

USAID Cooperative Agreement
GPO-A-00-04-00019
Population Council Product Development

Year Three Program Report

1 July 2006 – 30 June 2007



March 2008

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GLOSSARY

Population Council Product Development Cooperative Agreement (PCPD). USAID Cooperative Agreement GPO-A-00-04-00019 with the Population Council.

Activity. A conceptually and administratively discrete effort under one of the PCPD programs; and the unit for planning and reporting in workplans and annual program reports. One activity may comprise several studies. (Activities are sometimes referred to as projects.)

Contractor. An entity from which goods or services are purchased by the Population Council under the PCPD. Only contractors for contracts requiring USAID approval are listed [Agreement Attachment A, Article 10]. Consultants are not listed.

Contribution to results framework. For activities under the Microbicide Product Research and Development program, this designation is the USAID Global Health Bureau strategic objective (SO) toward which the activity contributes. For activities under the Contraceptive Product Research and Development program, this designation is the intermediate result (IR) expected from the activity, as specified in the USAID Office of Population and Reproductive Health results framework for Global Health Bureau SO1. The results frameworks are generated by USAID and are available from USAID.

Indirect costs, APC and SS. The Population Council, by agreement with USAID, has a two-tier indirect cost system, consisting of “additional program costs” (APC) and “supporting services” (SS).

Additional program costs are indirect costs incurred solely within the Council’s programs (HIV and AIDS; Reproductive Health; Poverty, Gender, and Youth), for such items as space, general supervision and management, insurance, communications, maintenance, office supplies, and depreciation.

Supporting services, often called “general and administrative” (G&A), are the central costs of sustaining the Council. Included in this category are items such as staff and other expenses incurred in the Office of the President, the Office of the Secretary-Treasurer (Accounting, Finance, Grants & Contracts), and the Corporate Affairs Division (Information Technology, Human Resources, Office Services, etc.).

Period. The expected period of the activity, beginning at the time USAID first funded the activity through a Population Council Program cooperative agreement (either under the current cooperative agreement or under an earlier cooperative agreement) and ending at the time it is expected no more such funds will be spent.

Program. A body of work funded by the PCPD. This document describes activities under or related to the Microbicide Product Research and Development program and the Contraceptive Product Research and Development program. Each body of work is divided into activities.

Results frameworks. Outlines generated by USAID to categorize strategic objectives (SOs), and the intermediate results (IRs) that build toward an SO.

Subawardee. An organization to which an award of financial assistance is made by the Population Council under the PCPD.

Technical coordinator. The Population Council staff member who oversees the activity.

Year One. 1 July 2004–30 June 2005, the first program year of the PCPD.

Year Two. 1 July 2005–30 June 2006, the second program year of the PCPD.

Year Three. 1 July 2006–30 June 2007, the third program year of the PCPD.

Year Four. 1 July 2007–30 June 2008, the fourth program year of the PCPD.

Microbicide Product Research and Development

Program Summary

The goal of the Population Council's Microbicide Product Research and Development program is to develop a female-initiated vaginal microbicide to prevent heterosexual transmission of HIV and other sexually transmitted pathogens. For over 15 years, Council researchers have conducted basic research on HIV transmission and have been pioneers in developing *in vitro* and animal systems to evaluate potential products for microbicidal activity. A unique feature of the Council's program is that its development process is consumer-driven and transparent. Council researchers consult regularly with other scientists and industry partners, as well as with women's health advocates and representatives of the communities where products are tested. The most effective microbicides will be those that women can afford and most easily use. The Council is committed to performing the essential laboratory, product, behavioral, and clinical work required to ensure the timely development and accessibility of its lead candidate microbicide, Carraguard®, and promising second-generation microbicides.

Under the Population Council Product Development cooperative agreement, the Council's microbicides program will focus on activities designed to determine "proof of concept" in developing a vaginal microbicide to prevent transmission of HIV. Development will focus on Carraguard, for which a Phase 3 efficacy trial was recently completed, and the promising new formulation PC-815, which combines Carraguard and the non-nucleoside reverse transcriptase inhibitor MIV-150. Researchers will also continue to improve microbicide clinical trial methodology as needed to promote the research and development of the specific products supported by this agreement. These efforts are intended to facilitate the eventual introduction of one or more successful vaginal microbicides, thus giving women a new option for protecting themselves from HIV infection and helping to slow the AIDS pandemic.

USAID funding has played a key role in supporting the Council's work on microbicides. This funding has been invaluable in attracting other donors (such as the Bill & Melinda Gates Foundation) to support the microbicides program.

Carraguard® Clinical Development: Large-Scale Phase 3 Efficacy Trial

Project Number/s: 88301 (formerly 08301)

Country/ies: South Africa, United States

Technical Coord.: Stephanie Skoler, Sumen Govender, Pekka Lahteenmaki

Period: September 2002 – June 2009

Objective: To determine, by completing a Phase 3 trial, if Carraguard gel can prevent HIV infection in women when used vaginally during sex; if efficacious, to collaborate on a New Drug Application submission.

Activity Description:

Researchers conducted a randomized, controlled, double-blind study to ascertain if Carraguard gel prevents HIV seroconversion in women. At three South African sites, 6,202 women were enrolled. The trial began in March 2004 and lasted three years. Each woman participated from her enrollment until the sooner of two years or the trial's end. Non-pregnant, HIV-negative female volunteers 16–40 years old who lived in the site catchment areas were eligible. Participants were instructed to insert the study gel into their vaginas prior to vaginal intercourse. They returned to the clinic regularly for pelvic exams, HIV testing, testing and treatment for curable sexually transmitted infections (STIs), counseling, interviews, to receive study supplies, and to return used applicators. Site management was aided by a custom-made bar code system and database. Case record forms were faxed to the Population Council (PC) in New York via the DataFax data management system. STI tests, HIV confirmatory testing, and Pap smears were sent to BARC/Lancet Laboratories, an independent laboratory in Johannesburg. Clinic laboratories processed pregnancy tests, HIV rapid tests, and other bedside tests. PC liaised with the study sites, managed gel distribution and regulatory paperwork, facilitated financial administration, and conducted data entry and management. ClinDev (Pty.) Ltd., a contract research organization, monitored the sites to ensure protocol adherence and good clinical practice. A data safety monitoring board (DSMB) convened three times during the trial to ensure participant safety and to monitor trial progress. All applicators that were returned opened were tested to determine if the applicator had been inserted into the vagina. These results will be used with other behavioral indicators to identify adherent participants. There will be both a primary intent-to-treat analysis, as well as a restricted, per-protocol analysis to determine Carraguard's efficacy. The clinics will follow up with all women who seroconverted during the trial to offer them a one time monitoring assessment. The Bill and Melinda Gates Foundation (BMGF) also provides funds for this activity, by supporting the University of Limpopo/Medunsa Campus and Medical Research Council (MRC) subawards, and most laboratory, monitoring, and international travel costs. USAID supports PC salaries and benefits, the University of Cape Town subaward, PC Johannesburg office expenses, DataFax and related costs, and domestic travel.

Report of Year Three

July-December 2006: Follow-up of enrolled women continued. At their one-year visit, 85 percent of women who had enrolled were still in the study, which exceeded the projected retention rate of 80 percent. Applicator testing and participant interviews were ongoing, with 243 of the 1,500 planned exit interviews completed. In early September, senior PC staff and the MRC principal investigator presented the trial to representatives from the South African Medicines Regulatory Affairs (MRA), a new chief directorate within the health ministry tasked with making recommendations on product registrations following scientific review by the Medicines Control Council. The MRA responded positively to the study, and the

possibility of a fast-track registration was explored. Also in early September the statistical analysis plan (SAP) was submitted to the FDA. In late September, the DSMB met for a final interim review of the data, which focused on safety and efficacy. It was not recommended to stop the trial prematurely. In preparation for the DSMB meeting, PC performed several analyses, which per the SAP will also be used in final report. Consequently, slight revisions and clarifications were made in the SAP, and a revised draft was circulated among the relevant PharmaLink and PC staff. PC data management continued to collaborate with the sites and the central laboratory to resolve data queries. To expedite the determination of the gel's efficacy, it was decided to outsource execution of the SAP to PharmaLink, allowing PC programmers to focus exclusively on data cleaning in 2007. PharmaLink staff visited PC and submitted a formal proposal in late December.

January-June 2007: Participant follow up at the sites was concluded on March 31, 2007. This was a milestone in the microbicide field, as the Carraguard trial is the first Phase 3 clinical study of a product designed specifically to be a microbicide to be completed without safety concerns. Staff in New York, the trial sites, and at Lancet Laboratories continued to resolve data queries. The Council signed a contract with Pharmalink in January 2007 to execute the SAP and sent sample data at that time. Pharmalink began programming the analysis and tables for the final report, based on this data, in February. In March 2007, staff from Pharmalink met with PC staff in New York. During the meeting, it was decided that once the data is clean, Council programmers will share the workload for the final report with Pharmalink in order to speed timelines and reduce the overall cost of outsourcing. Currently, the data processed through DataFax is on schedule to be clean by the end of May 2007, and the entire database (including lab data which is not processed through DataFax) is on track to be clean by the end of June 2007.

In April, the PC study team began writing the first nine sections of the FDA report because they can be prepared prior to having study results. The final report for the FDA and the MCC is planned to be completed in the last quarter of 2007 as planned. Five abstracts were submitted for the 3rd South African AIDS Conference, which will be held in Durban, South Africa from June 5-8. Two were accepted as oral presentations and three were accepted as posters. An Investigator meeting will be held in June 2007 during the two days prior to the conference. The meeting will focus on finalizing plans for the release of results to the participants, local media, collaborators, and other stakeholders, as well as manuscript preparation for the main outcome and subanalyses on adherence, pregnancy, STI risk, and acceptability. Following the meeting, the Council's Director of Public Information will conduct private media training sessions with key personnel in order to improve interviewing skills in preparation for the release of trial results in early 2008. Finally, through the end of 2007, the clinics will be following up with all women who seroconverted in the trial (approximately 300), and offering a one time monitoring assessment. (This follow-up and assessment will be funded through the sites' subawards with lab tests supported by Gates and, if necessary, supplementation by the PC's own funds. See "Carraguard Informed Consent" activity for more information.)

Subawardee(s): University of Cape Town (CB05.101A)
Medical Research Council (cost share)
University of Limpopo / Medunsa Campus (cost share)

Contractor(s): Clindev (Pty.) Ltd. (cost share)
DF/Net Research, Inc.
Lancet Laboratories (USAID and cost share)
MRP Solutions

PharmalinkFHI, Inc.

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Carraguard® Nonclinical Development

Project Number/s: 88302 (formerly 08302)

Country/ies: Sweden, United States

Technical Coord.: Robin Maguire

Period: July 2001 – June 2009

Objective: To conduct the nonclinical activities necessary to support the Phase 3 clinical trial of Carraguard and to advance Carraguard through the development pipeline.

Activity Description:

Carraguard nonclinical development supports the Phase 3 trial and completes the necessary testing and development steps to bring Carraguard to market. To date, all funds supporting Carraguard nonclinical projects come from USAID.

Production and supply of study gels to trial sites

Phase 3 production includes manufacture of the study gels (Carraguard and methyl cellulose placebo), filling of the gels into single-use vaginal applicators, and packaging and shipping of the filled applicators to the trial sites in South Africa. Clean Chemical Sweden (CCS) executes these tasks under contract. For the trial, 15 to 18 batches of each gel (approximately 65,000 applicators per batch) are needed.

Control testing of each production batch of gel

The manufacturing process involves control testing each production batch to ensure that the gel is free of impurities, meets chemical and physical criteria, and is either biologically active (Carraguard) or inactive (placebo). The various control tests are performed by the Population Council, The National Food Laboratory, Inc. (The NFL), CCS, ImQuest BioSciences, Inc. and Sterilization Technical Services.

Stability testing of gels

Carraguard will undergo a five-year stability analysis: a five-year stability profile would provide major support for obtaining over-the-counter product labeling. Samples from the first three production batches of Carraguard and the methyl cellulose placebo gel have been stored by CCS since February 2004 under various conditions. At specified time points, samples are tested by the Population Council, The NFL, CCS, and ImQuest. The stability program follows the guideline of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Patent protection and trademark rights for Carraguard

The Council will finalize and file a patent application to the U.S. Patent and Trademark Office (USPTO) by October 2004, with further filing and legal activities necessary throughout the agreement. In addition, Carraguard's registered trademark will be maintained.

Registration of Carraguard and its active pharmaceutical ingredient (API) with the United States Pharmacopeia and National Formulary (USP/NF)

If Carraguard proves efficacious, comprehensive chemical monographs for Carraguard and for its API must be developed and submitted to the USP/NF for registration of these entities as active pharmaceutical ingredients. These registrations are a necessary step toward U.S. Food and Drug Administration (FDA) approval to market Carraguard. Preparation of the monographs is planned for 2007, after the completion of the Phase 3 trial, for submission in 2008. The monographs will also be submitted to the European

Pharmacopeia and the Japanese Pharmacopeia.

Preparation of a New Drug Application (NDA) to the FDA

If Carraguard proves efficacious, an NDA will be prepared in collaboration with the clinical team for submission to the FDA in 2008.

Report of Year Three:

Production and supply of study gels to trial sites

July–December 2006: Gel was shipped to sites as needed for conclusion of the Phase 3 trial. Logistical plans were made with CCS for the production of five batches of Carraguard for post-trial needs.

January–June 2007: Gel was shipped to sites as needed for conclusion of the Phase 3 trial. No additional gel production was necessary.

Control testing of each production batch of gel

July–December 2006: Control testing and release testing was completed on all batches of gel produced March–June 2006.

January–June 2007: Gel was shipped to sites as needed for conclusion of the Phase 3 trial. No additional gel production was necessary

Stability testing of gels

July–December 2006: Passing results of the 24-month stability tests were received.

January–June 2007: 36-month stability began. The samples passed the chemical and physical identity tests and the HIV-activity assays. Results were expected late May/early June for the impurities testing. It was decided to continue stability testing on the methyl cellulose placebo gel past the end of the Phase 3 trial because methyl cellulose gel may prove to be a safety vehicle for vaginal drug delivery.

Patent protection and trademark rights for Carraguard

July–December 2006: An Information Disclosure Statement (IDS) was filed with the USPTO in November.

January–June 2007: An IDS was filed with the USPTO in February.

Registration of Carraguard and its active pharmaceutical ingredient with the United States Pharmacopeia and National Formulary

July–December 2006: No activity.

January–June 2007: No activity, since development and validation of the monographs will commence upon favorable results from the Phase 3 trial, expected in the fourth quarter of 2007.

Preparation of a New Drug Application to the FDA

July–December 2006: In preparation for possible registration of Carraguard, the conversion of the regulatory file for Carraguard to an electronic Common Technical Document was undertaken.

January–June 2007: Work continued to convert the regulatory file for Carraguard to an electronic Common Technical Document. PC staff worked closely with CCS to gather CMC (Chemistry, Manufacturing and Controls) documents in preparation for submission to regulatory agencies.

Contractor(s): Clean Chemical Sweden (CCS)
ImQuest BioSciences, Inc.

Lerner, David, Littenberg, Krumholz & Mentlik, LLP
Sterilization Technical Services
The National Food Laboratory, Inc. (The NFL)

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Informed Consent and Behavioral Aspects of Carraguard® Trials

Project Number/s: 44211

Country/ies: South Africa, United States

Technical Coord.: Barbara Friedland

Period: July 2001 – June 2008

Objective: To manage the behavioral aspects of the Population Council's Phase 3 Carraguard trial, including development, implementation, and evaluation of materials and procedures for informed consent, recruitment and retention, counseling, care and support for HIV-positive women, and community relations.

Activity Description:

Behavioral research, with a focus on the ethical treatment of research participants, has been a fundamental aspect of the Population Council's microbicide program since its inception in the early 1990s. In particular, researchers at the Council, one of the first organizations to mount a Phase 3 efficacy trial, have been at the forefront of research on informed consent and efforts to improve standard of care for trial participants within the microbicides field. Complementing the activity "Carraguard Clinical Development," this activity includes management of the behavioral aspects of the Carraguard Phase 3 trial, including developing, implementing, and evaluating materials and procedures for informed consent, recruitment and retention, counseling, care and support for HIV-positive women, and community relations. The behavioral coordinator at the Population Council (Barbara Friedland) will lead periodic meetings and conference calls to address ongoing behavioral issues that arise during the trial.

Informed consent: A quantitative evaluation of the effect of the recruitment video on comprehension and willingness to participate in the Phase 3 Carraguard trial will be completed. The results of this evaluation will be critical to guiding the development of materials for the Phase 2/3 trial of PC-815, as well as for the microbicide field.

Recruitment and retention: Recruitment and retention will be monitored on a monthly basis in order to adapt procedures as needed. Workshops and site exchanges will be implemented among relevant study staff, as needed, throughout the trial.

Counseling: Ongoing monitoring of the counseling process will occur through monthly reports from the study sites as well as bi-annual evaluations of each counselor.

Care and support for HIV-positive women: Population Council staff will assist site investigators with careful monitoring of the referral strategies for HIV-positive women to ensure that they have access to appropriate support and care, and where possible, will foster new collaborations to facilitate the care and support of women who test positive at screening or during the trial.

Community relations: Population Council staff monitor community relations at the clinical trial sites, including review of minutes from community advisory group meetings and community meetings, as applicable.

Report of Year Three:

Behavioral staff collaborated with biomedical staff to develop the outline for the final Carraguard Phase 3 study report, including finalizing the statistical analysis plan [See Carraguard Clinical]. In addition, the behavioral team worked with the trial sites and the clinical team to begin the development of messages for communicating trial results to study participants and local and international communities, in preparation for the results which are anticipated to be available in the last quarter of 2007. In the first quarter of 2007, messages were crafted to explain the scheduled end of data collection, the data analysis process, and when results would be available. These messages were then translated into local languages at each site for distribution to trial participants and community members while the data analysis proceeds. Once the results of the trial are known, messages will be developed to explain them to participants and community members.

Exit Interviews

July–December 2006: The exit interviews developed during the July 2005–June 2006 program year were administered to women completing trial participation starting in October 2006.

January–June 2007: A total of 1,597 exit interviews were received by May 8, though we expect to receive another 15 once all forms have been faxed through. Data from the exit interviews will be analyzed as part of the main study data, with additional analysis being conducted in conjunction with the qualitative Acceptability Study (see Social Science project 44213). Preliminary data indicate that fewer than 5% of the women reported having squeezed out study gel that they had not inserted vaginally, the majority of whom did this to please the study staff.

Informed consent

July–December 2006: Preliminary analysis was completed for the quantitative informed consent study which is assessing the impact of the video on the informed consent process. An abstract on this study was prepared for submission to the 3rd South African AIDS Conference to be held in June 2007, and preparation began on a manuscript for submission to a peer-reviewed journal.

January–June 2007: The abstract submitted to the South African AIDS Conference was accepted as a poster presentation, and is being produced by staff at the Population Council. Data analysis has been completed and we anticipate submission of the paper to a peer-reviewed journal by the end of June or beginning of July 2007. Our original plan had been to complete the project by December 2006, however, the research assistant originally hired to work on this project left in the summer of 2006 and a new research assistant did not start until October 2006, which led to delays in completing analysis and write-up of the study.

Recruitment and retention

July–December 2006: A successful workshop was held in July 2006 for study staff to exchange challenges to and strategies for retention through the end of the Phase 3 trial in March 2007. A report from the meeting was being prepared for publication together with the results from the recruitment workshop held in March 2006.

January–June 2007: The last participant visit was on March 31, 2007. The strategies implemented by the three sites enabled a high rate of retention [see Carraguard Clinical]. Ms. Alana de Kock from the University of Cape Town will be giving an oral presentation at the South African AIDS Conference on the challenges and successful strategies for recruiting and maintaining a large cohort (funded under Carraguard Clinical). The July 2006 meeting report as well as the paper for submission to a peer-reviewed journal

were being prepared for publication.

Counseling

July–December 2006: Monthly monitoring of counseling reports from each site continued, as well as the bi-annual counseling evaluations. Issues arising were addressed, as needed, by periodic conference calls among the behavioral group.

January–June 2007: The behavioral team had several conference calls between January and March 2007 to address issues arising during counseling sessions which were related to study close out and to the early closure of the Cellulose Sulfate trial. Messages were developed for study participants and communities regarding the CS trial to emphasize the differences between that trial and the Carraguard trial and to emphasize that the Carraguard Phase 3 Data Safety Monitoring Board (DSMB) had reviewed the study three times and found no safety concerns. The team also addressed specific messages for how participants could continue to negotiate condom use with their partners once the trial is over, as well as alternative lubricants for women who said they would miss the lubricating quality of the gels. This was also an important opportunity to reinforce to women the unknown efficacy of the gel and to remind them if they purchase other lubricants, they would not provide any protection against HIV or other sexually transmitted infections.

Care and support for HIV-positive women

July–December 2006: The proposed collaboration with BroadReach Healthcare has been on hold as the Population Council and BroadReach work together to establish the appropriate memoranda of understanding with the provincial ministries of health necessary in order to implement the expanded monitoring program.

January–June 2007: After many attempts to collaborate with BroadReach Healthcare to expand access to ARVs for women who screened out of or seroconverted in the Phase 3 trial, we learned that BroadReach had already spent the \$1 million given to them by PEPFAR in order to meet their quotas for the fiscal year. Therefore, we are now pursuing an approach that focuses on the women who seroconverted in the trial, only, in which each of the women (approximately 300) will be offered a one-time monitoring assessment. This assessment will be funded through the sites' sub-awards (under the Carraguard Clinical activity), with lab tests supported by Gates and, if necessary, supplementation by the Population Council's own funds. The goal is to contact each of the seroconverters to document what services she has and is receiving and to offer each woman a check-up at the clinic. The check-up would entail a physical exam with clinical staging per the WHO guidelines, a CD4 test, and a pelvic exam with Pap smear for women whose last Pap smear was more than one year ago. During this period we will be finalizing the questionnaire that will be administered to as many women as we are able to contact and developed the lab testing protocols and procedures. The goal is to begin implementing these monitoring visits as soon as possible and to complete them by the end of December 2007.

Subawardee(s): Community Agency for Social Enquiry (CASE) (I05.43A)

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

PC-815 Nonclinical Development: Phillips Laboratory

Project Number/s: 88303 (formerly 08303)

Country/ies: United States

Technical Coord.: Robin Maguire, David Phillips

Period: January 2003 – June 2014

Objective: To determine the optimal concentrations and chemical form of each ingredient in PC-815 and the best method of combining the compounds for safety, ease of production, and the highest degree of effectiveness in preventing transmission of HIV and other sexually transmitted infections (STIs); and to develop protocols and administer a manufacturing scale-up of PC-815 for use in clinical trials.

Activity Description:

PC-815 combines the non-nucleoside reverse transcriptase inhibitor (NNRTI) MIV-150 with Carraguard® in a proposed novel second-generation microbicide. Carraguard serves as the vehicle base for MIV-150.

The Phillips laboratory developed a screening and development regimen for novel microbicides to systematically narrow the focus of research to the safest formulations demonstrating the highest degree of efficacy against the broadest range of STIs. PC-815 formulations will be put through this multistage evaluation. The first stages of screening will allow for preliminary selection of formulations for further evaluation, including the selection of formulation(s) for use in a Phase 1 clinical trial. Later screening stages employ increasingly more extensive and sensitive assays that allow researchers to make comparisons and establish parameters for lead candidate formulations. It is prudent to advance multiple formulations through the development pipeline should outcomes from nonclinical or clinical testing show that the lead formulation is unsuitable. In the final stages of development, the laboratory will focus on one (or possibly two) candidate formulation(s) and on aspects of formulation optimization such as preservative efficacy and condom integrity testing.

In support of clinical trials, an Investigational New Drug (IND) application and an Investigator's Brochure (IB) will be written and the trial gels (PC-815 and Carraguard) produced for use in Phase 1 clinical trials. For the Phase 2/3 trial, technical transfer and scale-up of manufacture for production of larger amounts of the gels will take place. Laboratory technicians will chemically characterize trial formulation(s) to establish a chemical profile, critical to ensuring batch-to-batch consistency in production and for gaining regulatory approval for the clinical trials.

Funding from the Swedish Ministry for Foreign Affairs will be used to help support this activity beginning in 2005, and the Council expects to continue seeking support for this activity.

Report of Year Three:

July–December 2006: The nonclinical team continued to compile a response to the FDA's March 2006 comments on the IND, including addressing concerns regarding use of an anti-viral as a prophylactic agent against HIV. The FDA's request to receive in one package the supplemental study reports and the results of the additional rabbit and rat repeat dosing vaginal irritation tests (both requested by them in March 2006), combined with contractor Toxikon's delay in executing the rat repeat dosing test, put submission of the Council's response in the first half of 2007.

In August, a meeting was held at CCS to discuss scale-up for production of study gels for the Phase 2/3 trial.

In the lab, a new formulation manufacturing room was established. With this, a new stability regimen was established, and new incubators were added. In addition, the PC-815 formulations underwent further optimization, with the establishment of a new manufacturing protocol to ensure better incorporation of MIV-150, and the development of a more appropriate measuring technique of MIV-150 within the formulations. Stability tests commenced on each new optimized formulation. Additional testing in the lab showed that PC-815 had no effect on the growth of *Lactobacillus acidophilus* or spermatozoa, as shown by the Sander Cramer test.

A 14-day rabbit and rat vaginal irritation test that mimicked the dosing regimen to be used in the first Phase 1 trial was completed by Toxikon.

The lab began testing PC-815 against two multi-drug-resistant HIV strains. In addition to the traditional MAGI assay used for control and stability testing of formulation activity against HIV, an assay has been developed in the lab where immunofluorescence is used to show HIV-1MN uptake by TZM-bl cells to isolate Carraguard activity. By using two different strains of the virus and two different methods we can isolate the specific activity of carrageenan and of MIV-150. We are also developing, after transfection with different plasmids, a T cell line-based reporter cell line (SupT1) that expresses CCR5 and CXCR4 HIV-1 co-receptors. Once fully developed, this assay allows for a quick screening process, as well as minimal manual work, which are both advantageous when screening large amounts of different formulations at one time.

In addition, the nonclinical team continued to provide the necessary gels to the Robbiani lab for the monkey studies, and to work with the Intellectual Asset Management team to find a possible new manufacturer for PC-815 as well as a provider of carrageenan.

January–June 2007: The main set of responses to FDA's March 2006 comments on the IND, including the revised Protocol 362, was sent in early May. The nonclinical team expects to send an additional submission by June to complete its response to the FDA's March 2006 comments. The FDA did not comment on the revised protocol or IND in 30 days from receipt, therefore Protocol 362 may proceed. In-house production of gels and control testing for the Phase 1 trials commenced. The PC-815 gel is the most optimal low-strength formulation to have passed necessary stability tests.

In May, a meeting was held at CCS to further discuss transfer of technology and scale-up for production of study gels for the Phase 2/3 trial.

A new stability program was established, which includes testing for efficacy and consistency between batches, as well as for the physical properties. Three batches of the formulation will be made, and then each will be divided into three jars, to be stored at the three testing temperatures. On a monthly basis, each batch at each temperature will be tested for physical properties, with efficacy being tested in the HIV *in vitro* model and

HSV-2 mouse model on a rotating basis.

In April, results from the 14-day rabbit and rat vaginal irritation tests were received from Toxicon. The test compared PC-815 with Carraguard (negative control) and Methyl Cellulose w/MIV-150 (positive control). All three gels showed none to minimal irritation in both sets of animals, showing that neither MIV-150, nor the combination of MIV-150 and Carraguard in PC-815 caused irritation..

Building on work from the first half of the program year, the lab continued to develop a high throughput *in vitro* fluorescence assay to test anti-HIV drugs. Work began on a mono/mac-1 (DSMZ monocytic) cell line that has been proven susceptible to HIV-1 infection. The cell line will be transfected with plasmid that contains a reporter gene under the control of LTR HIV-1 sequence. Once a clone is isolated, the previous cell line reported (SupT-1 cells) and the new clone are combined in an assay that mimics the target cells in PBMCs (lymphocyte CD4+ T cells and monocytes).

Planned acute pharmacokinetic studies using radioimmunoassay to detect systemic absorption of MIV-150 both *in vitro* and *in vivo* in rat models and ReproTox Segment I testing will now take place during the July 2007–June 2008 program year.

Additionally, the nonclinical team continued to provide gels to the Robbiani lab for monkey studies. Work continued to find a carrageenan manufacturer, and to find a manufacturer for PC-815, with Robin Maguire traveling to South Africa in March for this purpose.

Contractor(s): Chilean Institute of Reproductive Medicine (ICMER)
Clean Chemical Sweden (CCS)
ImQuest BioSciences, Inc.
Lerner, David, Littenberg, Krumholz & Mentlik, LLP
North American Science Associates
SouthernBiotech
Sterilization Technical Services
The National Food Laboratory, Inc. (The NFL)
Toxikon Corporation

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

PC-815 Nonclinical Development: Robbiani Laboratory

Project Number/s: 87303 (formerly 09303)

Country/ies: United States

Technical Coord.: Melissa Robbiani

Period: July 2004 – June 2009

Objective: To test PC-815 for efficacy in a variety of *in vitro* dendritic cell (DC) and *in vivo* monkey systems developed by Population Council senior scientist Melissa Robbiani.

Activity Description:

The Robbiani laboratory will test the ability of PC-815 (Carraguard® with MIV-150) to block the transmission of HIV and/or SHIV-RT (chimera of SIV with the HIV reverse transcriptase [RT]) by dendritic cells (DCs) across the mucosa. Agents like PC-815 act in a general manner to block virus–cell interactions and potentially to inactivate immunodeficiency virus. *In vitro* DCs or DC–T-cell mixtures will encounter HIV or SHIV-RT alone or in combination with model STIs (HSV-2) in the presence or absence of PC-815, to determine whether PC-815 blocks virus capture by DCs and/or impedes the transmission of virus from DCs to T cells. Results from these studies will support the extensive *in vivo* studies, which are the primary focus of this project.

The *in vivo* studies, executed by the TNPRC, will use SHIV-RT to test (1) the ability of PC-815 vs. the methyl cellulose (MC) placebo to prevent SHIV infection in healthy and STI-infected macaques; and (2) the optimal timing for use of the gel — pre or post virus exposure. All *in vivo* studies will involve the use of formulations provided by the Phillips laboratory. PC-815 formulations containing different doses of MIV-150 are being tested when applied before and after virus exposure to best parallel human studies and advance product development.

The Aaron Diamond AIDS Research Center provides a liaison at TNPRC to coordinate sample procurement and shipping, schedule animal experiments, and help troubleshoot.

Report of Year Three:

July–December 2006: Results from the last three years indicate that PC-815 prevents SHIV-RT infection comparably to Carraguard when applied 30 minutes before virus challenge (Table 1). Of note, after careful analysis of complete data from all animal sets including recycled animals used to test virus dosing, the 10^4 SHIV-RT dose appeared to overwhelm the system with some animals becoming infected. Therefore, it was decided the lower 10^3 TCID₅₀ dose would be used to evaluate PC-815 further.

By recycling uninfected animals, during this period we performed additional challenges and tested the activity of MIV-150 in MC. As expected, MIV-150 alone is not as effective as PC-815, but can restrict SHIV-RT infection. Results indicate that a single dose of MIV-150 given 30 minutes prior to SHIV-RT exposure exhibited little or no activity. When MIV-150 was administered the day before (d-1), day of (d0), and day after (d+1) for a total of three doses, comparable activity to a single dose of PC-815 was observed.

We initiated testing PC-815 in HSV-2–infected animals. The animals from the July 2005 - June 2006

program year were HSV-2 infected and co-challenged with 2×10^8 pfu HSV-2/ 10^3 TCID₅₀ SHIV-RT in the presence of MC or PC-815. The animals from the July 2006 - June 2007 program year were HSV-2 infected and will be challenged with HSV-2/SHIV-RT in the presence of the gels in early 2007. Blood and swabs are being sampled at specific time points and assayed for viral loads and immune activation, and results are expected in the first half of 2007.

We are also exploring if PC-815 is effective in naïve animals when applied 24 hours before SHIV-RT exposure. In addition, with co-funding from Sweden's Ministry for Foreign Affairs (SMFA), we are studying if PC-815 continues to inhibit infection when applied 1 or 4 hours post vaginal 10^3 TCID₅₀ SHIV-RT challenge. Due to space restrictions at TNPRC, just half of the animals for these timing studies were purchased during this period. The pre and post treatment studies will be run in parallel, and the first studies were initiated.

January-June 2007: We began compiling all data in which Carraguard and PC-815 were compared, and plan to submit the following manuscript detailing their protective capacities by September 2007: Turville, S.G., Miller, T., Aravantinou, M., Teitelbaum, A., Li, J., Romero, J., Phillips, D., Piatak, M., Bess Jr., J.W., Lifson, J.D., Blanchard, J., Gettie, A., and Robbiani, M. 2007; Efficacy of carrageenan-based microbicides *in vivo* is discordant with their *in vitro* activity against CCR5-tropic infection; *In preparation*.

Additionally, the studies investigating the efficacy of PC-815 in the HSV-2 infection model continued. Data points from the HSV-2-infected animals co-challenged with HSV-2/ 10^3 TCID₅₀ SHIV-RT (in the presence of MC vs. PC-815) continued to be collected and analyzed. Preliminary results indicate that while the 4 placebo MC-treated animals are infected with SHIV-RT, the 8 PC-815-treated animals appear negative for SHIV-RT up to six weeks post challenge. Immune analyses have verified the presence of HSV-2-induced immune responses within vaginal fluids and blood collected from the animals. The final sampling of these animals will continue through October 2007 and all data analysis should be completed by December 2007, at which point it will be prepared for publication. These preliminary data provide additional support for the ability of PC-815 to protect against SHIV-RT, and reveal the first evidence that PC-815 appears as effective in HSV-2-infected animals as it is in naïve animals, even though the frequency of SHIV-RT infection in MC-treated HSV-2-infected animals is greater (90%) than in MC-treated naïve animals (50%).

The testing of PC-815 for its ability to block infection when applied 24 hours before, or 1 or 4 hours after, SHIV-RT challenge of naïve animals continued in the first set of animals. (Additional support from SMFA helps fund the post-challenge study.) The remainder of the animals was ordered and they are expected to arrive during the last half of 2007. Due to the inevitable delays in procuring the animals, this study will extend beyond mid 2007 into early 2008.

In order to explore the effects of MIV-150 more closely, we again recycled uninfected animals and applied MIV-150 in MC at both d-1 and d0 prior to challenge or on d0 and d+1 after challenge. The pre-treatment combination resulted in 66% protection compared to 0% protection when MIV-150 was applied on d0 and d+1 post challenge. This requirement for the presence of MIV-150 during the initiation of infection parallels what we observed in our *in vitro* assay systems. Once the final data sets are collected, we plan to submit a manuscript describing these observations by early 2008. These studies are exceedingly promising for the potential use of gels independent of coitus in situations in which the gels could be applied up to a

day or more before exposure and still remain effective. Moreover, this is also promising for the potential development of MIV-150 alone and/or in combination with other anti-viral compounds utilizing the vaginal ring as the delivery mechanism.

Subawardee(s): Tulane National Primate Research Center (TNPRC) (B06.120XA)

Contractor(s): Aaron Diamond AIDS Research Center

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

PC-815 Clinical Development

Project Number/s: 88304 (formerly 08304)

Country/ies: Dominican Republic, South Africa, United States

Technical Coord.: Stephanie Skoler, Sumen Govender, and Pekka Lahteenmaki

Period: July 2004 – December 2012

Objective: To determine the efficacy of the candidate second-generation vaginal microbicide PC-815, and to collect data for supporting the New Drug Application, by carrying out five Phase 1 trials and a large Phase 2/3 trial.

Activity Description:

PC-815 combines the non-nucleoside reverse transcriptase inhibitor MIV-150 with Carraguard® in a second-generation microbicide. Carraguard serves as the vehicle for MIV-150. Clinical testing on PC-815 contributes to the development of female-initiated HIV prevention technologies.

The PC-815 clinical development plan includes five Phase 1 trials, proceeding directly to a Phase 2/3 trial. The first Phase 1 trial, to ensure vaginal safety in HIV-negative women and determine preliminary pharmacokinetic properties of the formulation, will be conducted under the direction of International Committee for Contraception Research (ICCR) member Vivian Brache at the Asociación Dominicana Pro-Bienestar de la Familia (Profamilia/DR) clinic in the Dominican Republic. Pending approval of the US FDA, the study will commence in mid-2008. Per the protocol, 20 women will be enrolled and randomized to either Carraguard or PC-815. Carraguard will serve as the control gel, as it has been shown to cause minimal irritation to the vagina and cervix. After an initial application of either gel, participants will apply one 4-ml dose of that gel for six consecutive days, followed by two doses a day for seven additional consecutive days. After a washout period, the participant will apply the other gel under the same regimen. Colposcopy will be taken at baseline, after initial application of gel, during the washout period, and at the final visit. The local irritation effects of the two gels will be compared, each participant serving as her own control. Blood samples will also be taken to determine the absorption of MIV-150 after vaginal administration of PC-815.

Assuming success, this study will be repeated under the direction of ICCR member Dr. Livia Wan of the New York University (NYU) Medical Center, Family Planning and Reproductive Health Division, at Bellevue Hospital in New York, in an effort to collect additional safety data while ensuring that safety studies are conducted in study populations other than the underserved, and those in developing countries.

Three more Phase 1 trials will assess safety and absorption in HIV-negative men. These trials will take place at the Setshaba Research Center in South Africa, one of the Carraguard Phase 3 trial sites, managed by the University of Limpopo/Medunsa Campus; and at both the Profamilia/DR and the Bellevue/NY sites that will manage the Phase 1 studies in women.

While the Phase 1 trials are in progress, a Phase 2/3 protocol will be developed and submitted for regulatory and ethical approvals. The Phase 2/3 trial will aim to determine the efficacy of PC-815 at preventing HIV infection in women. The trial is expected to begin in 2009, and will compare PC-815 to Carraguard. Similar to the Carraguard Phase 3 trial, this randomized, controlled, and double-blind study will take place in South Africa.

Through implementation of the Carraguard Phase 3 trial, Population Council (PC) researchers have established a strong infrastructure for the management of large microbicide trials, and a close collaboration with several clinical trial sites in South Africa. Existing standard operating procedures and DataFax-specific case record forms will provide ideal templates for PC-815 data collection and protocol implementation.

The budget for this activity does not include subawards to trial sites. The Swedish Ministry of Foreign Affairs has committed funds toward the development of PC-815, and some of these funds will be used to support this activity. Additional funding for Phase 2/3 trial sites must also be secured.

Report of Year Three:

July–December 2006: The Profamilia/DR's IRB granted approval for Amendment 2 to the female safety study of PC-815 (Protocol 362), in late June 2006; however the study could not begin until at least 30 days after the Council submits responses to the US FDA's March 2006 comments on the IND. In December, the FDA requested that an analysis of vaginal flora, and the test to determine whether an applicator has been inserted into the vagina, be added to Protocol 362. A final draft of the penile safety protocol was circulated for review by the investigators

January-June 2007: The revision to Protocol 362 requested by the FDA, which added the applicator test and analysis of vaginal flora, was made in January and submitted to the IRBs. The Population Council's IRB approved this amendment; however, it was still pending approval with the Profamilia/DR IRB as of mid-June. Responses to the March 2006 comments sent by the US FDA on the IND were submitted in early May, and no additional comments were received within the 30-day period. Therefore, pending approval of the latest amendment from the DR IRB (expected in late June), the initial PC-815 safety study will begin in early August 2007.

Previously, the product development plan for PC-815 included a study to determine if PC-815 reduces the infectivity of vaginal fluid of HIV positive women (Protocol 366). This study was put on hold, mainly due to methodological challenges of measuring infectivity.

The penile safety protocol was reviewed by the Population Council IRB in May, and was approved pending a few minor changes; it was also submitted to the University of Limpopo IRB that same month. Due to the overall delays on the testing of PC-815, finalizing the penile safety protocol was not prioritized. For the same reason the Phase 2/3 protocol was not yet drafted.

Further development of the Phase 1 trials yielded the decision to repeat the female and male safety studies in better-served and developed-country populations. Doing so maximizes safety data on PC-815 thereby addressing concerns about ARV-containing microbicides, and ensuring that the balance of testing between developed and developing countries is fair and ethical, without a significant increase in the cost of the clinical trials.

Contractor(s): Clindev (Pty.) Ltd.
DF/Net Research, Inc.
Synexa Life Sciences

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Informed Consent and Behavioral Aspects of PC-815 Trials

Project Number/s: 44214

Country/ies: South Africa, United States

Technical Coord.: Barbara Friedland

Period: January 2006 – December 2011

Objective: To manage the behavioral aspects of the Population Council's PC-815 trials, including development, implementation, and evaluation of materials and procedures for informed consent (IC), recruitment and retention, counseling, care and support for HIV-positive women, and community relations.

Activity Description:

Behavioral research, with a focus on the ethical treatment of research participants, has been a fundamental aspect of the Population Council's microbicides program since its inception in the early 1990s. As noted by Council researchers and colleagues at the 1997 Symposium on Practical and Ethical Dilemmas in the Clinical Testing of Microbicides, behavioral measures are critical for interpreting trial data. In addition, researchers at the Council, one of the first organizations to mount a Phase 3 efficacy trial, have been at the forefront of research on informed consent and efforts to improve standard of care for trial participants within the microbicides field. Complementing the activity "PC-815 Clinical Development," this activity includes management of the behavioral aspects of clinical trials of PC-815, including developing, implementing, and evaluating materials and procedures for informed consent, recruitment and retention, counseling, care and support for HIV-positive women, and community relations.

For PC-815, the clinical development plan includes five Phase 1 trials followed by a large, multicenter Phase 2/3 trial. The first Phase 1 safety trial among HIV-negative women will be conducted through the Council's International Committee for Contraception Research in the Dominican Republic. This activity will focus on the subsequent Phase 1 trials, and on the Phase 2/3 trial to be conducted in South Africa and potentially at other sites in southern Africa.

For these trials, the behavioral coordinator, Barbara Friedland, and the rest of the behavioral team will collaborate with the clinical team on the development of the protocols as well as on standard procedures for informed consent and participant education, recruitment and retention, counseling, standard of care, and community relations. Informed consent forms and materials will be adapted, where applicable, from the materials used in the Phase 3 trial of Carraguard. As was the case for the Phase 3 Carraguard trial, we will work with local communities to ensure that the informed consent forms, participant educational materials, and recruitment plans are appropriate for settings in which the trials of PC-815 will be conducted. All materials will be pre-tested in collaboration with local researchers and approved by all ethics committees involved in the trials.

Report of Year Three:

July–December 2006: During this period, the behavioral coordinator participated in protocol development for a penile safety study in HIV-negative men to be conducted by the University of Limpopo/Medunsa Campus at the Setshaba Research Centre in Soshanguve, South Africa. The behavioral coordinator also participated in discussions about protocol design issues for the Phase 2/3 trial.

January–June 2007:

It was decided that the HIV-infectivity study among HIV-positive women would not proceed (see PC-815 clinical). Therefore, during this period, the behavioral coordinator focused on participation in the development of the protocol and informed consent forms for a penile safety study in South Africa, which was submitted to the Population Council's IRB in April 2007 and reviewed at the May 2nd meeting. The protocol was approved, however, the timeline for this study was shifted pending the US FDA's reaction to PC responses to FDA comments on the IND. Therefore, this study will not be implemented until the last quarter of 2007. The informed consent forms for this study have been developed, and will be translated, and back-translated by the end of June 2007; pre-testing will occur after June. In addition to the trial site in South Africa, sites in New York and Santiago, Dominican Republic were identified for implementing the protocol, in order to share the research burden equitably among developed and developing country communities.

Work on the Phase 2/3 trial informed consent will not occur until the July 2007–June 2008 program year, as that trial is now expected to begin mid-2009.

Subawardee(s): TBD

Contractor(s): TBD

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Social Science Research in Population Council Microbicide Trials

Project Number/s: 44213

Country/ies: South Africa, United States
Technical Coord.: Barbara Friedland, Sharon Abbott
Period: July 2006 – June 2009
Objective: To conduct relevant social science research to examine aspects of clinical trial participation and microbicide use necessary to improve the development and implementation of clinical trial procedures in Population Council (PC) microbicide trials.

Activity Description:

Three social science studies, ancillary to the Carraguard Phase 3 trial, are planned at the trial sites (Medical Research Council [MRC], University of Limpopo/Medunsa Campus, and University of Cape Town [UCT], all in South Africa), with co-funding from the International Partnership for Microbicides (IPM). Results from these studies will provide information on procedures used within the Carraguard trial and inform the development of the PC-815 Phase 2/3 trial. Additional social science research will be conducted in association with the PC-815 trials.

Qualitative evaluation of the informed consent (IC) process in the Phase 3 Carraguard trial

This qualitative study will involve in-depth interviews (IDIs) and focus group discussions (FGDs) with Phase 3 trial participants and their willing male partners to explore women's decision-making processes, their understanding of trial concepts, and their reactions to materials such as the study booklet, recruitment video, and IC form. Study counselors and recruiters will be interviewed to gain their insights into how the IC process can be improved in further trials.

Evaluation of referrals in the Phase 3 Carraguard trial

At each Carraguard Phase 3 trial site, counseling sessions at the study clinics and referrals to existing services in the trial communities help ensure that women who test positive for HIV at screening and those who seroconvert during the trial are provided with adequate care and support. This study will assess whether the strategies established within the referral networks are meeting the needs of women diagnosed with HIV. We are also conducting a survey of healthcare providers at facilities in the established "referral network" to gather suggestions for improving the referral system.

Exploration of sexual norms and practices affecting microbicide acceptability in the Phase 3 trial

Council researchers and colleagues from UCT developed a study to examine sexual norms and practices as they influence gel use. Researchers will interview trial participants about their experiences with gel use, their sexual activities, and vaginal practices such as intravaginal cleansing. Interviews will also be conducted with willing male partners, women who withdrew from the trial early, and study staff.

Report of Year Three:

Qualitative evaluation of the informed consent process in the Phase 3 Carraguard trial

July–December 2006: The protocol was reviewed by the MRC and Medunsa ethics committees in July and August 2006. An interviewer training was held at UCT in October. MRC was not able to hire interviewers in time for the training, and therefore it was decided that they would not participate in the

study. The guides for the FGDs and staff IDIs were developed by Council researchers in collaboration with co-investigators and piloted in November. Data collection began in December, and will continue through June 2007.

January–June 2007: Approximately 150 in-depth interviews with participants and study staff were conducted at both sites, and will be transcribed and translated by early June. A second training session for the focus group discussions was conducted at UCT in February, and piloting for the FGDs began in March. Data collection for the FGDs will be completed by the end of May. Council researchers began preliminary coding for analysis using Atlas.ti. An investigators meeting will be held in Pretoria in early June to finalize the coding list and begin planning manuscripts. We expect to submit an article to a peer reviewed journal by the end of 2007. Abstracts for the Microbicide 2008 meeting will be developed using these data.

Evaluation of referrals in the Phase 3 Carraguard trial

July–December 2006: In July 2006, the MRC ethics committee reviewed the protocol. Training was conducted at the MRC site in Isipingo under the guidance the study's principal investigator (PI). IDIs were completed at the UCT and Medunsa sites and initiated at the MRC site. The survey instrument for healthcare providers at facilities in the established "referral network" was developed by the PIs of the study in collaboration with Council researchers and implementation of the surveys occurred during this period.

January–June 2007: In-depth interviews were completed at the MRC site, although due to delays in ethical approval and stipulations in the study design, only ten interviews were conducted. Interviews with service providers were also completed during this period. Transcripts for the in-depth interviews were coded and analyzed by the co-investigators at each site using Atlas.ti software. The data from all three sites were merged to facilitate cross-site analysis. An investigator meeting was held in April 2007 at UCT, during which investigators also developed plans for a poster to be presented at the South African AIDS Conference in June. Delays in the completion of data collection led to adjustments in the overall timeline for the study. A paper will be submitted to a peer-reviewed journal during the first quarter of 2008, and a meeting with policymakers and other stakeholders will occur in conjunction with the dissemination of the main Carraguard Phase 3 trial results, rather than in a stand-alone meeting.

Exploration of sexual norms and practices affecting microbicide acceptability in the Phase 3 trial

July–December 2006: The protocol was reviewed by the Medunsa and MRC ethics committees and approved in September 2006. The IDI guide for trial participants was developed by the PIs at UCT, in collaboration with Council staff, and was finalized in September. Data collection will begin in June 2007. Although this study was originally planned to precede the qualitative IC study, the order was changed to accommodate study design.

January–June 2007:

A training session for this study was held at UCT in April. Informed consent forms were translated and back translated. The PIs continued to develop the guide for staff interviews, and will develop the FGD guides during the next program year, following an initial examination of emerging themes from the in-depth interviews. Transcription of recorded interviews in the other qualitative projects has taken longer than expected, and one of the investigators has been out intermittently on medical leave, which has resulted in unanticipated delays. Data collection is expected to begin in June, once all outstanding transcribing and translating has been completed on the qualitative informed consent study.

Subawardee(s): University of Limpopo / Medunsa Campus (I06.54A)
Medical Research Council (I06.53A)

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Preparatory Studies for Population Council Microbicide Trials

Project Number/s: 44216, 88306

Country/ies: South Africa

Technical Coord.: Stephanie Skoler, Barbara Mensch, Sharon Abbott, and Sumen Govender

Period: July 2006 – December 2008

Objective: To conduct preparatory studies to inform design of future Council and other microbicide trials.

Activity Description:

In preparation for the PC-815 efficacy trial, two studies will be conducted to address study design questions raised during the Phase 3 Carraguard trial.

ACASI Study

The objectives are to 1) evaluate the effectiveness of audio computer-assisted self-interview (ACASI) for collecting sensitive data, relative to face-to-face (FTF) interviews; 2) assess how key components of computerized interviewing can be integrated with FDA guidelines for electronic records in clinical trials (21 CFR 11); and 3) introduce and evaluate ACASI at future PC-815 Phase 2/3 study sites. Evaluations of microbicide efficacy rely on accurate reporting of sexual behavior and gel use. Courtesy bias may lead to over-reporting of gel use, and under-reporting of unprotected sex, weakening the observed association between HIV status and microbicide use. The Population Council (PC) developed a test to determine whether the gel applicator was vaginally inserted; however, the test cannot determine how many times sex occurred without gel insertion, or vice versa. Thus, evaluation research on collecting sensitive data must continue. Previous USAID-funded PC experiments have revealed the affect of courtesy bias in face-to-face interviews and suggest that ACASI generates more valid estimates of behavior. This study will simulate a microbicide trial at the three Phase 3 Carraguard clinics to determine if ACASI, compared to FTF, reveals lower reporting of gel use prior to sex and higher reporting of unprotected sex. External validation will be conducted through the PC applicator test, and by a Rapid Stain Identification of Human Semen test (RSID®-Semen), a biomarker of sex without a condom in the prior 48 hours. The incidence of STI's at the end of the study will also be used to validate reporting. Protocols for data collection, security, validation, auditing, and backup will be established and documented, to assess how ACASI can adhere to FDA guidelines for electronic records in clinical trials. Staff will develop ACASI training and implementation protocols.

In early 2007, 800 HIV-negative women, aged 18–40, sexually active and not pregnant, will be enrolled using Phase 3 Carraguard trial procedures, and randomly assigned to either FTF or ACASI. Women will be instructed to use a placebo gel and condom with each sex act. At each of three monthly visits, women will return used applicators, receive new gel and condoms, have a pelvic exam, and complete the behavioral interviews. Forty-five in-depth interviews will be conducted to explore participant experiences using ACASI. Data analysis will occur in late 2007. If ACASI reveals lower reporting of adherence, higher reporting of sensitive behaviors, and stronger associations with collected biomarkers, future PC microbicide trials will use ACASI, if respondent acceptability is adequate and FDA requirements are met.

IUD Study

For safety reasons, current microbicide protocols require women who become pregnant to stop using study product. Time off gel reduces statistical power and can complicate analyses. Despite eligibility criteria

advising against pregnancy during trial participation, pregnancy is the leading reason for product interruption in ongoing microbicide trials. In South Africa, women often return late to public clinics for family planning appointments and are consequently turned away. Intrauterine devices (IUDs) require little user maintenance and may successfully reduce unintended pregnancies. A study will begin in mid-2007 to determine the acceptability of two IUDs, the levonorgestrel intrauterine system (LNG IUS) and the Copper T IUD, compared to widely used contraceptive injections. An IUD introduction intervention will be implemented with providers and users in two South African clinics for the PC-815 Phase 2/3 trial (Medunsa and the University of Cape Town). The 400 enrolled women will select an IUD or hormonal injections. The acceptability of all three methods will be compared over one year. If the IUD is acceptable, its introduction at PC-815 Phase 2/3 clinics would increase study retention, and contraceptive options for local women. Funding for this study will be shared between USAID and the Swedish Ministry of Foreign Affairs.

Report of Year Three:

July–December 2006: The ACASI protocol was written, submitted to the relevant IRBs, and approved by the Council IRB by September. Also in September, PC laboratory staff evaluated the use of RSID-Semen, a forensic test to validate reports of unprotected sex in the past 48 hours by detecting a protein in semen. The lab validated the test and confirmed that the placebo gel would not inhibit test results. A protocol amendment to replace the prostate-specific antigen test with the RSID-Semen, which is less costly, easier to perform, and more specific, was submitted to the IRBs and approved by the PC IRB in November. Despite sites' immediate responses to queries and constant communication with the local IRBs, none of them received approval for either version of the protocol in 2006, which delayed the start of the trial. This delay significantly increased the cost of the study, by reducing overlap and shared site support with the Phase 3 Carraguard trial.

In October, the Sexually Transmitted Infection Research Laboratory at Medunsa was chosen as the central laboratory. The study questionnaire, case report forms, standard operating procedures, recruitment materials, a laboratory manual, and a Web site to facilitate sharing of study documents were developed. Sites translated materials into local languages. PC provided human capacity-building by conducting training on the protocol, ACASI software, and study materials in Johannesburg in November. Clean Chemical Sweden produced a batch of placebo gel.

Although not yet PCPD-funded, activities began on the IUD study. In December a final protocol draft was circulated among co-investigators. In late 2006, the International Contraception Access Foundation agreed to donate the full supply of LNG IUSs needed, and study staff began development of an acceptability questionnaire.

January–June 2007: Gel and RSID tests were shipped to the sites in early January. The ACASI study began at the UCT and Medunsa sites during the last week of March. The MRC replied to several rounds of comments from their IRB, and the protocol was not approved until early June. As of May 10, a total of 117 women had been screened and 38 had been enrolled. Sites have and will increase recruitment efforts, in response to the IRB delays, in order to reach the enrollment target in less time than originally planned. Prior to study start up, the Director of Information Technology at the Council visited each site to conduct refresher training on the ACASI software; and initiation visits were conducted at each site and the

laboratory. Each site has also had one monthly monitoring visit. A protocol amendment was approved by the PC IRB, which added STI testing to all close out visits. The amendment is currently pending with the site IRB's. Performing STI results at close out visits is a medical benefit to participants, and also enhances the study by serving as an additional biomarker for comparison with interview results. Study sites use the study website to access documents as well as load audio files from the ACASI system as a back up measure. An in depth interview guide focusing on the participant's experience using the ACASI software was drafted and finalized in late May. Training for the in-depth interviewers is scheduled for early June in conjunction with the 3rd South African AIDS Conference. This training was postponed from the original April date to ensure that it happened as close to the first Month 3 close out visits as possible, which will occur in July.

Although not yet PCPD-funded, activities continued on the IUD study. The protocol was submitted to the PC and Medunsa IRB's in April 2007 and the UCT IRB in May 2007; all are pending approval as of mid-May. Before the protocol was submitted, the total number of enrollees was reduced from 600 to 400 women due to expected budgetary constraints. The questionnaire and CRF's were being finalized mid-May. Practical training on intrauterine devices will be conducted during the last week of May at both study clinics, as previously planned. Protocol training will be conducted early in the July 2007–June 2008 program year once all data management tools are final.

Subawardee(s): Medical Research Council (SC07.105A)
University of Limpopo / Medunsa Campus (CB07.103A)
University of Cape Town (CB07.102A)

Contractor(s): Clean Chemical Sweden (CCS)

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Evaluating and Improving the Informed Consent Process in Microbicide Clinical Trials

Project Number/s: 44212

Country/ies: United States, Others TBD (in Africa)

Technical Coord.: Barbara Friedland

Period: July 2004 – June 2009

Objective: To improve the informed consent process in microbicide clinical trials by (1) identifying concepts (e.g., safety, placebo, partial-effectiveness) that are difficult for participants and communities to understand, and developing and assessing ways of explaining these concepts; and (2) evaluating which materials or combination of materials are most successful in conveying information to potential participants.

Activity Description:

Population Council researchers, with ongoing assistance from USAID, have devoted considerable resources to developing and evaluating the informed consent process in Carraguard® trials. Throughout the development and testing of materials, particular terms and concepts, such as “placebo,” remain difficult to convey. Researchers changed the term to “comparison gel” for the Phase 3 trial, and in pretesting, more than half of the women understood the concept of comparing two groups. Some women, however, still did not understand that the comparison gel was a “neutral” product to which Carraguard was being compared. The objectives of this activity, therefore, are: to improve explanations of difficult terms and concepts and to explore methods for assessing comprehension. Two specific projects include: 1) a workshop on informed consent in HIV prevention trials, and 2) the development of a handbook/lexicon for explaining clinical trial concepts.

Workshop on Informed Consent in HIV Prevention Trials

The objective of the workshop, to be co-hosted by Family Health International, is to provide an opportunity for researchers to share experiences, review informed consent materials, identify ways to improve communication of difficult terms and concepts, explore evaluation of the consent process, identify areas for further research, and disseminate information and recommendations from the workshop. An NIH small meeting grant (\$6,000) will help support the meeting, and a \$50,000 grant from the International Partnership for Microbicides (IPM) will support the attendance of meeting participants from the field. This meeting will help to identify successes and areas for future research on how to explain difficult concepts, assess and improve comprehension, and evaluate the overall informed consent process.

Handbook/lexicon for explaining clinical trial concepts

Recognizing that language and translation can have an enormous impact on all aspects of microbicide trials, researchers at the Population Council developed a lexicon for translating difficult concepts, to be used in the Council’s Carraguard trials. The development of the lexicon helped identify ways to explain research terms and concepts, as well as sexual and reproductive health terminology, in a culturally relevant manner in several South African communities, and ensured that all terms were translated consistently across all study documents. In collaboration with colleagues from FHI, Population Council researchers plan to build on this lexicon to create a data base of terms and suggested translations that will be easily accessible by researchers conducting HIV prevention trials around the globe. This expanded lexicon will build on the wealth of information gleaned during qualitative studies from previous and ongoing trials conducted by the Population Council and FHI.

In addition, an elicitation tool will be developed for researchers to use when developing translations in research naïve settings. The tool will include techniques for eliciting terminology on various topics including sexual behavior, sexual relationships, reproductive health, and medical research, and will allow researchers to learn how people talk about and describe these topics both among peers and in medical settings. This will enable researchers to determine the appropriate terms and types of analogies to use for explaining elements of the trial, as well the best ways to ask questions during interviews about adherence and acceptability in order to optimize communication during the trial and allow for accurate comprehension and interpretation of the data by the researchers.

A handbook containing the lexicon and the elicitation tool will also be published. The goal is to have the database online and the handbook published by the end of 2009.

Report of Year Three:

July–December 2006: We began work on the four-page brief highlighting the main outcomes of the IC Workshop. The meeting with FHI originally scheduled for the fall of 2006 to map out all aspects of the handbook/lexicon project was postponed to the spring of 2007 due to competing priorities at both institutions.

January–June 2007: The IC Workshop brief was drafted in English and potential translators identified. The audience for the brief is local researchers, advocates, and clinical trial staff; as such, it was decided that the brief will be produced in English and French only for the time being. Depending on the demand once the English and French versions have been produced, a decision may be made to translate the brief into other languages in the future. Production and dissemination had been originally planned by June 2007; however, competing demands may necessitate pushing the dissemination into the last half of 2007.

In mid-May, Barbara Friedland and Natasha Mack of Family Health International will meet for several days at FHI headquarters in North Carolina to begin working on the handbook/lexicon for explaining difficult concepts. The meeting agenda will include: brainstorming what the product we are aiming for will look like, who will use it, etc.; mapping out specific activities for the project; identifying the types of collaborators we will need, and specific people if possible; establishing a timeline; meeting with others at FHI to present our proposal and get reactions on whether it meets perceived needs; and reviewing some existing data. Further work will be pushed back into the July 2007–June 2008 program year.

Subawardee(s): TBD

Contractor(s): None

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Microbicides Introduction and Access: A Consultative Meeting

Project Number/s: 44215

Country/ies: United States
Technical Coord.: Martha Brady
Period: November 2006 – August 2007
Objective: To identify key strategies for microbicide introduction efforts by convening a one-day consultation of individuals with direct field experience in product introduction in developing country settings.

Activity Description:

If proven effective enough, Carraguard® is likely to be the first microbicide ready for commercialization and introduction. As of mid-2006, several other microbicide candidates are in Phase 3 trials, and second-generation products are well into safety studies. While unrealistic expectations about the availability and timing of an effective product must be avoided, at the same time, the Council must be prepared to launch Carraguard as soon as it is feasible to do so. It is therefore timely to develop forward-looking plans to bring Carraguard (or another Council-developed microbicide) to the “marketplace.”

Microbicide availability will be influenced by developments at the global level. It is essential to address issues associated with intellectual property, financing, manufacture, and distribution, as all these factors will influence the price at which a product can be made available to governments, donors, and users (see activity “Intellectual Asset Management”). Experience suggests, though, that the successful introduction of a microbicide product ultimately depends in large part upon local authorities perceiving a need and assuming responsibility for the introduction, adequate financing, and provision of the commodity; client demand for the product; and the health system’s capacity to adequately and responsibly deliver the technology. Issues at both the global and local levels are critical for the successful introduction of a microbicide.

The Council’s experience in technology introduction tells us that much can and should be done to prepare country programs and health systems for the incorporation of new products. The Population Council has been a pioneer in the field of technology introduction, with explicit attention to the incorporation of user perspectives and quality of care into the process. Decades of experience in introduction, health systems research, HIV/AIDS programming, and evaluation will be brought to bear on the preparation of a Carraguard introduction strategy.

While initial discussions concerning access and country preparedness for a microbicide have begun, debate and discussion of introduction models must move forward to help shape future introduction strategies. To this end, in early 2007 the Council will convene a one-day consultative meeting with 45-50 carefully selected individuals and agencies with direct field experience in product introduction in developing country settings. Lessons learned from the fields of contraception and HIV/AIDS and from selected consumer product marketing and commercialization efforts will be drawn upon. Using selected product introduction case examples, the group will identify key elements that can help guide microbicide introduction efforts. This consultation will build on a meeting on microbicide introduction dynamics, “Expert Consultation on Understanding Microbicide Introduction in Africa and India,” convened by the International Partnership for Microbicides (IPM) during the XVI International AIDS Conference in Toronto in August 2006.

The outcome of this consultation will be a more nuanced understanding and appreciation of a range of product introduction models, their strengths and weaknesses, and their application to the field of microbicides. This learning will be consolidated in the form of a written summary of the day's deliberations.

This consultation is one step in a series of interlocking activities that will enhance our microbicide product development plans.

Given the Council's pioneering role in the field of technology introduction and preeminence in the microbicide arena with the lead candidate, the Population Council is uniquely qualified to take a leadership role in defining, shaping, and catalyzing microbicide introduction and access strategies.

Report of Year Three:

July–December 2006: In November and December 2006, Martha Brady conducted interviews with key individuals to discuss the scope of the Consultative Meeting, select speakers, and develop the list of organizations and individuals to be involved. Initial feedback was positive and as a result of the strong response, the size of the meeting expanded from 20-25 participants to 45-50. The decision to increase the number of participants was made because the goal of this meeting is to create a bridge between those working on clinical trials and groups that are working in HIV/AIDS as well as reproductive health more generally; in order to accommodate the number of people with an investment in these three arenas, additional guests will be invited.

Based on the initial discussions, it was decided that the meeting will be centered on a range of existing prevention products that are currently being introduced in developing countries. Presenters will draw on these examples to highlight particular features applicable to microbicides:

- Building a platform for women's HIV prevention
- Providing information to facilitate correct product use (Emergency Contraception)
- Positioning a female-initiated, coitally dependent prevention product (Female Condom)
- Introducing a "package" of products with complex messages (CycleBeads plus Condom)
- Marketing "taboo" products: private sector approaches
- Preventing disease: examples from social marketing
- Sparking a process of innovation through a product (First-generation Contraceptive Implants)
- Exploring new HIV prevention approaches (Male Circumcision)

In order to save on travel costs and include field expertise, we scheduled the meeting when key Population Council field staff will be in New York for other meetings.

The activity budget now includes additional staff time for planning and hosting the meeting, funds for a consultant to write the summary report, additional funds to cover the costs of travel for four people to attend the meeting, and additional funds to cover the full report production costs.

January–June 2007: On March 12th, the Population Council convened a daylong meeting of experts in the fields of product introduction and social marketing, clinical trials and product development, and

reproductive health and HIV/AIDS to identify key features that can guide microbicide efforts. Led by Council Associate, Martha Brady, the Day of Dialogue was attended by 45 leaders of two dozen nongovernmental, governmental, advocacy, and donor organizations; speakers and meeting participants brought extensive experience in designing and implementing introduction programs in developing country settings. The meeting generated considerable interest and lively discussion. A CD with presentations was prepared and distributed to meeting participants and beyond. A meeting summary with key observations and emerging issues is being prepared.

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Intellectual Asset Management

Part of project Number/s: 99503

Country/ies: Chile, India, South Africa, Sweden, United States
Technical Coord.: James Sailer
Period: July 2005 – June 2015
Objective: To locate and reach agreement with partners who will manufacture and distribute the microbicide Carraguard® to the people who need it, at affordable prices; and to manage other business relationships related to product development.

Activity Description:

The Intellectual Asset Management (IAM) group seeks to locate and reach agreements with partners to manufacture and market the products supported by the Population Council Product Development cooperative agreement. A Population Council microbicide would provide a female-controlled way to reduce HIV transmission during sexual intercourse. For Carraguard, the Council's "local strategy" envisions a manufacturer/marketer in each region of the developing world, beginning with sub-Saharan Africa, for Carraguard to be manufactured and distributed close to where the epidemic is worst, and to facilitate logistics, product delivery, regulatory approval, and acceptance by the end-user. The Council plans to license products prior to regulatory approval to minimize the time to availability. The Carraguard Phase 3 study ended March 31, 2007.

IAM staff conduct research to identify appropriate partners, networking with Council, USAID, and other colleagues and professionals at pharmaceutical, licensing, and public health meetings, and reviewing public sources. Each prospective company is contacted to determine its interest. Confidentiality agreements are negotiated, and IAM staff meet with company principals. The Council discloses technical information and discusses license terms. After assessing and confirming a company's interest, abilities, and compatibility, the IAM group negotiates terms, including low pricing and public sector provisions. Agreements may be negotiated with several companies. Based on the public sector pricing and many other factors, IAM selects one or more manufacturers and marketers. After an agreement is in place, the IAM group continues to manage relationships and monitor production and distribution to ensure that the products get to the people who need them.

IAM staff coordinate the patent process among external patent counsel, inventors, product development teams, and the Council's Patent Committee, according to the Council's patent policy.

IAM also manages relationships with the current manufacturer of the microbicide gel (Clean Chemical Sweden AB) to ensure supplies for the clinical studies; and with the U.S. producer of carrageenan, Carraguard's active ingredient. IAM also seeks additional sources of carrageenan.

The IAM group is located in the Council's headquarters, and consists of Director of Corporate Affairs James Sailer, General Counsel and Secretary Patricia Vaughan, Senior Business Analyst George Young, Special Assistant Rebecca Brodsky and two staff assistants. The group works in coordination with staff in the Council's HIV and AIDS and Reproductive Health programs. Through PCPD, USAID microbicide funds support efforts on behalf of the microbicide.

Report of Year Three:

July–December 2006: For Carraguard, IAM continued discussions and correspondence with prospective companies, and met with new prospects from Chile, India, Sweden, and the United States, executing a confidentiality agreement with the new prospect from India. Of the four companies in South Africa, one withdrew from discussions and three indicated continued interest.

IAM continued to seek alternate sources for carrageenan. Five additional prospects were identified, for a total of 15. Seven prospects in Korea, Chile, the U.S., Canada, the United Kingdom, and the Philippines completed confidentiality agreements. The Council received samples from seven companies, and two of these were tested and identified as adequate. Two IAM staff traveled to Chile to meet with one company and evaluate its capacity.

James Sailer met in Sweden with Carraguard's current manufacturer, Clean Chemical Sweden (CCS), to address technology transfer, production of the next-generation microbicide, and production for trial participants post-trial. CCS reiterated its commitment to transfer manufacturing technology to a new manufacturer. CCS acquired technology to produce small and medium-sized batches of microbicide gel for PC-815 trials. CCS agreed to produce enough Carraguard to supply trial participants after the trial and expressed interest in continuing Carraguard production, should the Council seek regulatory approval for Carraguard in Europe.

January–June 2007: IAM continued discussions and correspondence with prospective companies, meeting with one continuing prospect in India, and with two companies in South Africa in conjunction with the conclusion of data collection for the Phase 3 study, finally executing a confidentiality agreement with the second of three prospects in South Africa. Further discussions with the third South African company are contingent on parallel discussions with their Indian affiliate.

At the meetings with the two potential partners in South Africa, IAM representatives discussed general terms, including low pricing, public sector provisions and many other factors, to continue to assess which company will be a more suitable manufacturing and marketing partner. IAM staff toured research and development manufacturing facilities in Johannesburg, confirming representations about one company's particularly impressive development and pilot scale manufacturing capacities.

Patricia Vaughan met with one well connected company in India in early 2007. However, scheduling conflicts delayed meetings planned with a leading Indian prospect affiliated with the third South African company.

IAM staff met with Clean Chemical Sweden primarily to discuss production of a second-generation microbicide, which includes the incorporation of an anti-retroviral in the formulation, as well as to discuss their potential role in future Carraguard production. IAM also continued discussions with the carrageenan producers from the United States and Chile, as well as continuing to seek and assess additional sources of carrageenan elsewhere. The Council is in the midst of negotiations with the two manufacturers that provided acceptable carrageenan samples.

IAM staff have scheduled a Patent Committee meeting with senior Council staff at the end of June, to include discussion of the status of the Council's patent application for carrageenan-based antimicrobial

compositions.

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Contraceptive Product Research and Development

Program Summary

The Contraceptive Product Research and Development program at the Population Council's Center for Biomedical Research in New York City applies laboratory and clinical research to develop and register new methods of contraception and other reproductive health products. Staff members design new drugs and delivery systems, undertake the requisite animal and preclinical research, analyze and publish findings, and submit documentation of results to regulatory authorities for permission to undertake human trials or to distribute methods after Phase 3 trials. The Council's International Committee for Contraception Research, a core of distinguished scientists and investigators, conducts the clinical trials of the program.

Under the Population Council Product Development cooperative agreement, the Council's contraceptive program will focus on the development of a contraceptive ring releasing the synthetic progestin Nestorone® in combination with ethynylestradiol. The goal of this research is to carry out the requisite studies and assemble the documentation needed to file a New Drug Application for the product by the end of the cooperative agreement period in order to achieve the goal of registering the device and introducing it into family planning programs worldwide. Support for regulatory activities associated with three marketed products developed by the Council will also occur.

USAID has provided major funding for the Contraceptive Product Research and Development program. These funds were instrumental in developing the Council's marketed contraceptive methods: the Copper T family of intrauterine devices; Norplant® and Jadelle® implants; and Mirena®, the levonorgestrel-releasing intrauterine system.

Nestorone®/Ethinylestradiol Contraceptive Ring

Project Number/s: 77600, 77902 (formerly 07600, 07902)

Country/ies: Australia, Brazil, Chile, Dominican Republic, Finland, France, Germany, Hungary, Spain, Sweden, United States

Technical Coord.: Regine Sitruk-Ware, Ruth Merkatz

Period: Pre-Year One – June 2009

Objective: To carry out the requisite studies and assemble the documentation needed to file a New Drug Application (NDA) with the U.S. Food and Drug Administration (FDA) for a contraceptive ring releasing the synthetic progestin Nestorone (NES) in combination with ethinylestradiol (EE).

Activity Description:

The contraceptive ring is particularly suitable for steroid administration. When a ring is placed in the vagina, steroid within the ring slowly diffuses into the blood and tissues, releasing enough steroid to block ovulation and thereby providing a contraceptive effect. Because a ring is inserted and removed by the woman herself, a minimum of attention by medical personnel is required, and initiation and discontinuation of ring use are entirely under the user's control. The Population Council is committed to the development of a ring releasing NES and EE that will last for 12 months. With funding from the Population Council Program III (PCP3), USAID cooperative agreement HRN-A-00-99-00010, Phase 2 trials were conducted to determine the most effective dose and use regimen of a NES/EE ring for female contraception. A ring releasing NES/EE in a dose of 150/15ug per day was selected to be used on a three-weeks-in/one-week-out schedule.

During the term of the Population Council Product Development cooperative agreement (PCPD), the objective is to carry out a pivotal Phase 3 trial and file an NDA. In preparation for the trial, batches of NES will be produced by the source contractor, Crystal Pharma (Valladolid, Spain), which will also perform stability and validation studies on NES samples it produces. The mass manufacturer of the ring, QPharma AB (Malmö, Sweden), will complete steroid core manufacturing trials and core manufacturing process optimization and scale-up. QPharma will then manufacture, package, and ship the rings, while performing stability studies on a sample of the rings to cover the time period of the Phase 3 clinical study. This stability study will include accelerated (40°C/75% relative humidity), intermediate (30°C/65% relative humidity), and long-term (25°C/60% relative humidity) testing conditions.

The original Phase 2 dose-ranging and schedule variation studies were carried out using rings handmade in laboratories at the Population Council's Center for Biomedical Research; these rings were fabricated using different materials and different sources of materials from those that will be used in the mass-manufactured rings for the Phase 3 trial. For this reason, a pharmacokinetic (PK) trial is required as a nested study within the pivotal Phase 3 clinical trial. This PK segment of the Phase 3 clinical trial is to begin in December 2005.

The primary objective of the nested PK segment of the trial is to examine the potential contraceptive efficacy of the mass-manufactured NES/EE ring on ovulation suppression by determining serum estradiol and progesterone levels. A secondary objective is to determine the pharmacokinetics and burst effect of NES and EE during cycles one and three immediately following ring insertion and to determine clearance of the study drugs in the cycle following ring removal. Three International Committee for Contraception Research clinics in Los Angeles, Santiago, and Santo Domingo will enroll a total of 39 subjects for a three-

month treatment period. Serum NES and EE levels will be determined using the sensitive liquid chromatography mass spectrometry/mass spectrometry (LCMS/MS) assay method, as it is now required by the FDA.

Once results are in hand from the PK study, the other clinics involved in the Phase 3 trial will commence enrolling volunteers. Although in 2002 the FDA indicated that data from 10,000 cycles would be adequate for the NDA and plans proceeded to have 16 sites enroll a total of 1,280 women, in late 2005 the FDA unexpectedly increased the requirements for the number of cycles to 20,000 and for the number of women completing one year of use to 400. For this reason, USAID/PRH staff, in consultation with the Council, contacted the National Institute of Child Health and Human Development (NICHD), which agreed to fund participation in the study by 15 sites in its Contraceptive Clinical Trials Network (CCTN).

A total of 2,200 women at 27 sites will be enrolled (including the 39 subjects from the nested PK segment who will be invited to continue in the Phase 3 segment), in order to obtain data on 20,000 cycles and demonstrate the ring's contraceptive efficacy and safety during a one-year period of use. We will also evaluate cycle control, bleeding patterns, side effects, and acceptability. Enrollment will begin first in Protocol 300B, the 12 sites managed by the Population Council (10 funded by the PCPD and 2 by the World Health Organization). This protocol includes an acceptability study to be conducted at all sites, including use of ACASI (audio computer-assisted self-interview) technology in 4 sites. Afterward enrollment will commence in Protocol CCN006 (formerly 300A), the 15 NICHD CCTN sites. This protocol includes three safety studies (microbiology, hepatic factors, and endometrial safety).

Following completion of the trial, a final report will be written, all documentation will be assembled, and the NDA documents will be submitted to the FDA.

In order to complete the safety profile of NES for NDA submission, additional preclinical studies must be undertaken. In the course of the PCPD, one study will determine the absorption, distribution, metabolism, and excretion of NES following administration of a single subcutaneous dose of ³H-NES to rats. Another study will determine the excretion and metabolism of NES in women. Finally, FDA guidelines require that carcinogenicity studies be conducted in two animal species. During the PCP3, a two-year carcinogenicity study of NES showed it to be noncarcinogenic in rats. During the PCPD, a 26-week carcinogenicity study of NES in mice will be initiated.

Report of Year Three:

July–December 2006: Enrollment was completed in Protocol 300, the nested PK study. The primary objective of this study is to evaluate the efficacy of the NES/EE contraceptive vaginal ring (CVR) from a contract manufacturer compared with the results of the PK trial done with the CVR produced at the Council's Center for Biomedical Research for the Phase 2 studies. Ovulation suppression as determined by serum estradiol and progesterone levels was measured twice a week during cycles 1 and 3, and measurements will be repeated in cycle 13. Secondary PK objectives were assessed using various other parameters (listed below), during the first and third cycles, and these assessments will be repeated in the last (13th) cycle of CVR use.

- A. kinetics of EE and NES over the first 24 hours of cycles 1, 3 and 13
- B. kinetics of EE and NES over the 7 day period after removal of the ring

- C. Cmax and area under the curve (AUC) for EE on day 1 of cycles 1, 3 and 13
- D. Cmax and AUC of NES on day 1 of cycles 1, 3 and 13
- E. steady-state EE and NES levels measured during cycles 1, 3 and 13
- F. AUC and C max for NES and EE for the entire 21-day cycle in cycles 1, 3 and 13.

Our data as of December demonstrated suppression of ovulation in all subjects, and there were no pregnancies. As in the Phase 2 PK study, we observed an initial burst effect for both EE and NES that peaks in the first 8–16 hours, but then falls rapidly to approach a steady state by day 4. This burst effect is decreased significantly when measured in cycle 3. Other data from this trial suggest a favorable bleeding profile, with most women bleeding on schedule during the ring-free period and with very little bleeding while women are using the ring. Continuation rates are also acceptable. As of December, of the 39 subjects who were enrolled according to plan, 32 subjects were continuing, the majority of whom were approaching or completing the end of treatment (13 cycles).

Final preparations for conducting the Phase 3 clinical trial of the NES/EE CVR were completed by Population Council (PC) staff in the fall of 2006. This involved extensive communication with the FDA, including a Special Protocol Assessment Review of the final protocols.

As part of the Council's responsibility as the IND holder and sponsor of the product, PC staff had extensive interactions with NICHD and Health Decisions, NICHD's contract research organization (CRO) responsible for managing the trial with the CCN006 sites. This included coordination of protocol approvals, regulatory documentation, shipment of clinical trial materials, case record form (CRF) development, and data management issues.

In preparation for initiating Protocol 300B by the PC, site initiation visits were carried out to clinics in Sweden, Finland, Brazil, Chile, the Dominican Republic, San Francisco, Chicago, and Los Angeles. In conjunction with these initiation visits, timely monitoring visits were carried out at the three sites also conducting the nested PK study (Chile, the Dominican Republic, Los Angeles) in order to ensure compliance with current Good Clinical Practice guidelines. Enrollment in 300B began in October, and by December 2006 clinics in Australia, Los Angeles, the Dominican Republic, Chile, and Sweden had commenced enrollment. As of December, we were monitoring closely the overall enrollment numbers in order to take further action as needed to assure that we enroll successfully in Protocol 300B the required number of women to meet regulatory expectations. Such actions were planned to include allocating recruitment of more than 100 subjects at certain sites that have good recruitment results and/or considering the addition of one or two more sites as needed, with the resulting reallocation of budgets among the sites (and any new sites) in 300B.

The Investigational Medicinal Product Dossier (IMPD) was submitted to the European Medicines Agency (EMA), and approved by that body, clearing the path for submission to national authorities. Extensive interaction was also required between Council staff and representatives of the CRO FGK Clinical Research, the Council's legal and pharmacovigilance-qualified representative in Europe. FGK is our liaison with the EMA and national European regulatory bodies. Three-way interface between the Council, FGK and the CRO CRID Pharma, our qualified pharmaceutical representative in Europe, was required to submit the IMPD to national authorities and resolve several regulatory issues at the national level. By early fall 2006, the authorities in Sweden and Finland had accepted our application to conduct the trial; however, we

were still awaiting approval in Hungary as of December.

We also worked closely with CRID Pharma, whose main responsibility is to package, label, and ship rings directly to the clinic sites in Europe, Latin America, and Australia, and to their American subsidiary Xerimis, who in turn has responsibility for shipping drug to the CCN006 and 300B sites within the US. A freelance monitor contracted in Australia through ContractTalents ensured regulatory follow-up with that site.

Preliminary results of QPharma's stability studies on the rings were indicative of a two-year shelf life.

January–June 2007:

Evaluation of subjects continued in Protocol 300, the nested PK study. As of June 30, 2007, all but one participant had completed the study. Continuation rates at one year are estimated at 70–71 per 100. There was one pregnancy, in a subject in the Dominican Republic.

In the two pivotal Phase 3 studies of the NES/EE CVR, enrollment began at all remaining sites. Two centers were added to Protocol 300B and commenced enrollment in January: Columbus Center for Women's Health Research in Ohio and Montefiore Medical Center in the Bronx, New York. In order to increase enrollment in CCN006, 3 clinics were added to the study and began enrollment, bringing the total sites in that study to 15. As of June 30, 2007, enrollment stood at 270 in Protocol 300B; there had been 15 discontinuations, 8 for medical reasons. In study CCN006, enrollment stood at 382 women, and there had been a total of 27 discontinuations.

PC staff continued to have extensive interactions with NICHD and Health Decisions, including coordination of protocol approvals, regulatory documentation, shipment of clinical trial materials, CRF development, and data management issues.

Data management proceeded with regular quality reviews of information transmitted from 300B sites through our DataFax system to DF/Net Research in Seattle, and preparation by DF/Net Research of data summary reports. DF/Net Research staff continued to provide data management support to Council staff during Year Three.

Clinical monitors conducted site initiation visits to clinical sites at Albert Szent-Györgyi Medical University in Hungary and to the new sites at Columbus Center for Women's Health Research and Montefiore Medical Center. The monitors also carried out periodic monitoring visits to the 8 other Protocol 300B sites in Europe and the Americas that were enrolling women in the study, in order to ensure compliance with current Good Clinical Practices. A Hahn Healthcare Recruitment (formerly ContractTalents) freelance monitor continued working in Australia, to ensure regulatory follow-up with that site.

Interaction between Council staff and representatives of the CRO FGK Clinical Research resulted in approval by the European and Hungarian authorities for the study to go forward in Hungary in January. Our working relationship continued with CRID Pharma, who packaged, labeled, and shipped rings directly to the 7 clinic sites in Europe, Latin America, and Australia, and to their American subsidiary Xerimis, who in turn shipped drug to the 15 CCN006 and 5 300B sites within the US.

QPharma continued to conduct stability studies on the rings. Results continue to indicate a two-year shelf life. Crystal Pharma continued stability studies, validated process development, and drafted a drug master file for Nestorone.

As part of the effort to complete the safety profile of NES for the NDA submission, a clinical study to determine the excretion and metabolism of NES in six women began commenced in the first quarter of 2007. Radioactively labeled NES was being administered subcutaneously to six women, and blood samples collected for a week. The metabolite profiling will be determined by LCMS/MS. Planning for a mouse carcinogenicity study of NES took place, which will begin in Year Four.

Subawardee(s): Columbus Center for Women's Health Research (SC07.03A)
Montefiore Medical Center (SC07.02A)
Family Planning Association of New South Wales, Australia (CB06.108A)
Chilean Institute of Reproductive Medicine (ICMER) (CB06.107A)
Centro de Pesquisas em Saude Reprodutiva de Campinas (CEMICAMP) (CB06.106A)
Karolinska Institutet, Sweden (CB06.105A)
Dominican Association for the Well-Being of the Family (Profamilia/DR) (CB06.104A)
Health Research Association, LAC/USC (CB06.103A)
University of Chicago Hospitals (CB06.102A)
University of California San Francisco (CB06.101A)
Chilean Institute of Reproductive Medicine (ICMER) (CB05.123A)
Dominican Association for the Well-Being of the Family (Profamilia/DR) (CB05.122A)
Health Research Association, LAC/USC (CB05.121A)

Contractor(s): Accium BioSciences
Chilean Institute of Reproductive Medicine (ICMER)
Covance
CRID Pharma
Crystal Pharma, SA
DF/Net Research, Inc.
FGK Clinical Research GmbH
Lerner, David, Littenberg, Krumholz & Mentlik, LLP
Micron Technologies
Pharma Net Developing Group
QPharma AB
SFBC Taylor
Voisin Consulting

Activity Funding: Pop Core

Contribution to Results Framework: IR 2.4

Regulatory Maintenance of Marketed Products

Project Number/s: 77701, 77702, 78002 (formerly 07701, 07702, 08002)

Country/ies: United States

Technical Coord.: Fred Schmidt, Irving Sivin

Period: Pre-Year One – Post-Agreement

Objective: To conduct all necessary regulatory maintenance associated with three marketed products (Norplant,[®] Jadelle,[®] and the Copper T 380A intrauterine device) developed by the Population Council.

Activity Description:

The Population Council was instrumental in developing three highly effective, long-acting contraceptive methods, Norplant, Jadelle, and the Copper T 380A intrauterine device (IUD). Norplant is an implant now widely supplied in developing countries as a five-year method; efforts to relabel the method for seven years are underway. Jadelle is an improved implant, in that it utilizes two rods (as opposed to six for Norplant). It is approved for five years of use. Efforts to introduce Jadelle into a number of Middle Eastern and sub-Saharan countries (e.g., Yemen and Zimbabwe) continue, and it is expected gradually to replace Norplant. The Copper T 380A IUD has been in use for more than 20 years and has been used by more than 40 million women. Its role in Africa may increase since doubts about the relationship between IUD use and HIV infection have been diminished by the results of nine studies, conducted from 1988 to 1998, showing that sexually active women using IUDs are at no greater risk of acquiring HIV than sexually active women not using IUDs.

The purpose of this activity is to manage and carry out the requirements of all pertinent regulatory agencies in regard to these three contraceptive methods.

In order to maintain the Council's New Drug Applications (NDAs) for Norplant and Jadelle, Council staff must prepare U.S. Food and Drug Administration (FDA)-required postmarketing reports. Each year an annual report on each product must be submitted that includes a summary of any significant new information from the previous year that might affect the safety, effectiveness, or labeling of the product; distribution data; a summary of labeling changes; a description of manufacturing changes not requiring a supplemental application; summaries of unpublished and published nonclinical and clinical studies for the previous year; and status reports of postmarketing study commitments. In addition, the FDA requires "manufacturing supplements," that is, NDA supplemental application(s) for any new chemistry and manufacturing information provided by the manufacturer that would require a change in the actual manufacturing and control method(s) and procedure(s).

Regarding extension of the use-life of Norplant from five to seven years, as of the beginning of the agreement, a supplemental application by the Council in support of this purpose was deemed "approvable" by the FDA pending response to several queries. During Year One, these responses will be submitted to the FDA in an amendment to the Norplant NDA. Thereafter, Council staff will engage in any necessary additional interaction with the FDA to achieve the extension of Norplant's use-life. If the FDA requests it, additional laboratory work on the daily release of levonorgestrel from implants removed from subjects after seven years of use will be undertaken.

For the Copper T 380A IUD, assistance will be offered to FEI Women's Health (FEI), the owner of the

NDA at the beginning of the agreement, to extend the device's approved use-life beyond ten years. Council staff will continue to provide to USAID, and to ministries of public health in developing countries, consultation on clinical effectiveness and duration, manufacturing specifications, labeling matters, and adverse event rates, as well as information on the Council's experience through the years with the Copper T 380A IUD.

Report of Year Three:

Norplant

July–December 2006: Council staff initiated the preparation of the annual report for Norplant, to be submitted to the FDA in the first quarter of 2007. On December 22, 2006, the FDA approved the final report for the post-marketing commitment to continuously monitor the long-term (for five years) *in vitro* dissolution levonorgestrel release rates from three production lots of Norplant that were made of Leiras Oy tubings. (The Council had submitted the report in November 2005.) This approval completes all post-marketing study commitments acknowledged in the FDA's letter of August 25, 1999.

January–June 2007: Council staff continued to work on the annual report for Norplant and expect to submit this report to the FDA during the third quarter of 2007. In relation to extending Norplant's use-life from five to seven years the Council expects to submit to the FDA during Year Four the amended labeling for Norplant as requested by the FDA.

Jadelle

July–December 2006: Council staff initiated preparation of the annual report for Jadelle, to be submitted to the FDA in the first quarter of 2007. In November 2006, the Council received the manufacturer's response to the FDA's request dated June 1, 2006 for additional information for the manufacturing supplement relating to the change in *in vitro* release/dissolution test medium and test method and revised dissolution test specification. The information from the manufacturer was reviewed in preparation for submission to the FDA of an amendment to the manufacturing supplement. The manufacturer continued its clinical pharmacology and biopharmaceutics study commitment to collect five years of *in vitro* release rate data from commercial production lots.

January–June 2007: On January 22, 2007, the Council received from the manufacturer documentation to be included in the annual report for Jadelle. Council staff continued to work on the annual report for Jadelle and expect to submit it to the FDA during the third quarter of 2007.

For the manufacturing supplement relating to the change in *in vitro* release/dissolution test medium and test method and revised dissolution test specification, on March 6, 2007 the Council submitted an amendment to the FDA with the manufacturer's complete response to the FDA's June 1, 2006 request for additional information. On April 13, 2007 the FDA acknowledged that this amendment constituted a complete response to the FDA's June 1, 2006 action letter. The FDA's user fee goal date (the date by which an action by the FDA is expected) is July 8, 2007.

On March 27, 2007 the Council submitted to the FDA a post-marketing study final report for the final set of tests for a clinical pharmacology and biopharmaceutics commitment for Jadelle, as received from the manufacturer. The purpose of this commitment was to determine the *in vitro* dissolution rate of unused Jadelle implants in a series of three different dissolution media at initial, six months, and three years of storage.

Copper T 380A IUD

July–December 2006: Council staff initiated preparation of a paper for publication on the safety and effectiveness of collared copper T devices with 380mm² of copper during twenty years of continuous use. Additionally, the Council organized and hosted the Fifth International Symposium on Intrauterine Devices and Systems for Women’s Health in New York in October 2006 (with non-PCPD funding). Council staff addressed the unmet needs for long-term, effective contraception in lesser and more developed countries. In particular, Council staff and invited experts reviewed the continuing need for highly effective contraception in women aged 40–49 and the effectiveness of the Copper T 380A IUD in providing protection in the second decade of continuous use.

January–June 2007: Irving Sivin’s paper, “Utility and Drawbacks of Continuous Use of a Copper T IUD for 20 Years,” was published in a special issue of the journal *Contraception* [*Contraception*. 2007 Jun;75(6 Suppl 1):S70-S75] devoted to the October 2006 5th International Symposium on Intrauterine Devices and Systems for Women’s Health. This special supplement includes all the scientific presentations of this symposium, including 27 review articles. The abstract of the Sivin paper follows.

Abstract: This article examines interrelated questions concerning the extent of need for contraception in women 40 years and older and the degree to which that need can be served when use of collared T IUDs is initiated in women aged 25–35 years. Differentials in the impacts of intrauterine device (IUD) use on health issues in the second decade of contraception are also addressed. Although fertility of all women aged 40–44 years is below 100 per 1000 in all regions of the world today, the risk of pregnancy among married or cohabiting women who do not use contraception is estimated at 270–300 per 1000 or 27–30% per year. At ages 45–49 years, the annual risk of pregnancy to women in union who do not use contraception lies at or above 10% per year. Data from three studies show that users of collared copper IUDs who continued using the same device beyond the completion of 10 years experienced no pregnancies through the end of 15 years. A small number of women continued with the same IUD through 20 years and still experienced no pregnancies. Use of collared copper T IUDs beyond 10 years was not associated with intensification of side effects nor with an increase in the relative frequency of those effects, with the exception of the experience of perimenopausal symptoms and problems. Neither increased bleeding nor increased severity of pelvic disease was manifest in the second decade of continuous use of the same IUD, as compared with the first decade of such use. Under our current understanding of the duration of IUD effectiveness, only a small percentage of women complete 10 years of use. Even with revised understanding of the duration of effectiveness of long-acting copper devices, average annual continuation rates must be quite high in order that 20% of women aged 25–35 years initiate a second decade of continuous IUD use. Those who do so would find considerable protection against pregnancy and reasonable economic benefits in continuing to use the same device.

Activity Funding: Pop Core

Contribution to Results Framework: IR 2.4

Intellectual Asset Management

Part of project Number/s: 99503

Country/ies: Chile, India, South Africa, Sweden, United States
Technical Coord.: James Sailer
Period: July 2005 – June 2015
Objective: To locate and reach agreement with partners who will manufacture and distribute the NES/EE contraceptive vaginal ring to the people who need it, at affordable prices; and to manage other important business relationships related to product development.

Activity Description:

The Intellectual Asset Management (IAM) group seeks to locate and reach agreements with partners to manufacture and market the products supported by the Population Council Product Development cooperative agreement. The NES/EE contraceptive vaginal ring would serve as a female-controlled contraceptive for women. Based on manufacturing and distribution requirements, the Council seeks partners for the ring in the developed and developing world. The Council plans to license products prior to regulatory approval to minimize the time to availability. The ring Phase 3 study is scheduled to end in 2009.

IAM staff conduct research to identify appropriate partners, networking with Council, USAID, and other colleagues and professionals at pharmaceutical, licensing, and public health meetings, and reviewing public sources. Each prospective company is contacted to determine its interest. Confidentiality agreements are negotiated, and IAM staff meet with company principals. The Council discloses technical information and discusses license terms. After assessing and confirming a company's interest, abilities, and compatibility, the IAM group negotiates terms, including low pricing and public sector provisions. Agreements may be negotiated with several companies. Based on the public sector pricing and many other factors, IAM selects one or more manufacturers and marketers. After an agreement is in place, the IAM group continues to manage relationships and monitor production and distribution to ensure that the products get to the people who need them.

IAM staff coordinate the patent process among external patent counsel, inventors, product development teams, and the Council's Patent Committee, according to the Council's patent policy.

IAM also manages relationships with the current manufacturer of the NES/EE ring (Qpharma) to ensure supplies for the clinical studies.

The IAM group is located in the Council's headquarters, and consists of Director of Corporate Affairs James Sailer, General Counsel and Secretary Patricia Vaughan, Senior Business Analyst George Young, Special Assistant Rebecca Brodsky and two staff assistants. The group works in coordination with staff in the Council's HIV and AIDS and Reproductive Health programs. Through PCPD, USAID population funds support half of the budget for IAM staff time and travel on behalf of the NES/EE ring.

Report of Year Three:

July–December 2006: The IAM team continued to work to identify, contact, ascertain interest from, and meet with potential manufacturers and distributors for the NES/EE ring. Very early in the program year, the

Council created a color brochure (with non-USAID funding) to promote the ring, and used this brochure in a solicitation to representatives of over thirty pharmaceutical and venture capital companies. In addition, the Council distributed the brochure at conferences and other public events (e.g. the XVIII FIGO World Conference of Gynecology & Obstetrics in Malaysia in November). Staff also networked informally with other NGOs and with attendees at a meeting of licensing executives.

The response to the product has been very positive. Most companies declining interest either were not interested in marketing contraceptives or were comfortable with their current product array.

By the end of 2006, seven companies had expressed interest in licensing the ring. The Council had executed confidentiality agreements and met with representatives of six of these companies and discussions with those companies and others were ongoing.

The current manufacturer of the ring, QPharma, completed a study on reducing manufacturing costs; the Council believes more cost reduction possibilities are available to a new manufacturer. QPharma also agreed to facilitate technology transfer to the new manufacturer when needed.

IAM continued its staff support for the Council's Patent Committee, which met early in the program year.

January–June 2007: IAM staff continued discussions and correspondence with several prospective manufacturing and distribution partners for the NES/EE ring, particularly in the United States and India. Two leading prospects in the United States are preparing licensing proposals for the Council's review and comparison. One of the prospects in the United States has proposed a novel business model to arrange the public/private partnership necessary to bring this product to market. Meetings and conferences with another prospect in the United States, including introductory discussions of general licensing terms, should lead to an additional preliminary proposal by mid-2007 and follow-up meetings in July or August. IAM staff continued to solicit and assess interest from additional prospects worldwide, with a French company and another company in the United States expressing interest in late May.

Specifically focusing on provisions for the public sector, especially where women need new and inexpensive contraceptive options the most, IAM staff met with a prospective partner in India to investigate how to collaborate with regulatory authorities in India to facilitate eventual registration and distribution there.

IAM staff continued to support the Council's Patent Committee, coordinating patent prosecution for the NES/EE ring in particular, as well as the Council's ring patents issued around the world. A meeting is planned for late June.

Activity Funding: Pop Core

Contribution to Results Framework: IR 2.4

PUBLICATIONS AND OTHER WRITTEN WORKS

Publications

Contraceptive Product Research and Development

None under Year Three

Microbicides Product Research and Development

None under Year Three

Other Written Works

Contraceptive Product Research and Development

Population Council. 2006. "The One-Year Contraceptive Ring: A Technology in Development," informational brochure. <http://www.popcouncil.org/pdfs/OneYearRing.pdf>

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Population Council Center for Biomedical Research. 2006. "Minutes of the 89th Meeting of the International Committee for Contraception Research (ICCR)."

———. 2007. "Minutes of the 90th Meeting of the International Committee for Contraception Research (ICCR)."

Microbicide Product Research and Development

Abbott, S., and B. Friedland. 2007. "Behavioral/social science research supporting Population Council microbicide trials," presentation at 90th meeting of the International Committee for Contraception Research, New York, 12 April.

de Kock, A., N. Morar, N. Williams, B. Friedland, S. Skoler, V. Mtimkulu, N. Ngcozela, S. Gumede, V. Mehlomakulu, and S. N. Govender. 2007. "Engaging Participants in a Phase 3 study of the efficacy and safety of the microbicide Carraguard® in preventing HIV sero-conversion in women," presentation at 3rd South African AIDS Conference, Durban, 5-8 June.

Fernández-Romero, J.A., M. Thorn, S.G. Turville, K. Titchen, K.M. Sudol, J. Li, T. Miller, M. Robbiani, R.A. Maguire, R.W. Buckheit Jr., T.L. Hartman, and D.M. Phillips. 2007. "Carrageenan/MIV-150 (PC-815), a combination microbicide," *Sexually Transmitted Diseases* 34(1): 9-14.

Friedland, B. 2006. "Social Science Research in the Carraguard Phase 3 Trial," presentation at 89th meeting of the International Committee for Contraception Research, 26 October.

Friedland, B., S. Skoler, A. de Kock, L. Katzen, N. Williams, V. Mehlomakulu, V. Mtimkulu, and S. Abbott. 2007. "Evaluation of a video to enhance the informed consent process in a Phase 3 trial of the

microbicide Carraguard® in preventing HIV seroconversion in women,” presentation at 3rd South African AIDS Conference, Durban, 5-8 June.

Harries, J, S. Patel, N. Cassim, B. Friedland, T. Palanee, N. Morar, and K. Ahmed. 2007. “An evaluation of care and support of women who test HIV positive during the Phase 3 microbicide Carraguard® trial in South Africa,” poster presentation at 3rd South African AIDS Conference, Durban, 5-8 June.

Lähteenmäki, P., and B. Friedland. 2006. “Population Council carrageenan formulations in clinical trials,” presentation at 89th meeting of the International Committee for Contraception Research, 26 October.

Mensch, B.S. 2006. “Assessing the reporting of sensitive behaviors in microbicide trials,” PowerPoint presentation at training session, Rosebank Hotel, Johannesburg, South Africa, 15 November.

Mensch, B.S., S. Skoler, and R. Maguire. 2006. “Assessing the reporting of sensitive behaviors in microbicide trials,” PowerPoint presentation at PCPD meeting at USAID, Washington, DC, 9 November.

Marumo, M. 2007. “Barriers to Providing Effective Risk Reduction Counselling,” presentation at HIV Vaccine Trials Network (HVTN) meeting, South Africa, 17 January.

RamaRao, S., B. Friedland, and J. Townsend. 2006. “A Question of Ethics: Research to Practice,” presentation at the International Union for the Scientific Study in Population (IUSSP) Seminar on Ethical Issues in Reproductive Health, The Netherlands, 21-24 September.

Skoler, S. 2006. “Assessing the Reporting of Sensitive Behaviors in Microbicide Trial,” presentation at 89th Meeting of the International Committee for Contraception Research, 26 October.

———. 2006. “Phase 3 Carraguard Trial Update,” presentation at 89th Meeting of the International Committee for Contraception Research, 26 October.

Trapp, S., S.G. Turville, and M. Robbiani. “Slamming the door on unwanted guests: Why preemptive strikes at the mucosa may be the best strategy against HIV,” *Journal of Leukocyte Biology* 80(5): 1076–1083.

