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

Year One Program Report

1 July 2004 – 30 June 2005

August 2005

CONTENTS

GLOSSARY

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

Activity. A discrete effort under one of the PCPD programs. (Activities are sometimes also referred to as projects.)

Contractor. An entity from which goods or services are purchased by the Council under the PCPD. Only contractors with substantial contracts are 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.

Division. The Population Council is organized into several divisions. PCPD activities are carried out in two of these divisions, the Center for Biomedical Research (CBR) and the International Programs Division (IPD). CBR undertakes basic research in the reproductive sciences and develops technologies that enable individuals to have safe, planned pregnancies and that improve their reproductive health. IPD undertakes research on population and reproductive health in developing countries.

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 incurred solely in the Center for Biomedical Research. They are the PCPD's share of CBR's indirect costs for such items as space, general supervision and management, insurance, communications, maintenance, office supplies, and depreciation. These costs are incurred in both the Johannesburg and New York offices. 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 and the Corporate Affairs Division, including the Office of Finance, Information Systems, Human Resources, Office Services, and the Office of Grants and Contracts.

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. 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 under the PCPD by the Population Council.

Technical coordinator. The 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.

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, currently being tested in a Phase 3 efficacy trial, 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: 08301

Country/ies: South Africa, United States
Technical Coord.: Stephanie Skoler, Sumen Govender, and Pekka Lahteenmaki
Period: September 2002 – June 2008
Objective: To determine, by completing a Phase 3 trial begun in March 2004, whether Carraguard gel is efficacious in protecting women from HIV infection when used vaginally during heterosexual intercourse; if proved efficacious, to collaborate with the nonclinical team in submission of a New Drug Application.

Activity Description:
To determine the efficacy of Carraguard, Population Council (PC) researchers are conducting a randomized, controlled, double-blind study to ascertain whether Carraguard gel prevents HIV seroconversion in women. Researchers are recruiting 6,639 women from the general population at three South African sites. The trial began at the first site in March 2004. At each site, the study will last 30 months from initiation, with recruitment taking place through August 2005. Each woman will participate from her enrollment until the sooner of two years or trial's end at her site.

Dr. Lydia Altini at the University of Cape Town (UCT) and Dr. Khatija Ahmed at the University of Limpopo, Medunsa campus, both of whose teams implemented the Council's expanded safety and acceptability trials of Carraguard, each manage one site; Dr. Gita Ramjee at the Medical Research Council of South Africa (MRC), who implemented a Phase 1 safety and acceptability study of Carraguard with HIV-positive women and men, manages the third. Non-pregnant, HIV-negative female volunteers who live in the site catchment areas are to be recruited. Participants insert the study gel into their vaginas prior to every act of vaginal intercourse and are instructed not to use it orally or rectally. They return to the clinic regularly for pelvic exams, HIV testing, testing and treatment for curable sexually transmitted infections (STIs), HIV and safer sex counseling, interviews about adherence, and to receive more study supplies and return used applicators.

Product accountability, participant flow, and clinical laboratory samples are managed on-site using a custom-made bar code system and database (developed by MRP Solutions). Case record forms are faxed to the Council's Center for Biomedical Research in New York using the DataFax data management system (developed by Clinical DataFax Systems Inc.). STI tests, including HIV confirmatory testing and Pap smears, are sent to Lancet Laboratories, an independent laboratory in Johannesburg, while clinic laboratories process pregnancy tests, HIV rapid tests, and, when clinically indicated, other bedside tests to facilitate immediate treatment.

The PC teams in New York and Johannesburg liaise with the study sites, manage gel distribution, facilitate financial administration, manage regulatory paperwork, and conduct daily monitoring via DataFax for data collection errors. ClinDev (Pty.) Ltd., a contract research organization (CRO), performs regular monitoring at the sites to ensure protocol adherence and good clinical practice. A data safety monitoring board will convene twice during the course of the trial to ensure participant safety and monitor trial progress.

One of the biggest challenges in microbicide trials is measuring adherence, or gel usage. To help to assess gel usage, a comprehensive product accountability system is in place. Bar codes allow the tracking of gel

applicator distribution and return, and returned applicators are tested using a method that can determine whether the applicator has been inserted into the vagina. This system enhances the ability of researchers to determine the efficacy of Carraguard, by enabling a subanalysis on a restricted set of data on adherent women.

The Bill and Melinda Gates Foundation also provides funds for this activity. The Gates Foundation currently supports the MEDUNSA and MRC subawards, most laboratory and international travel costs, and CRO monitoring. USAID currently supports PC salaries and benefits, the UCT subaward, PC Johannesburg office expenses, DataFax and related costs, and domestic travel. Additional funding for the sites is being sought from the Swedish International Development Cooperation Agency, which recently funded other PC microbicides projects; however, prospects are low due to the level of funding already committed to this activity by USAID and the Gates Foundation.

Report of Year One:

July – December 2004: Successful enrollment, begun in March, continued at UCT and MEDUNSA. At the MRC site in Isipingo, near Durban, capacity-building preparations such as clinic renovations and training were completed by August. South Africa's regulatory authority, the Medicines Control Council (MCC), approved a protocol amendment in August that revised HIV and STI testing procedures and eliminated the nested safety study, enabling 16- and 17-year-olds to enroll in the main trial. The amendment was implemented at the sites on September 2. Trial initiation at the MRC site was delayed until October pending Institutional Review Board approval, which took several months despite our persistence and timely response to queries. A successful revalidation of the applicator test was conducted at MEDUNSA and UCT, made necessary by the unexpected effects of air pressure variations during shipping on applicators used in the first validation. The test was implemented in November at the first two sites. As of December 31, 2,011 women were enrolled. To achieve this enrollment rate, approximately 3,400 women were screened, and even more attended recruitment sessions where information about the trial, HIV, and safer sex practices was disseminated.

January – June 2005: Successful enrollment continued at all three sites and by April 15, approximately 3,200 women had been enrolled. Clinical trial audits were conducted at all three sites in January. The applicator test was implemented at the MRC site, and the dye used for that test was replaced with a non-toxic dye, after validation in both New York and South Africa.

On January 31 and February 1, an investigators' meeting was held in Pretoria, South Africa, where the team discussed challenges, solutions, and lessons learned. Applicator test results presented at the meeting suggested that gel use was low. To help increase adherence, changes in clinic flow were implemented immediately (women began returning applicators to counselors rather than receptionists, thus creating a sense of accountability). Site investigators were instructed to temporarily focus their applicator testing on a select cohort of women, in order to quickly clarify use dynamics. This sample analysis revealed that gel use was higher than was suggested by the results reported at the investigators' meeting. Both sets of applicator test results were shared with the microbicides field at a PC-hosted meeting held in New York on April 6.

All ethics committees and the MCC approved a protocol amendment changing the primary analysis to intent-to-treat. A secondary per-protocol analysis will be performed on a restricted data set of adherent women. The amendment was submitted to the U.S. Food and Drug Administration, and at their request a conference call was held with the FDA to explain the adherence data.

The study has been running smoothly without the use of a Web site or newsletter, and therefore it was decided these avenues will not be pursued so that human and financial resources can be focused elsewhere. Observed rates of seroconversion are consistent with underlying statistical calculations. However, in response to the late start date of the MRC site (October 2004), and the irregular occurrence of seroconversions, the first meeting of the data safety monitoring board was delayed to late August.

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)
Clinical DataFax Systems Inc.
Lancet Laboratories (USAID and cost share)
MRP Solutions

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Carraguard® Nonclinical Development

Project Number/s: 08302

Country/ies: 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 is undergoing a Phase 3 clinical trial to determine its efficacy (see activity "Carraguard Clinical Development: Large-Scale Phase 3 Efficacy Trial"). Carraguard nonclinical development encompasses the efforts of the nonclinical microbicides team at the Center for Biomedical Research to support the trial and complete the necessary testing and development steps to bring Carraguard to market. All funds supporting Carraguard nonclinical projects come from USAID.

Production and supply of study gels to trial sites

The nonclinical team manages the manufacture of the study gels (Carraguard gel and methyl cellulose placebo gel), 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. Fifteen to 18 batches of each gel (approximately 65,000 applicators produced per batch) are needed for the trial. Three batches of each were produced beginning in December 2003 under the Population Council Program III cooperative agreement; through April 2006, 12 to 15 more batches of each will be produced under the Population Council Product Development cooperative agreement.

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 (methyl cellulose placebo gel). The nonclinical team will execute or manage these tests throughout production. Chemical identity is tested by the Population Council; impurity testing is contracted to The National Food Laboratory, Inc. (The NFL); evaluation of rheological parameters to CCS; activity, or strength, testing to ImQuest BioSciences, Inc.; and preservative efficacy testing to Sterilization Technical Services.

Stability testing of gels

Stability studies seek to measure how the quality of a formulation varies over time under the influence of various environmental factors. Carraguard will undergo a five-year stability analysis: a five-year stability profile would provide major support for obtaining over-the-counter product labeling. Methyl cellulose placebo gel will undergo stability testing only through the end of the Phase 3 trial. Samples from the first three production batches of the gels have been stored by CCS since February 2004 in incubators at various temperatures and humidity conditions that approximate ambient and extreme storage conditions. At specified time points, samples are removed for testing: by the Population Council for chemical identity; by The NFL for impurities; by CCS for rheological parameters; and by ImQuest for activity. The stability program closely follows the guideline of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use for testing the stability of investigational new drugs. If Carraguard gel does not fall out of specification before the end of five years, testing will be complete in February 2009.

Patent protection and trademark rights for Carraguard
The Council will finalize and file a patent application to the U.S. Patent and Trademark Office during Year One, with further filing and legal activities necessary throughout the agreement. The nonclinical team will also administrate the maintenance of Carraguard's registered trademark status in Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Mexico, the Netherlands, Portugal, South Africa, Spain, Sweden, Thailand, the United Kingdom, and the United States.

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 (a combination of two types of carrageenan) must be developed and submitted to the USP/NF for registration of these entities as active pharmaceutical ingredients. These registrations (called Requests for Revision) are a necessary step toward U.S. Food and Drug Administration (FDA) approval to market Carraguard. Each monograph includes the name, definition, packaging and storage information, labeling, USP reference standards, chemical specifications, and definition (including biological activity); each of these elements requires validation of chemical methods. Several of these elements can be determined only after completion of the Phase 3 trial at the end of 2006. Preparation of the monographs is planned during 2006 and 2007 for submission in early 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 (see activity "Carraguard Clinical Development: Large-Scale Phase 3 Efficacy Trial") for submission to the FDA in 2008.

Report of Year One:

Production and supply of study gels to trial sites
July – December 2004: Two batches of each study gel were shipped to clinical sites in December. No gel production occurred.
*January – June 2005:*One batch of each gel was produced in March and were packaged and delivered to study sites. Three more batches of each gel were produced at the end of April. Fewer batches were produced during this year than originally planned because of changing needs at the study sites. Product liability insurance was paid on the study gel.

Control testing of each production batch of gel
July – December 2004: Because no study gel was produced during this period, no control testing was required.
January – June 2005: Both batches of gel produced in March successfully passed control testing. The six batches scheduled to be produced in April will complete control testing by June.

Stability testing of gels
July – December 2004: Six-month Carraguard and methyl cellulose stability samples were evaluated, and they remained within specified limits. Evaluation of nine-month samples was begun.

January – June 2005: The nine-month samples of Carraguard and methyl cellulose were evaluated and remained within the specified limits for chemical, physical, and biological change. Testing of the 12-month samples will have been completed by mid-May.

Patent protection and trademark rights for Carraguard
July – December 2004: Consideration was made by the Council's lawyers and program staff on how to proceed with a patent filing for carrageenan-containing compounds for prevention of HIV infection and other STIs. It was decided to proceed with filing a patent application in the United States. A patent was filed with the U.S. Patent and Trademark Office, and the Council awaits word on the acceptance or denial of the submission.
January – June 2005: No new activity. The Council awaited the decision of the U.S. Patent and Trademark Office on the patent application submitted during the last half of 2004.

Registration of Carraguard and its active pharmaceutical ingredient with the United States Pharmacopeia and National Formulary
July – December 2004: No activity.
January – June 2005: No activity.

Preparation of a New Drug Application to the FDA
July – December 2004: Work continued on converting Carraguard's regulatory file to the ICH format, which includes the creation of a Common Technical Document. Council staff also continued the process of selecting a cost-effective software package that will facilitate electronic submissions to regulatory agencies.
January – June 2005: No activity.

Contractor(s): Clean Chemical Sweden
ImQuest BioSciences, Inc.
Sterilization Technical Services
The National Food Laboratory, Inc.

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

PC-815 Nonclinical Development: Phillips Laboratory

Project Number/s: 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, as well as being an active ingredient.

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 include assays for strength, stability, and toxicology that 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 test strength (against an increasingly broad range of STIs), stability, toxicity, and pharmacokinetics. These assays 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 concentrate on aspects of formulation optimization such as preservative efficacy and condom integrity testing.

In support of clinical trials (see activity "PC-815 Clinical Development"), 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.

The budget for this activity proposed and accepted in the PCPD agreement provides for only 30% of this activity's funding during Years Two through Five. Funding from the Swedish International Development Agency will be used to support this activity in Year Two.

Report of Year One:
July – December 2004: Investigators continued optimizing the formulation. Various PC-815 formulations were compared to Carraguard against HIV-1 in a syncytial assay, and against HIV-2, and were found to be more effective than Carraguard alone. A spinoculation assay was used to test the PC-815 formulations

against subtype C clinical isolates of HIV; preliminary results suggest that PC-815 effectively blocks all strains tested (including two strains that Carraguard failed to block), and at lower effective concentrations. An XTT assay was employed to determine the cytotoxicity of the PC-815 formulations in peripheral blood mononuclear cells; little to no cytotoxic effect was observed as compared with the cell control, with the exception of extremely high doses greater than 2 mg/ml (well above what would be employed in PC-815).

Regarding production methodology, it was discovered that a suspension of MIV-150 and carrageenan produced a non-homogenous formulation. However, the formulation made with ethanol as a solvent was found to remain homogenous over time. Ethanol-containing samples at 4, 25, and 40 degrees Celsius were found to be stable at three and six months. Through the use of an ethanol solvent we discovered that it is possible to use micronized MIV-150 to produce a homogenous formulation; therefore, we will not pursue use of nanocrystallized MIV-150, as its only advantage was superior solubility, but at far greater expense.

The remaining variable in formulations is concentration of MIV-150. Two new PC-815 formulations, containing higher concentrations of MIV-150, began to be tested for strength, stability, and toxicity.

January – June 2005: The three different formulations of PC-815, containing low, medium, and high concentrations of MIV 150, are being compared by analysis of differences in strength, stability, and toxicity. The initial low-dose formulation of PC-815 successfully completed ten-month stability testing. The medium- and high-dose formulations completed two-month stability testing and both are stable at this time point. Stability analysis on all formulations is ongoing. The three formulations were also compared via the microtiter syncytial-forming assay and the spinoculation assay for activity against HIV-1 and show a dose-dependent response, with the high-dose formulation showing greater efficacy against HIV-1 than the two lower doses. Our results confirmed that PC-815 formulations show greater efficacy than Carraguard alone against HIV-2.

Rabbit vaginal irritation testing was completed on the low-dose formulation of PC-815; nonoxynol-9 was used as a positive control. The PC-815 formulation scored exceptionally well, showing minimal irritation, and scoring well below toxic level. Other assays planned for Year One—lactobacillus assays, monitoring for activity in the HSV-2/mouse system, and *in vitro* dialysis testing to analyze the rate at which MIV-150 is released—were not performed until a stable production methodology had been achieved. They will be performed on the three different formulations during the end of Year One and during Year Two. The one-year toxicology/ pharmacokinetic study testing vaginal administration of PC-815 in rodents was temporarily put on hold.

The IND application and the accompanying IB for PC-815 will be submitted to the Food and Drug Administration (FDA) in June. The Phase 1 protocols were drafted by the clinical team. (See "PC-815 Clinical Development" activity.)

Contractor(s): Clean Chemical Sweden
ImQuest BioSciences, Inc.
North American Science Associates
The National Food Laboratory, Inc.
Toxikon Corporation

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

PC-815 Nonclinical Development: Pope Laboratory

Project Number/s: 09303

Country/ies: United States
Technical Coord.: Melissa Pope
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 Pope.

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, as well as being an active ingredient. The combination formulation has a number of highly attractive properties.

The Pope laboratory will employ various *in vitro* and *in vivo* systems to test the ability of PC-815 to block transmission of HIV by DCs. DCs, a type of white blood cell, are located throughout the body, most importantly at the body surface. They normally capture infectious microbes (e.g., viruses and bacteria) and present them to other white blood cells of the immune system (T and B cells) in order to activate immune responses that clear the infection and prevent re-infection. However, HIV and other sexually transmitted infections (STIs) that breach the body surface can target DCs and exploit the DC system to facilitate infection instead of activating immunity. This exploitation is fostered by the fact that DCs efficiently capture HIV/SIV (and other pathogens), thereby driving infections by these pathogens, especially when HIV-bearing DCs interact with T cells (one of the natural functions of DCs). This paradox, whereby a DC that is programmed to activate an immune response in the presence of an antigen can actually be manipulated by HIV/SIV and other pathogens to encourage virus spread, enables HIV to propagate effectively in human hosts. Agents like PC-815 that act in a general manner to block virus and cell interactions and potentially inactivate virus (independent of the receptors involved) represent extremely attractive microbicide strategies.

All studies will involve the use of formulations provided by the Phillips laboratory (see activity "PC-815 Nonclinical Development: Phillips Laboratory"). In *in vitro* assays, DCs or DC–T cell mixtures from human and macaque donors will encounter HIV/SIV alone or HIV/SIV in combination with model STIs such as herpes simplex virus type 2 (HSV-2), *Chlamydia trachomatis*, or *Trichomonas vaginalis*, with and without PC-815, to determine whether PC-815 blocks virus (pathogen) capture by DCs and/or impedes the transmission of virus from DCs to T cells. Results from these studies will provide necessary data to support the extensive *in vivo* studies in which the ability of PC-815 to prevent SHIV infection in healthy versus STI-infected animals will be assessed. The *in vivo* studies, contracted to the Tulane National Primate Research Center (TNPRC), will utilize macaques as our non-human primate model system. For each group of macaques, samples of blood and tissue will be assayed for baseline values. The animals will be treated with Depo-Provera to synchronize their cycles, after which the animals will have either PC-815 or the methyl cellulose (MC) placebo applied to the vaginal vault and the challenge virus administered within approximately 30 minutes. The animals will then be closely monitored for viral loads and immune responses by collecting blood samples weekly for the first six to 12 weeks and then every two to four weeks thereafter. Viral loads will be assayed by bDNA, reverse transcriptase PCR analysis, PCR, and coculture studies. Immune responses will be monitored by measuring antibody and cellular responses using

ELISPOT, ELISA, fluorescent bead cytokine kit, and proliferation assay systems. Lymphoid and mucosal samples will also be monitored as needed. The first groups of macaques will be naive (no STI infection) before SHIV challenge. The next groups will be pre-infected with HSV-2, and subsequent animal groups will be infected with other STIs, in order to ascertain how effectively PC-815 will block HIV/SIV infection in the presence of different existing STIs.

Report of Year One:

July – December 2004: In vitro assays were initiated to evaluate PC-815, using other established microbicides for comparison, in the DC–T cell assays. These experiments demonstrated that SHIV162P3 has limited use as a target virus; therefore attention was refocused on another virus isolate, SHIV RT, which proved much more susceptible to MIV-150 *in vitro.* MIV-150 did not react as well against SHIV162P3's SIV reverse transcriptase (RT) as it did against the HIV RT contained within SHIV RT. Since in humans it is HIV RT that must be targeted, attention was shifted to SHIV RT as the more useful challenge virus to provide the most accurate data as to whether MIV-150 can enhance the efficiency of carrageenan-based microbicides in humans.

For the *in vivo* studies, because of the change of challenge virus from SHIV162P3 to SHIV RT, it was crucial to do preliminary *in vivo* tests to verify SHIV RT infectivity via the vaginal route and to determine the challenge dose. Therefore, 16 additional animals (purchased and supported with non-PCPD funds) were incorporated into these studies. Blood from 20 naive Chinese female macaques (16 from previous USAID funding and four of the 12 animals budgeted for Year One) were assayed for antibody and cellular responses as well as viral loads in plasma to record baseline parameters. To do this, four blood samples were taken from each animal over an 8- to 12-week period, the cells assayed immediately, and the plasma stored for subsequent analyses.

In preparation for studies planned in Year Two, a non–USAID-funded pilot study through Tulane National Primate Research Center investigating the establishment of an HSV-2 infection macaque model system yielded promising results. *In vitro* assays demonstrated that myeloid dendritic cells (MDCs) and plasmacytoid dendritic cells (PDCs) circulating in Chinese rhesus macaque blood behave similarly to their Indian Rhesus macaque counterparts. In addition, we observed that monocyte-derived DCs from Chinese macaques could be productively infected by HSV. (These results are similar to those of past Indian macaque studies.) HSV-infected DCs were observed to have diminished phenotypic and immunogenic abilities. Specifically, HSV-infected DCs stimulated lower SIV-specific immune responses *in vitro,* further supporting the notion that HSV infection might dampen immunity to SIV and increase infection. This ongoing pilot began its *in vivo* HSV vaginal infection study to establish the HSV infection macaque model system during the last half of Year One. This study provides pivotal insight necessary for the planned Year Two HSV/SHIV RT pre-infection studies to monitor the efficacy of PC-815 in a multiple pathogen setting.

January – June 2005: During the last half of Year One, additional SHIV RT stocks were grown up, titered for dose efficacy, and used in *in vitro* assays to ascertain the efficiency of PC-815 activity *in vitro.* These initial *in vitro* assays compared the efficiency of Carraguard, MIV-150, and PC-815 in established DC-HIV assay systems. We confirmed that MIV-150 was able to block the infection of DCs with R5 HIV as well as block the transmission of R5 HIV from the infected DCs to T cells. While these *in vitro* studies did not progress as far as initially planned, because of the need to expedite the *in vivo* project (the major focus of this program), other comparisons of MIV-150 and PC-815 were underway at the end of the program year.

Once optimized, these assays will be used to evaluate PC-815 activity against SHIV-RT.

The *in vivo* microbicide studies continue to unfold. After the baseline data were gathered (July – December 2004), the first ten animals were challenged to verify that the SHIV RT is infectious vaginally and to give us the first insight into the activity of Carraguard vs. PC-815 against this virus isolate. These controls are critical and involved dividing the ten animals into three groups (3, 3, and 4 animals in each group) that received one of three blinded gels—MC, Carraguard, or PC-815. Analyzed data confirmed that the SHIV RT is infectious vaginally. However, the high virus inoculum used in this first set of animals appeared to overwhelm the microbicide effects of Carraguard (previously shown to block 70% SIV infection). All animals treated with Carraguard became infected, but importantly the peak levels of virus in the plasma appeared later and were lower than those detected in the infected animals treated with the MC placebo. While all three of the animals in the PC-815 group also got infected, the viral loads were lower and the peak of viral load appeared later in two of the three animals in this PC-815 group. These results are encouraging for carrageenan-based microbicides, since partial activity was observed even in the face of a high challenge dose of SHIV RT (10^5 infectious doses).

The second set of ten animals (six non–PCPD-funded and four of the 12 budgeted for Year One) was challenged in April with a lower dose of SHIV RT (1000 infectious doses), and this set of animals is being followed as described in the Activity Description. Preliminary examination of the cultures from these animals indicates that the MC-treated animals are already infected at the earliest time points, verifying that the lower dose of virus is infectious for all control animals. Data continue to be gathered from the three differently treated groups (as above) to ascertain how effectively PC-815 (vs. Carraguard) impedes vaginal infection with SHIV RT.

The separate non–PCPD-funded Tulane pilot study was renewed for a second year. This study involves the establishment of HSV-2 infection in the macaque model and examines the effects of HSV-2 infection on DC viability and function. The *in vitro* study demonstrating the effect of HSV-2 infection on macaque monocyte-derived DCs (reported on above), which sets the stage for our *in vivo* work, is reported on in an article that was recently accepted for publication (Peretti et al., 2005, *Blood*, In Press). The first samples from animals vaginally challenged with HSV-2 are being collected and processed. The presence of virus and immunity to HSV, as well as circulating DC biology, are being monitored in the blood and mucosal fluids following vaginal exposure to HSV-2. The progress made in this study directly addresses the scientific questions posed in this USAID-funded activity (starting in Year Two), concerning the ability of PC-815 to protect against infection with SHIV RT in the presence of an existing or coincident STI.

The last eight animals of the twelve slated for use in Year One were ordered and are set to arrive before the end of the program year. Baseline values for these animals will be gathered toward the end of the program year; however, the treatment of these eight animals with Depo-Provera and challenge with SHIV RT will continue in Year Two.

Contractor(s): Tulane National Primate Research Center

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

PC-815 Clinical Development

Project Number/s: 08304

Country/ies: Dominican Republic, South Africa, United States
Technical Coord.: Stephanie Skoler, Sumen Govender, and Pekka Lahteenmaki
Period: July 2004 – June 2010
Objective: To determine the efficacy of the candidate second-generation vaginal microbicide PC-815, and to collect clinical data for supporting the New Drug Application, by carrying out three Phase 1 trials and a large multicenter Phase 2/3 trial.

Activity Description:
PC-815 combines the non-nucleoside reverse transcriptase inhibitor MIV-150 with Carraguard® in a proposed novel second-generation microbicide. Carraguard serves as the vehicle base for MIV-150 and as an active ingredient. The combination formulation has a number of highly attractive properties.

The PC-815 clinical product development plan includes three Phase 1 trials, proceeding directly to a larger, multicenter Phase 2/3 trial. The first Phase 1 trial, to ensure vaginal safety, is to be conducted in early to mid-2005 under the direction of International Committee for Contraception Research member Vivian Brache at the Asociación Dominicana Pro-Bienestar de la Familia (PROFAMILIA) clinic in the Dominican Republic. Assuming successful results, two additional, expanded Phase 1 trials, each with a particular primary endpoint to the protocol, will be conducted to further assess product safety. The second Phase 1 trial, also to be performed by PROFAMILIA, will be similar to the first, but include a pharmacokinetic component to measure the absorption of MIV-150 in the blood after vaginal use of PC-815. The third Phase 1 trial will evaluate lavages taken from HIV-positive women one hour after vaginal exposure to PC-815, to examine the effect of PC-815 on the survival of HIV in the vaginas of HIV-positive women post product use. This study will take place at the Setshaba Research Center, managed by the University of Limpopo/Medunsa Campus (formerly MEDUNSA), one of the sites for the Carraguard Phase 3 trial.

Traditional Phase 2 trials focus on expanded safety and dose-finding. However, one of the unique challenges of conducting a clinical trial of a microbicide is that, unlike other prevention research, HIV infection has no surrogate endpoint, and it is doubtful that one will be identified. Therefore, because no true Phase 2 microbicide trial can be executed, a Phase 2/3 "proof of concept" study of PC-815 will be conducted to assess efficacy. While the expanded Phase 1 trials are in progress, a Phase 2/3 protocol will be developed and submitted for regulatory and ethical approval. This trial is expected to begin in late 2006.

PC-815 will be compared to Carraguard alone in this randomized, controlled, double-blind Phase 2/3 trial, planned for implementation in South Africa. Similar to the Carraguard trial, the goal of the PC-815 trial is to determine efficacy against HIV. Approximately 3,000 women are to be enrolled over 18 months for a total trial duration of approximately three years, with each woman participating for a maximum of two years. The protocol will allow for the addition of more sites should the sample size and/or recruitment capabilities be insufficient, or should the efficacy of Carraguard be too low. Early results of the review by the data safety monitoring board for the Phase 3 Carraguard trial (see activity "Carraguard Clinical Development: Large-Scale Phase 3 Efficacy Trial") will provide guidance on planning for this trial.

To carry out the Phase 3 Carraguard trial, Council researchers established a strong infrastructure to facilitate the management of large microbicide trials, and a close collaboration with several clinical trial

sites in South Africa. The standard operating procedures and DataFax-specific case record forms will provide ideal templates for data collection and protocol implementation for clinical trials of PC-815.

Because of USAID's expressed limit on HIV/AIDS Core funds available for 2004 – 2009, the budget for this activity proposed and accepted in the PCPD agreement does not include subawards to trial sites for the Phase 2/3 trial, and therefore provides for only part of this activity's funding during Years Three through Five. The Swedish International Development Cooperation Agency (SIDA) has committed funds toward the development of PC-815, and some of these SIDA funds will be used to support this activity. Additional funding for Years Three through Five will also have to be secured.

Report of Year One:

July – December 2004: No PCPD funds were expended on the PC-815 Clinical Development activity during the first half of Year One. The first Phase 1 protocol was finalized later than expected, due to a considerable workload at the PROFAMILIA clinic. It was approved by the Population Council Institutional Review Board (IRB) in November. Informed consent forms were translated into Spanish by PROFAMILIA.

January – June 2005: The first Phase 1 protocol was submitted to the PROFAMILIA IRB. The trial is anticipated to begin by June, pending IRB and IND approval. (See activity "PC-815 Nonclinical Development: Phillips Laboratory" for more information on the status of the IND.) The protocol for a second Phase 1 trial at PROFAMILIA, similar to the first but including a pharmacokinetic component to measure the absorption of MIV-150 in the blood after vaginal use of PC-815, was preliminarily drafted by the Population Council. A third Phase 1 protocol was submitted to the Population Council IRB, and will be submitted to the University of Limpopo/Medunsa Campus IRB in early June. This South African trial will enroll HIV-positive participants, to determine the effect of the gel on viral shedding. The clinical team began working on a draft of the Phase 2/3 trial protocol, using experience and knowledge gained from the Carraguard Phase 3 trial.

In the Year One Workplan, we expected to conduct research on possible collaborations in India, because of reports that the HIV infection rate in South Africa may have been declining in certain cohorts. However, recent data show that HIV incidence in the Phase 3 Carraguard study communities is steady, and therefore South Africa remains more suitable than India for the PC-815 trials. We also expected to carry out one of the Phase 1 trials at the Medical Research Council (MRC) in South Africa. However, high rates of HIV in the MRC catchment area require the full attention of Population Council staff in order to fulfill recruitment goals for the Phase 3 Carraguard trial. As a result, the Medunsa Campus site was chosen instead for the expanded Phase 1 PC-815 trial.

Clinical testing on the second-generation microbicide PC-815 contributes to the overall development of female-controlled HIV prevention technologies.

Subawardee(s): Dominican Association for the Well-Being of the Family (PROFAMILIA)
University of Limpopo / Medunsa Campus
Others TBD

Contractor(s): Clindev (Pty.) Ltd.

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Developing Informed Consent and Recruitment Materials for Population Council Microbicides Trials

Project Number/s: 44211

Country/ies: South Africa, United States
Technical Coord.: Barbara Friedland
Period: July 2001 – June 2009
Objective: To develop, test, and evaluate the informed consent (IC) forms, educational materials, and counseling processes for Council microbicide trials.

Activity Description:
Ensuring truly informed consent and voluntary participation is one of the most difficult aspects of conducting any clinical trial. While critical to maintaining high ethical standards, the informed consent process can also have an impact on the outcome of a trial. Informed consent is directly tied to recruitment and retention efforts. The better the informed consent process, the more likely it is that participants who enroll will remain in a trial and will comply with the study protocol.

Recognizing its importance, Population Council researchers have devoted considerable resources to developing and evaluating the informed consent process in Phase 2 and 3 trials of Carraguard®. A recruitment video and study booklet were produced for the Phase 3 efficacy trial of Carraguard. In addition, the Council has worked with the South African study sites to establish local community advisory groups (CAGs) to help develop materials for participants and to serve as a liaison between trial researchers and the community. Involving CAGs helps to ensure that the educational materials developed are appropriate for specific communities. In addition, members of CAGs can help facilitate the recruitment process, particularly for large-scale clinical trials. An evaluation of the video and the overall informed consent process in the Phase 3 Carraguard trial will be completed under this activity.

For PC-815, the product development plan includes three Phase 1 trials followed by a large, multicenter Phase 2/3 trial. Because the Phase 1 trials involve only a few women, this activity will focus on the Phase 2/3 trial, to be conducted in South Africa. For that trial, Council researchers will develop informed consent and educational materials, adapted, where applicable, from the materials being 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 Phase 2/3 trial of PC-815 will be conducted. Council researchers and collaborators will also develop counseling guidelines and develop procedures for an evaluation of the overall informed consent process during the Phase 2/3 trial. All materials will be pre-tested in collaboration with local researchers and approved by all ethics committees involved in the trials.

Report of Year One:
July – December 2004: No PCPD funds were expended on the Informed Consent Materials activity during the first half of Year One, because the work continued to be funded under the Population Council Program III (PCP3) cooperative agreement HRN-A-00-99-00010. Under the PCP3, we translated and pre-tested the Zulu version of the Carraguard Phase 3 trial study booklet for use at the Isipingo site near Durban, managed by the Medical Research Council. We designed the study protocol for the quantitative evaluation of the Carraguard trial video and informed consent process, and created draft questionnaires for that evaluation. In addition, we developed a standard operating procedure for evaluation of the counseling process, which involves observation of the counselors to ensure that they are adhering to the messages in the counseling manual. Each site will conduct evaluations of the counselors twice a year, beginning in 2005.

January – June 2005: We identified the Community Agency for Social Enquiry (CASE), a social science research organization based in Johannesburg, to conduct the quantitative evaluation of the video and informed consent process in the Carraguard Phase 3 trial. (The subaward to CASE will be funded by the PCP3.) Training for the evaluation will take place in June. In addition to the formal evaluation, we have been streamlining the recruitment and informed consent procedures. To that end, we revised the recruitment script and video Q&A to make them more succinct, and we implemented a group informed consent process, which shortens the one-on-one time that each participant spends with counselors without compromising the comprehension assessment.

The informed consent form for the Phase 1 trial of PC-815 to be conducted in South Africa was drafted by staff at the Center for Biomedical Research as part of the "PC-815 Clinical Development" activity. Because of changes in the scope of that trial (see activity "PC-815 Clinical Development"), it was decided that it was not necessary to devote resources to pre-testing the consent form and developing additional materials for that trial. Development of the informed consent form and other educational materials for the Phase 2/3 trial of PC-815 will not begin until late in Year Two.

Subawardee(s): TBD

Contractor(s): TBD

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Evaluating and Improving the Informed Consent Process in Microbicides Clinical Trials

Project Number/s: 44212

Country/ies: United States
Technical Coord.: Barbara Friedland, Martha Brady
Period: July 2004 – June 2008
Objective: To continue to improve the informed consent process in microbicides clinical trials by (1) identifying specific concepts (e.g., safety, placebo, and 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:
Ensuring truly informed consent and voluntary participation is one of the most difficult aspects of conducting any clinical trial. It is particularly challenging when conducting trials in communities in which individuals may not have autonomy and the community plays a large role in the choices people make. To add to these factors, microbicides efficacy trials must be conducted among healthy, HIV-uninfected individuals in areas with a high incidence of heterosexually transmitted HIV infection. Researchers must explain to participants that by participating in a trial they will not be at increased risk for HIV infection, yet they also must convey that the efficacy of the test product is unknown so that participants do not feel a false sense of protection and increase risky behavior (e.g., abandon use of condoms or increase their numbers of partners).

Recognizing its importance, Population Council researchers devoted considerable resources to developing and evaluating the informed consent process in Phase 2 and 3 trials of Carraguard®. Between October 1998 and March 2002, the Council conducted a multistage evaluation of the informed consent process before, during, and after the Phase 2 expanded safety trial in South Africa. The materials developed for the Phase 2 trial, which included a booklet that used pictures and analogies to explain difficult study concepts, were adapted for the Phase 3 efficacy trial, which began in March 2004. In addition, with funding from USAID under the Population Council Program III, USAID cooperative agreement HRN-A-00-99-00010, the Council produced a recruitment video to inform potential study participants and their communities about the trial.

Throughout the development and testing of materials, particular terms and concepts remained difficult to convey. For example, women in the Phase 2 trial could explain what the placebo was (methyl cellulose), but they could not explain why it was being used. 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. However, some mistakenly believed that the objective of the trial was to determine which gel was better—Carraguard or the comparison gel— instead of understanding that the comparison gel was a “neutral” product to which Carraguard was being compared. Therefore, one of the main objectives is to identify the terms and concepts that have not yet been successfully communicated and explore alternatives for explaining them better. This issue will be one focus of discussion at the Informed Consent Workshop, to be held in 2005, that will include colleagues, study staff, staff from sponsoring organizations, and various professionals from the microbicides/HIV/reproductive health fields. Colleagues from Family Health International are co-hosting the meeting and are working with Council staff to develop the agenda

and participant list. A small meeting grant ($6,000) was received from the National Institutes of Health (NIH) to help support the meeting; we also received $50,000 from the International Partnership for Microbicides (IPM) to support additional meeting participants from the field. The recommendations from this meeting will help to identify successes and areas for future research in terms of explaining difficult concepts, assessing and improving comprehension, and evaluating the overall informed consent process.

Report of Year One:

July – December 2004: Although no PCPD funds were expended on the Informed Consent Process activity during the first half of Year One, we made progress in planning for the informed consent workshop to be held at the end of the program year. We identified Kate MacQueen and Cynthia Woodsong of Family Health International as partners to co-host the meeting and assist in planning the agenda and selecting meeting participants. We contracted Elizabeth McGrory to serve as a consultant, who will be the rapporteur at the meeting and is also advising on the agenda and participants list. We were successful in obtaining a small R13 meeting grant ($6,000) from the National Institutes of Health in support of the meeting, and identified several key speakers.

January – June 2005: An international workshop on informed consent in HIV prevention trials was held at the Population Council's New York headquarters on May 16 – 18. While several international meetings had been held previously to discuss ethical issues in the conduct of HIV prevention trials, and particularly those of vaginal microbicides, this was the first workshop devoted solely to informed consent. Our aim had been to have 55 to 60 participants during the first two days, and 30 during the last day. However, because of the enthusiastic response from researchers worldwide, we increased the number to 70 for the first two days. Feedback from meeting participants has been quite positive, and we hope that the success of this meeting will lead to regional meetings in the future.

We spent much of January through May planning the workshop, including developing the agenda, securing speakers, inviting participants, fundraising, and arranging logistics. We also collected informed consent materials (forms, booklets, flip charts, videos) from a variety of ongoing and completed trials and conducted a content analysis for presentation and discussion at the meeting. In April, we received a contribution of $50,000 from the International Partnership for Microbicides to support meeting participants whom we had hoped to support with a larger grant from the NIH. With the generous support from USAID and IPM, we were able to bring presenters from Ghana, Uganda, Tanzania, Zimbabwe, South Africa, India, Brazil, the Netherlands, and the United States.

The first two days of the workshop included 70 participants from varied backgrounds, including clinical trial sponsors, local investigators, counselors, and monitors; donors (USAID, NIH, The Bill and Melinda Gates Foundation); bioethicists; social scientists; umbrella organizations and advocacy groups (UNAIDS, IPM, International AIDS Vaccine Iniative, American Foundation for AIDS Research, the Alliance for Microbicide Development, the Global Campaign for Microbicides, Gay Men's Health Crisis, Gynuity Health Projects, Ibis Reproductive Health, and the AIDS Vaccine Advocacy Coalition); members of institutional review boards; adult learning experts, including those with expertise on the development and implementation of reproductive health communication strategies; and an expert on risk communication. The third day included a subset of participants from the first two days who are directly involved with materials development and implementation of the informed consent process in clinical trials. The meeting was an excellent opportunity for researchers to share experiences about successes and challenges for

informed consent in the context of HIV prevention trials, including the five ongoing Phase 3 microbicides trials (sponsored and/or implemented by the Population Council, the HIV Prevention Trials Network, the Microbicides Development Programme, CONRAD, and Family Health International [FHI]); the University of Washington "Partners for Prevention" HIV/HSV Couples study; the MIRA diaphragm trial (managed by the University of California, San Francisco and Ibis Reproductive Health); oral tenofovir trials (managed by the U.S. Centers for Disease Control and Prevention and FHI); and the AIDSVAX Phase 3 trial among injecting drug users in Thailand.

There were theoretical discussions about factors influencing decision-making, such as risk perception, sexual partners, and whether the community can help or hinder the informed consent process. Several presenters described informed consent procedures and the challenges they faced in the development of materials and implementation of the overall consent process in completed, ongoing, or planned clinical trials. Other researchers described methods for assessing comprehension at the time of consent, which led to a discussion about the merits of open-ended vs. closed-ended (true-false and multiple choice) questions for assessing competency level. The recommendation to use open-ended questions where possible was articulated by an adult learning expert, who enumerated problems with comprehension tests that used only closed-ended questions: that the fact that s/he must pass a "test" could hamper a participant's ability to communicate effectively; that people can guess on true-false tests; and that open-ended questions force people to articulate information themselves, which results in a much better indicator of how well they comprehend information than asking them to pick out correct information from a list of possible answers. By using open-ended questions, study staff will have a better sense of whether or not potential participants are competent to make a decision to join a trial. One presentation that reviewed the existing literature on evaluation of the informed consent process enumerated the dearth of data on informed consent in HIV prevention trials (only five references available as of October 2004), and particularly in the developing-world context (only one of the five). An important recommendation from the workshop was that researchers publish results from the formative research that led them to develop various educational materials, even if they do not plan to conduct a formal review of the overall consent process.

The third day of the meeting with the smaller group (32 participants) was dedicated to a more in-depth exploration of some of the "nuts-and-bolts" aspects of the informed consent process. In a small group exercise, we explored aspects of adult learning, to help plan ways for improving communication among adults. Another session involved an exchange of ideas for explaining difficult terms and concepts (e.g. "placebo," "randomization"), which was based on a content analysis that had been conducted on the materials received prior to the meeting. We also discussed methods for training study staff on informed consent. Meeting participants found the discussion to be particularly useful for planning refresher trainings for ongoing trials and for developing training plans for future trials.

A report summarizing meeting proceedings and recommendations for the field, where applicable, will be produced in Year Two; development of the outline for the contents of the report will begin at the end of Year One.

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 contraceptives 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. Regulatory support of 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®/Ethynylestradiol Contraceptive Ring

Project Number/s: 07902, 07600

Country/ies: Chile, Dominican Republic, Hungary, Mexico, Spain, Sweden, United States, Others TBD

Technical Coord.: Narender Kumar, Regine Sitruk-Ware, and Bruce Variano

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 ethynylestradiol (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 150/15 μg 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), and will be shipped to the mass manufacturer of the ring, QPharma AB (Malmö, Sweden). Crystal Pharma will perform stability and validation studies on NES samples it produces. QPharma will complete steroid core manufacturing trials and core manufacturing process optimization and scale-up. QPharma will then manufacture the rings and package and ship them, while performing stability studies on a sample of the rings.

The original Phase 2 dose-ranging and schedule variation studies were carried out using rings handmade in laboratories at the Center for Biomedical Research (CBR); 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 expected to begin in September 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 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 (ICCR) 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 assay method, as it is now required by the FDA. Once results are in hand, the 13 other clinics involved in the Phase 3 trial will commence enrolling volunteers. A total of 1,280 women will be enrolled to use the ring for one year, including the 39 subjects from the nested PK segment who will be invited to continue in the Phase 3 segment. 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 NES to be noncarcinogenic in rats. During Year Three of the PCPD, a 26-week carcinogenicity study of NES in mice will be initiated.

Report of Year One:

During Year One, NES synthesis process development was completed by Crystal Pharma, and production of three NES batches for the Phase 3 trial commenced. At QPharma, steroid core manufacturing trials were undertaken (using previously available NES), and core manufacturing process optimization and scale-up were commenced, in consultation with CBR staff. Trial batches of steroid cores continued to be shipped from QPharma to the Council, where they underwent *in vitro* release rate testing and were used for setting specifications.

A consultation with an expert in FDA regulatory affairs took place during Year One; one of her recommendations was to proceed with submission of the IND amendment, required in order to commence the Phase 3 trial, to the FDA without specifically requesting a meeting. In anticipation of submitting the IND amendment early in Year Two, study reports of five Phase 2 studies will have been completed by the end of Year One; the investigators' brochure for the Phase 3 trial will have been written; and the chemistry, manufacturing, and controls section of the IND will have been assembled, the last in collaboration with QPharma personnel. The Phase 3 study protocol will have been amended to include all changes since the protocol was originally approved in June 2001, submitted to the Council's Institutional Review Board, and also included in the IND amendment to the FDA. Two contract research organizations (CRO) in Europe will be visited by the end of Year One in order to determine the best candidate CRO to handle interactions with the European clinics and regulatory agencies relating to the Phase 3 trial, as required by new European Union regulations. A data management system was selected and integration of that system with the case record forms for the Phase 3 trial commenced.

A high-performance liquid chromatography machine, which has the capability to perform qualitative and quantitative analysis of multiple components in a sample, was purchased and is being used for analytical, test, and scale-up method development for NES and EE.

(The pharmacological studies in animals to investigate the antiestrogenic effects of NES in comparison with two other progestins, ketodesogestrel and levonorgestrel, were included in the Year One Workplan in error. These studies were completed prior to Year One.)

Subawardee(s): Albert Szent-Gyorgyi Medical University, Hungary
Chilean Institute of Reproductive Medicine (ICMER)
Department of Reproductive Biology, National Institute of Nutrition, Mexico
Dominican Association for the Well-Being of the Family (PROFAMILIA)
Health Research Associates, LAC/USC

Contractor(s): Crystal Pharma
QPharma AB
Contract Research Organization TBD

Activity Funding: Pop Core

Contribution to Results Framework: IR 2.4

Regulatory Maintenance of Marketed Products

Project Number/s: 07701, 07702, 08002

Country/ies: United States
Technical Coord.: 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 20 years and has been used by more than forty million women. Its role in Africa is expected to increase since doubts about the relationship between IUD use and HIV have been put to rest 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, a supplemental application by the Council in support of this purpose has been deemed "approvable" by the FDA pending response to several queries. These responses will be submitted to the FDA in an amendment to the Norplant NDA during Year One. 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 the owner of the NDA, FEI Women's Health (FEI), 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 One:
The Council submitted to the FDA in August 2004 an amendment to the Norplant NDA. The amendment responded to the FDA's queries on the Council's supplemental application to extend Norplant's use-life from five to seven years, which had been deemed "approvable" by the FDA pending response to its queries. We expected the FDA to respond to the amendment with information on whether a commitment from the Council would be required to conduct *in vitro* studies on the release rate of levonorgestrel from implants removed from subjects after seven years of use. However, the FDA responded to the amendment with a request for amended labeling. We will have submitted the amended labeling information by the end of Year One. The FDA's 180-day final review clock will start upon receipt of the labeling information, during which time they must approve the labeling, reject it, or request that we further amend the labeling. An annual report for Norplant will have been completed by the end of Year One or will be completed early in Year Two.

The Jadelle manufacturing supplement, originally filed in February 2004, with amendments submitted in February and June 2004, was approved by the FDA in July 2004. The Council submitted to the FDA in March 2005 an annual report for Jadelle. The Jadelle manufacturer's clinical pharmacology and biopharmaceutics study commitment to collect five years of *in vitro* release rate data from commercial production lots continued.

Regarding the Copper T 380A IUD, Council staff consulted with FEI on safety and effectiveness issues for extending its use-life beyond ten years, and provided FEI with analyses from WHO trials, proposals for labeling information, and responses to FDA queries. FEI has now submitted responses to what is probably the final set of FDA safety and effectiveness queries regarding extension of use-life.

Activity Funding: Pop Core

Contribution to Results Framework: IR 2.4

PUBLICATIONS AND OTHER WRITTEN WORKS

Publications

None.

Other Written Works

Contraceptive Product Research and Development

Fraser, Ian S., Edith Weisberg, Vivian Brache, Francisco Alvarez, Rebeca Massai, Daniel R. Mishell Jr., Dan Apter, Judi Gale, Yun Yen Tsong, Irving Sivin. 2005. "Serum Nestorone® and ethinyl estradiol levels, and ovulation inhibition in women using three different dosage combinations of a Nestorone progestogen-ethinyl estradiol contraceptive vaginal ring on a bleeding-signaled regimen," *Contraception* 72(1): 40-5.

Population Council Center for Biomedical Research. 2005. "Jadelle®" (Annual report) submission of New Drug Application (NDA) information to U.S. Food and Drug Administration (FDA), 5 March.

———. 2005. "Jadelle®" (Supplement for chemistry, manufacturing, and controls) submission of NDA information to FDA, 28 June.

———. 2004. "Minutes of the 85th Meeting of the International Committee for Contraception Research (ICCR)."

———. 2005. "Nestorone®/Ethinyl Estradiol Contraceptive Vaginal Ring" (Annual report; preclinical carcinogenicity final report on Nestorone; three preclinical final reports on absorption, metabolism, and excretion of Nestorone), submission of Investigational New Drug (IND) information to FDA, 24 June.

———. 2005. "Nestorone®/Ethinyl Estradiol Contraceptive Vaginal Ring" (Protocol Amendment: Phase 3 protocols; revised Investigator's Brochure; Information Amendment: clinical study report; synopses of three Phase 2 studies), submission of IND information to FDA, 27 June.

———. 2004. "Norplant®" (Complete response to approvable letter; complete response to discipline letter), submission of NDA information to FDA, 24 August.

———. 2004. "Norplant®" (Electronic data set) submission of NDA information to FDA, 8 September.

Sivin, Irving. 2004. "Failing in analysis of the performance of the GyneFix® 200 intrauterine system," *Contraception* 70(4): 353-4; author reply 354-5.

Sivin, Irving. 2005. "A reply to D. Wildemeersch's erring reply: Three-year efficacy and acceptability of the GyneFix® 200 intrauterine system," *Contraception* 71(4): 315.

Sivin, Irving, Daniel R. Mishell Jr., Francisco Alvarez, Vivian Brache, Kaisa Elomaa, Pekka Lahteenmaki, Rebeca Massai, Patricia Miranda, Horacio Croxatto, Catherine Dean, Margaret Small, Harold Nash, and Theodore M. Jackanicz. 2005. "Contraceptive vaginal rings releasing Nestorone® and ethinylestradiol: a 1-year dose-finding trial," *Contraception* 71(2): 122-9.

Weisberg, Edith, Vivian Brache, Francisco Alvarez, Rebeca Massai, Daniel R. Mishell Jr., Dan Apter, Judi Gale, Irving Sivin, Yun Yen Tsong, and Ian S. Fraser. 2005. "Clinical performance and menstrual bleeding patterns with three dosage combinations of a Nestorone® progestogen/ethinylestradiol contraceptive vaginal ring used on a bleeding-signaled regimen," *Contraception* 72(1): 46-52.

Microbicide Product Research and Development

Ahmed, K. and S. Skoler. 2005. "A multidisciplinary Phase 3 clinical trial of Carraguard® for the prevention of HIV seroconversion in women in Soshanguve, Pretoria, South Africa," poster presentation at the South African AIDS Conference, Durban, South Africa, 7–10 June.

———. 2005. "A multidisciplinary Phase 3 clinical trial of Carraguard® for the prevention of HIV seroconversion in women in Soshanguve, Pretoria, South Africa," poster and oral presentation at the Congress of Federation of Infectious Diseases Societies of Southern Africa, Sun City, South Africa, 24–26 July.

———. 2005. "A multidisciplinary Phase 3 clinical trial of Carraguard® for the prevention of HIV seroconversion in women in Soshanguve, Pretoria, South Africa," poster presentation at the International Society for Sexually Transmitted Diseases Research, Amsterdam, The Netherlands, 10–13 July.

Cassim, N. and K. Ahmed. 2005. "Services and treatment offered at referral clinics in Soshanguve, Pretoria, South Africa, to participants of a Phase 3 trial of the microbicide Carraguard™," poster presentation at the South African AIDS Conference, Durban, South Africa, 7–10 June.

———. 2005. "Services and treatment offered at referral clinics in Soshanguve, Pretoria, South Africa, to participants of a Phase 3 trial of the microbicide Carraguard™," poster presentation at the Congress of Federation of Infectious Diseases Societies of Southern Africa, Sun City, South Africa, 24–26 July.

———. 2005. "Services and treatment offered at referral clinics in Soshanguve, Pretoria, South Africa, to participants of a Phase 3 trial of the microbicide Carraguard™," poster and oral presentation at the International Society for Sexually Transmitted Diseases Research, Amsterdam, The Netherlands, 10–13 July.

Coumi, N, T. Palanee, N.S. Morar, S. Gumede, and G. Ramjee. 2005. "Challenges in implementing the Carraguard® microbicide Phase III clinical trial in Durban, South Africa," poster presentation at the South African AIDS Conference, Durban, South Africa, 7–10 June.

Dladla, S.A., R.M. Phofedi, K. Ahmed, and M. Gehret. 2005. "Assessment of sexual behaviour patterns in women screened in the Phase 3 Carraguard™ microbicide trial, in Soshanguve, Pretoria, South Africa," poster presentation at the South African AIDS Conference, Durban, South Africa, 7–10 June.

———. 2005. "Assessment of sexual behaviour patterns in women screened in the Phase 3 Carraguard™ microbicide trial, in Soshanguve, Pretoria, South Africa," poster presentation at the International Society for Sexually Transmitted Diseases Research, Amsterdam, The Netherlands, 10–13 July.

Friedland, B., A. de Kock, M. Marumo, N. Ngcozela, C. Monedi, P. Taylor, and S. Skoler. 2005. "Development of a recruitment video for a Phase 3 trial of Carraguard™," poster presentation at the South African AIDS Conference, Durban, South Africa, 7–10 June.

Khunou, J.L., C. Monedi, P. Moodley, K. Ahmed, and A. Mothle. 2005. "Experiences and challenges facing nurse clinicians in the Phase 3 Carraguard™ vaginal microbicide clinical trial in Soshanguve, Pretoria, South Africa," poster presentation at the South African AIDS Conference, Durban, South Africa, 7–10 June.

———. 2005. "Experiences and challenges facing nurse clinicians in the Phase 3 Carraguard™ vaginal microbicide clinical trial in Soshanguve, Pretoria, South Africa," poster presentation at the International Society for Sexually Transmitted Diseases Research, Amsterdam, The Netherlands, 10–13 July.

Marumo, M. and K. Ahmed. 2005. "Challenges of HIV testing and counselling in a Phase 3 trial of the microbicide Carraguard™, in Soshanguve, Pretoria, South Africa," poster presentation at the South African AIDS Conference, Durban, South Africa, 7–10 June.

———. 2005. "Challenges of HIV testing and counselling in a Phase 3 trial of the microbicide Carraguard™, in Soshanguve, Pretoria, South Africa," poster presentation at the International Society for Sexually Transmitted Diseases Research, Amsterdam, The Netherlands, 10–13 July.

Marumo, M.P., S.A. Dladla, R.M. Phofedi, K. Ahmed, and M. Gehret. 2005. "Assessment of sexual behavior patterns in women screened in the Phase 3 Carraguard microbicide trial in Soshanguve, Pretoria, South Africa," oral presentation at the South African AIDS Conference, South Africa, 7–10 June.

Monedi, M.C., K. Ahmed, J.L. Khunou, and A. Mothle. 2005. "Experiences of speculum examination in women participating in the phase 3 trial of Carraguard™, a vaginal microbicide, in Soshanguve, Pretoria, South Africa," poster presentation at the South African AIDS Conference, Durban, South Africa, 7–10 June.

———. 2005. "Experiences of speculum examination in women participating in the phase 3 trial of Carraguard™, a vaginal microbicide, in Soshanguve, Pretoria, South Africa," poster presentation at the International Society for Sexually Transmitted Diseases Research, Amsterdam, The Netherlands, 10–13 July.

Morcock, D.R., J.A. Thomas, T.D. Gagliardi, R.J. Gorelick, J.D. Roser, E.N. Chertova, J.W. Bess Jr., D.E. Ott, Q.J. Sattentau, I. Frank, M. Pope, J.D. Lifson, L.E. Henderson, and B.J. Crise. 2005. "Elimination of retroviral infectivity by *N*-ethylmaleimide with preservation of functional envelope glycoproteins," *Journal of Virology* 79(3): 1533-1542.

Moropeng, M.L., J. Skhosana, B.L. Mohale, K. Ahmed, A.A. Hoosen, and M. Gehret. 2005. "Quality control (QC) of clinical record forms (CRF's) in a large Phase 3 trial of Carraguard™, a vaginal microbicide, conducted in Soshanguve, Pretoria, South Africa," poster presentation at the South African AIDS Conference, Durban, South Africa, 7–10 June.

———. 2005. "Quality control (QC) of clinical record forms (CRF's) in a large Phase 3 trial of Carraguard™, a vaginal microbicide, conducted in Soshanguve, Pretoria, South Africa," poster presentation at the International Society for Sexually Transmitted Diseases Research, Amsterdam, The Netherlands, 10–13 July.

Palanee, T., S. Govender, F. Kizis, T. Kunene, N.S. Morar, T. Thebe, and G. Ramjee. 2005. "HIV and STI prevalence among women screened for inclusion in the Carraguard™ Phase III Trial in Durban, South Africa," poster presentation at the South African AIDS Conference, Durban, South Africa, 7–10 June.

Peretti, Silvia, Andrew Shaw, James Blanchard, Rudolf Bohm, Gavin Morrow, Jeffrey D. Lifson, Agegnehu Gettie, and Melissa Pope. 2005. "Immunomodulatory effects of HSV-2 infection on immature macaque dendritic cells modify innate and adaptive responses," *Blood, Blood First Edition Paper, prepublished online April 21, 2005.*

Skhosana, J.S., M. Gehret, K. Ahmed, G. Ramjee, L. Altini, and S. MacDonald. 2005. "Prevalence of STIs amongst women attending the Phase 3 Carraguard™ clinical trial in South Africa," poster presentation at the Congress of Federation of Infectious Diseases Societies of Southern Africa, Sun City, South Africa, 24–26 July.

Skoler, S., S. Govender, L. Altini, K. Ahmed, D. Waldron, L. Myer, and P. Lahteenmaki. 2005. "Risks in the use of an unblinded control group," *Journal of Infectious Disease* 191(7): 1378-1379.

Wallace, Andrea, Mitchell Thorn, Robin Maguire, Kristin Sudol, and David Phillips. 2004. "Assay for establishing whether microbicide applicators have been exposed to the vagina," *Sexually Transmitted Diseases* (31)8: 465-468.

Williams, M.M. and K. Ahmed. 2005. "The challenges in recruiting in the phase 3 clinical trial of the microbicide Carraguard™ in a high HIV prevalence area in Soshanguve, Pretoria, South Africa," poster presentation at the South African AIDS Conference, Durban, South Africa, 7–10 June.

———. 2005. "The challenges in recruiting in the phase 3 clinical trial of the microbicide Carraguard™ in a high HIV prevalence area in Soshanguve, Pretoria, South Africa," poster presentation at the International Society for Sexually Transmitted Diseases Research, Amsterdam, The Netherlands, 10–13 July.