were for evidence of a potentially harmful effect in the Carraguard arm or demonstration of superior efficacy in the Carraguard arm. The first DSMB safety meeting was convened when approximately 40 seroconversions occurred; and the second when 93 seroconversions occurred. The third meeting (the first meeting for efficacy) occurred when approximately two-thirds of the total follow-up time was available, approximately 1.5 months after the last participant was enrolled.

XVI. DATA MANAGEMENT

Participant Identification Numbers

At screening, each woman was assigned a unique ID number, which was recorded on all case record forms (CRFs) throughout the trial. The randomization number was recorded on the CRFs once for women who were eligible for study enrolment.

Case Record Forms (CRFs)

CRFs were used to record all clinical, interview, and most of the laboratory information obtained in this trial. When electronic laboratory data were available, these test results were electronically reported and incorporated into the trial database. Source documents included original laboratory reports, study clinician's notes, and off-site medical records. Completed CRFs and source documents were kept secure at all times. Only study staff, monitors, and auditors could access these files. The local Study Coordinator or Data Manager checked the forms before faxing them.

Each study site was responsible for translating the interview questions about sexual behavior and compliance into the local language(s). Translations were validated by independent back-translations. Translations and back-translations were kept on file at the study site and at the Population Council.

The CRFs were completed and stored at each study site. CRFs were completed at the study sites where participants were seen, but data entry was done in the Population Council's New York office.

Data Entry and Management using DataFax

Within a maximum of 2 days from the participants' visit: CRF images were sent from each site to the Data Management group located in New York City. At the site, images were encoded and attached to automatically generated emails which could only be sent to a secure server at the Population Council's Center for Biomedical Research, New York City. DataFax (www.datafax.com) software interpreted the received images using Optical Character Recognition software. DataFax is a complete Data Management system, validated and compliant with current Good Clinical Practice (cGCP). DataFax provides an electronic audit trail and quality control checks, and is a secure data management system. Errors were resolved by site staff in collaboration with the New York-based Data Management team (Population Council) and Clindev monitors.

XVII. ADVERSE EVENTS

Adverse Events (AE) were carefully monitored and an AE form included in the CRF. Serious adverse events (SAE) as defined below were reported on a SAE form.

All adverse experiences (AEs) were recorded in the study event record of the participant's CRF and include the following information (when applicable):

- Specific condition or event
- Indication of whether the condition was preexisting or not and, if yes, whether it worsened in severity (including an increase in frequency)

- Date of occurrence
- Date of resolution
- Relationship to study medication as evaluated by the investigator (causality assessment). Investigator's opinion of causality must be completed by the investigator on the AE forms.
- Action taken (study medication continued or not) and outcome
- Seriousness according to the approved regulatory classification (i.e. any event that is fatal, life-threatening, disabling, incapacitating, results in or prolongs hospitalization, or is a medically significant event, e.g. an intervention to prevent one of the above outcomes, or any other serious criteria [cancer, congenital anomaly, overdose, other significant] is considered serious).

When any serious adverse event, regardless of causality, was encountered during this clinical trial at an investigator's site, the investigator notified the Population Council's SAE Desk (Fax No: 212-327-8673) and the Study Coordinator or designee at the Population Council immediately ("Immediate" Report) by facsimile using the form provided as an appendix. This report was to be submitted no more than 2 calendar days from the time the investigator's staff was notified of the event.

All serious adverse events were also directly reported to local health/regulatory authorities and the local IRB or Ethics Committee by the investigator or designee after case assessment by the Population Council's SAE Desk staff. All serious adverse events were followed until fully characterized. The investigator was expected to collect and forward to the Population Council's SAE Desk, via fax, all available supporting documentation (with participant name redacted) for serious events, including, at a minimum, hospital discharge summaries and death certificates (where applicable). Additional supporting documentation to verify the medical diagnosis included autopsy reports (where applicable), surgical procedure summaries, histology reports, and imaging reports.

XVIII. COMMUNICABLE DISEASE REPORTING REQUIREMENTS

It was the responsibility of the PI of each study site to report communicable diseases identified among study participants to local health authorities as required by all applicable local guidelines.

XIX. ETHICAL CONSIDERATIONS

Informed Consent

Written informed consent was obtained from all study participants. The rationale of the study, procedural details, and investigational goals were explained to each participant and/or the participant's parent or guardian, together with potential risks and benefits, via the mandatory study booklet, study video, and informed consent form. Assent was obtained from potential minor participants if desired by the participant. Each participant was assured that she was free to withdraw at any time and was expected to understand that she was authorizing access to medical records as required for monitors, auditors, institutional review boards (IRBs) and regulatory authorities. Where relevant, an approved participant or Parent/Guardian Consent

Form and Assent was signed and dated prior to the initiation of any study procedures. The original was kept on file by the investigator with the participant's records. A copy of the signed participant or Parent/Guardian Consent Form and signed Assent were to be given to each study participant or Parent/Guardian.

Principal investigators provided the Population Council with a copy of the Informed Consent, booklet, and video approved by their local IRB or Ethics Committee. All of these materials were translated and approved in the local language(s). Translations were validated by independent back-translations. Translations and back-translations were kept on file at the study site and at the Population Council.

If the woman was illiterate, either her representative or a witness (not a member of the study staff) read her the booklet and informed consent form, and signed the consent form in her place. Alternatively, a thumbprint could be obtained, together with the signature of the study staff member who gave the information about the study and obtained consent.

Informed Consent Standard Operating Procedures

Recruitment

Participants were recruited from a range of sites in and around the study clinics including family planning clinics, primary health clinics, church groups, community groups, malls, taxi ramps, and other general locations surrounding the catchment areas. The study was described to potential participants during information sessions either in the community or at the study clinic according to a recruitment standard operating procedure (SOP). At each recruitment session, outreach workers distributed study booklets to potential participants and led a question-and-answer-session based on a standardized script. Whenever possible, an educational video was shown at the beginning of each recruitment session. This educational video was developed in response to recommendations from Phase II participants about how to improve the informed consent process in future trials.

Screening

After each recruitment session, women who expressed an interest in participating in the trial were invited to attend the study clinic at which time they went through a standardized informed consent process prior to being screened for eligibility. According to the informed consent SOP, women who had not seen the video at recruitment watched the video first before any other screening procedures. After viewing the video, women attended a group informed consent session with other women being screened at the clinic that day. The group review of the consent form enabled potential participants to ask questions and ensure that everyone heard every word of the consent form, regardless of individual literacy levels.

After the group informed consent review, each woman met in private with a counselor to further discuss trial participation. During this private meeting, the counselor assessed potential participants' comprehension of ten key study areas using open-ended questions that allowed for probing and discussion. If counselors determined that women understood the key points of the study, both the counselor and the participant then signed the informed consent form together. After signing the informed consent form, the participant proceeded to screening.

Conflicts of Interest

The investigators were paid part-time/full time salary during the trial (5-100%) by the Population Council, which was the sponsor of this study but will not profit from results, either positive or negative, with regard to the product being evaluated.

Confidentiality

The information on individual participants arising from this study was considered confidential and transmitted to the sponsor only in a form that did not permit identification of the individual. Regulatory and sponsoring agencies could request access to the study records and related medical records of each participating participant, and if requested, the participant's identity remained confidential to the extent permitted by the applicable laws and regulations. All records were kept in a secure storage area with limited access.

Risks

The main risks were:

- Minimal vaginal bleeding and/or discomfort during or after the pelvic exam, or bruising and discomfort at the site of blood drawing.
- Women may have felt embarrassed during the pelvic exam.
- Participants may have become embarrassed, worried, or anxious when receiving HIV counseling or when receiving a positive HIV test result. Trained counselors were available to help participants with these feelings.
- Being diagnosed with HIV or another STI may have caused stress on relationships.
- Although study staff made every effort to protect privacy and confidentiality, a participant's involvement in the study could become known to others, and social harms could have resulted if study participation was associated with being at high risk for HIV infection. To minimize the risk of participants being exposed to such stigma, study sites were placed in areas where women could be for several reasons (e.g., shopping, other community services); recruitment materials emphasized that there were several reasons women might not be eligible to participate in the study (not just HIV seropositivity); and much emphasis was placed on community outreach, to educate the community about HIV/AIDS, microbicides, and the microbicide trial.
- Participants may have experienced genital lesions and/or vaginal flora disturbances due to the potential toxicity of the gels.
- Although unlikely, based on phase II data, it is also theoretically possible that the study products could have increased one's risk of getting HIV, although data from earlier safety testing in animals and humans suggested this was unlikely.

Benefits

The following benefits were free of charge for all women:

- Diagnosis of sexually transmitted infections (STIs)/vaginal infections, and treatment of curable ones.
- HIV counseling, testing and condom distribution.

- Annual Pap smears and referral for treatment to a consulting colposcopist for those with cervical dysplasia.
- Women who tested positive for HIV at screening or who seroconverted during the trial were referred for psychosocial counseling and medical support.*
- Referrals for male partners of study participants for STI diagnosis and treatment, and HIV counseling and testing.
- Provision of STI treatment for male partners on site (if desired).
- The opportunity to help testing a vaginal microbicide that may be shown to prevent HIV infection.

Compensation

Participants received a monetary reimbursement at each scheduled study visit for transportation to and from the site, time spent at the site, and any other costs associated with the volunteer's participation in the study. Participants did not receive any monetary reimbursement for unscheduled visits. Site-specific reimbursement amounts were specified in the informed consent forms for each site and were in the amount of R150 for all visits after the screening visit, as mandated by the South Africa's Medicines Control Council. Sites could choose to provide reimbursement in the form of food/grocery coupons (also in the amount of R150), if they could not safely keep cash at the study site.

Trial Closure Considerations

The Population Council reserved the right to terminate the trial prematurely if study participant recruitment was too slow, if study participant retention in the study was insufficient, if there were serious deviations from the study protocol, and/or if undue risk or efficacy was determined prior to the scheduled trial termination as determined by the DSMB.

Community Outreach

Each study site developed an outreach process for consultation with the local community before, during, and after the trial to help ensure that the research teams were aware of and responsive to local cultural and political concerns. This included, in some cases, Community Advisory Groups (comprised of local researchers, activists, NGO representatives, health authorities), community meetings and information sessions, and posters, fliers, and advertisements about the trial.

* The sites collaborated with public sector clinics and/or private physicians in the trial communities to build a referral network that could cope with the large numbers of participants who could be diagnosed as HIV-positive at screening (for example, the UCT and Medunsa budgets contributed salary support for extra medical staff time at local clinics for the duration of the trial only).

Appendix A. Study Sites

University of Limpopo, Medunsa Campus - Soshanguve, near Pretoria, South Africa

The Soshanguve district is located approximately 30 km from Pretoria, at the border of the Gauteng province. During the apartheid era, Soshanguve comprised the Southern **Sotho**, **Shangaan**, **Nguni**, and **Venda** peoples, hence the name Soshanguve. The current population of Soshanguve is over 500 000. Soshanguve is located approximately 15km from Ga-Rankuwa, where the study management is based at the Medical University of Southern Africa (Medunsa). Medunsa is a large medical campus attached to the Ga-Rankuwa Hospital, now known as the George Mukhari Hospital. An Act of Parliament in 1976 created Medunsa in response to a growing need for black professionals in the health sciences. More than half of South Africa's locally trained black doctors, the majority of black dentists and paramedical staff, and all black veterinarians received their training at Medunsa. The University of the North and Medunsa merged in January 2005 to form the University of Limpopo. The previous Medunsa now forms part of the larger University of Limpopo which comprises the Medunsa Campus and the Turfloop Campus (in Limpopo province).

The Medunsa Campus site PI (Dr. Khatija Ahmed) and trial personnel were based at the Setshaba Research Centre in Soshanguve. The research centre is affiliated to the Department of Microbiological Pathology of the Medunsa Campus. Consultant gynaecological support for the trial was provided by Prof. G. Dreyer (Department of Obstetrics and Gynaecology - University of Pretoria) and Dr P C Nembahe, who provided the medical care and support for HIV positive screened out participants and those who seroconverted during the trial. The regional health department governs Soshanguve 2 and Soshanguve 3 Clinics, which are close together. Most community health services (such as family planning, STD, well-baby, and under-five services) were offered at Soshanguve 2 and 3 Clinic. The Setshaba Research Centre was renovated from the old Soshanguve 1 Clinic, which was offered to the Medunsa research team by the Department of Health. Setshaba has a total of 18 rooms and a large waiting area. Participants were recruited from a variety of centres in Soshanguve, including Soshanguve 1 and 2 Clinics, and all trial study procedures were conducted at the Setshaba Research Centre.

University of Cape Town -- Gugulethu/Nyanga District, Cape Town, South Africa

Gugulethu ("our pride") is a suburb in Nyanga district, which is located 20 km from Cape Town's business district by highway. Nyanga district has a population of approximately 300,000. The district was established in the 1950s for migrant workers, mostly from the Eastern Cape. Even today, the majority of the district's inhabitants are Xhosa speakers and its population is relatively stable compared to nearby, more recently established communities. In the Phase III trial, the HIV prevalence at screening was 18% in the Gugulethu trial population.

The University of Cape Town (UCT) site PI, Dr. Lydia Altini, Co-PIs, Dr. Smruti Patel and Ms Alana de Kock, and most UCT trial management personnel were based at UCT Health Sciences Faculty, in the Department of Public Health and Family Medicine. The team was supported by various specialists at UCT, including Dr. Laura Graves (consulting gynecologist).

All other study personnel were based at the study site in Gugulethu, located at Uluntu ("humanity") Community Center. Uluntu Center is located on a main road, approximately 20

minutes by car from UCT Medical Campus. It is a community center that houses a number of nongovernmental (NGOs) and health care organizations, a Health Department family planning clinic, and a private family physician. The UCT team had two fully equipped research centres within Uluntu. The study site is named Empilisweni: ('Place of Health') Center for Wellness Studies.

In 1999, the UCT trial team obtained approval from the City of Cape Town Health Department to use three rooms in the NY1 Clinic for the Phase II trial. The Phase II trial of Carraguard was conducted at the NY1 Community Health Clinic, which is 5 minutes by car from Uluntu Center. The NY1 Clinic offers a variety of health services to the Gugulethu community, including family planning, STD, well baby and under-five clinics. Furthermore, a shipping container was installed on NY1's premises, and converted into three counseling rooms. The UCT team built ties with all the primary health care facilities in its research catchment area as well as with NGOs, CBOs, FBOs, and civic organizations for consultation and recruitment purposes.

Medical Research Council – Isipingo, near Durban, South Africa

The Principal Investigator of the Durban site, Dr Gita Ramjee, and the study staff were based at the Central MRC, HIV Prevention Research Unit (HPRU) offices at 123 Jan Hofmeyer Road in Westville. This is the central office where duplicate copies of regulatory documents were stored while the original files were maintained at the study site. All financial, operational and human resource support was provided from this central office in Westville.

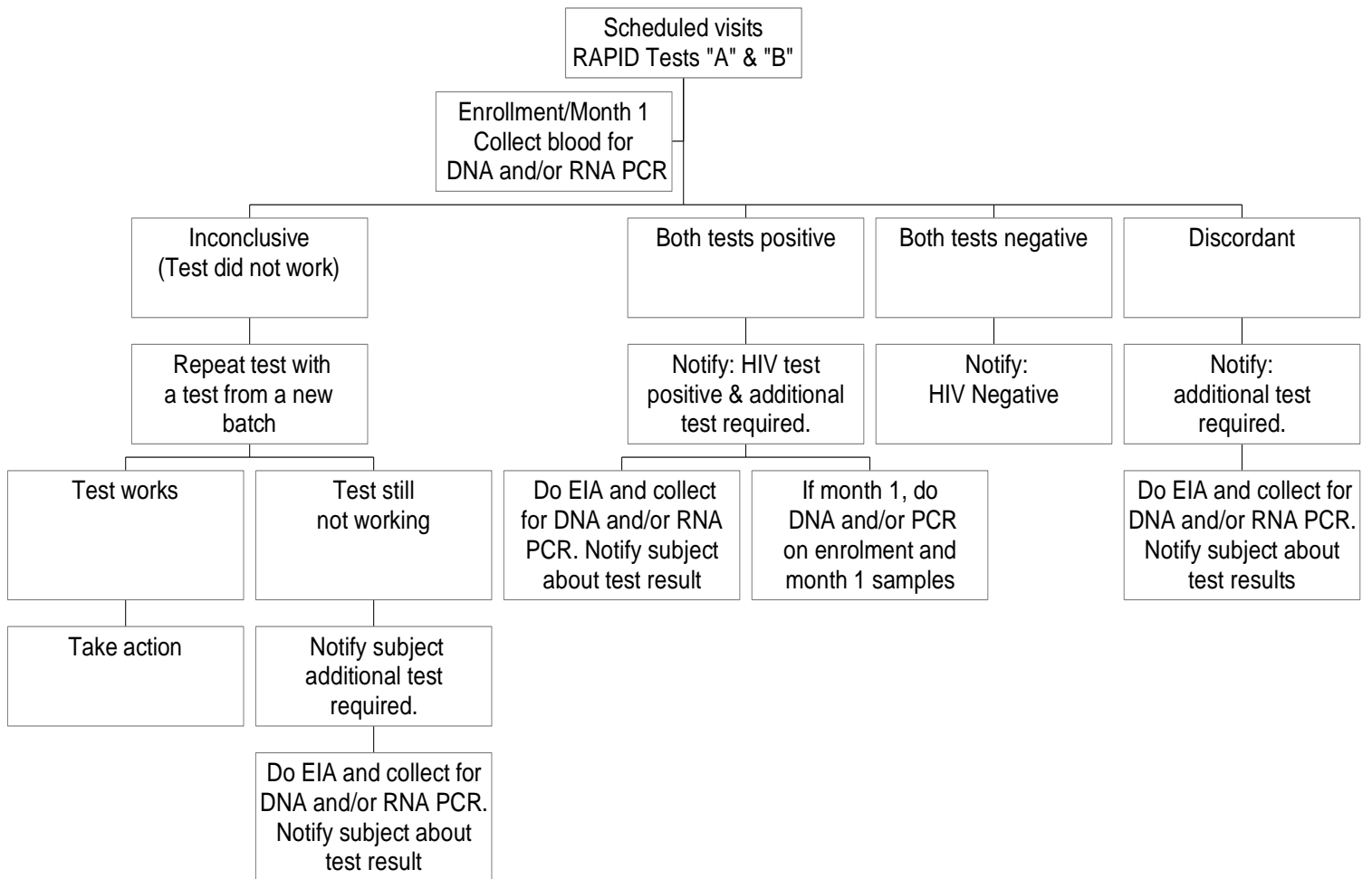
The MRC, HPRU provided study staff with transport to and from the Isipingo clinic site from Monday to Friday in designated MRC Population Council staff vehicles. The study staff travelling to and from the clinic site consisted of the: Project leader, Site Co-ordinators, a Clinician, Nurses, Research Assistants, Fieldworkers/Community Educators, a Community Liaison Officer, and study counsellors (~30 study staff).

The research site/clinic was housed in a pre-existing brick structure that was renovated to include a data room (for storage as well as data-faxing) of participant files, clinical exam rooms, a laboratory, informed consent/interview/counselling rooms, a reception area, toilets, a Carraguard video screening room, and waiting area.

Participants were recruited by a community outreach team, consisting of a community liaison officer, field workers, and educators. The outreach team was assisted by community groups, neighbouring clinics, and hospitals. The site is surrounded by many communities and as a result, based on a situational analysis, the study site had access to a large population of potential trial participants.

The area within the surrounding 10–15 km radius of the Isipingo site is made up of approximately 24 wards and it was from these areas that the study staff recruited participants. Details of the site and the surrounding areas are as follows: The Isipingo site is approximately 20 km south of Durban. The site is situated in Ward 90 next to the Isipingo Hospital Medical Towers. The population race groups resident within this area include Africans, Indians and Coloureds, of which Africans comprise the largest percentage of residents.

Appendix B. HIV Testing Algorithm



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