

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

Year Two Program Report

1 July 2005 – 30 June 2006



September 2006

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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. One activity may comprise several related studies. (Activities are sometimes also 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].

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.

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 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.

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 microbicide 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 microbicide 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:

Researchers are conducting a randomized, controlled, double-blind study to ascertain if Carraguard gel prevents HIV seroconversion in women. At three South African sites, 6,639 women are to be recruited. The trial began in March 2004 and will last three years. Each woman will participate from her enrollment until the sooner of two years or trial's end. Non-pregnant, HIV-negative female volunteers who live in the site catchment areas are eligible. 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 gel use, to receive more study supplies, and to return used applicators.

Site management is aided by a custom-made bar code system and database. Case record forms are faxed to the Council in New York via the DataFax data management system. STI tests, HIV confirmatory testing, and Pap smears are sent to Lancet Laboratories, an independent laboratory in Johannesburg. Clinic laboratories process pregnancy tests, HIV rapid tests, and other bedside tests. Population Council (PC) liaises with the study sites, manages gel distribution and regulatory paperwork, facilitates financial administration, and conducts data entry and management. ClinDev (Pty.) Ltd., a contract research organization, monitors the sites to ensure protocol adherence and good clinical practice. A data safety monitoring board (DSMB) will convene during the trial to ensure participant safety and monitor trial progress.

One of the biggest challenges in microbicide trials is measuring gel usage. In this study, all participant applicators that are returned opened are tested to determine whether the applicator has been inserted into the vagina. The results will be used with other behavioral indicators (e.g., questionnaire data) to create a composite score for participants' adherence to the protocol, thus allowing identification of adherent participants. While all participants will be included in the primary intent-to-treat analysis, data from adherent women will be used for a restricted, per-protocol analysis, which will help researchers determine Carraguard's efficacy.

The Bill and Melinda Gates Foundation also provides funds for this activity, currently by supporting the University of Limpopo/Medunsa Campus and Medical Research Council (MRC) subawards, and most laboratory, monitoring, and international travel costs. USAID currently 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 Two:

July–December 2005: The study continued successfully, and 5,101 women had been enrolled by the end of December. Recruitment was extended by six months, to March 2006, at all three sites in order to enroll as close to the goal of 6,639 women as possible. The DSMB met in August, reviewed the data (for safety only), and recommended that the trial continue. Observed rates of seroconversion remained in the expected range. To ensure this trend continues, a protocol amendment was submitted to the ethics boards and regulatory bodies that would allow only women less than 40 years old to enroll, as younger women are more likely to become HIV-infected. Subsequently, the seroconversion rate within the study did increase. However, while at higher risk for HIV, young women are also the most likely to get pregnant, and therefore more difficult to retain. In November, a review of the data revealed that despite ongoing counseling on family planning, free referrals for contraception, and eligibility criteria deterring women who want to get pregnant from enrolling, the pregnancy rate in the study was 12% and represented the leading reason for early discontinuation. By providing family planning methods at the study clinics, this rate was subsequently reduced to 8%. Weekend and extended clinic hours, increased contact between visits, continuing education on study goals, and the provision of activities in the waiting room were also employed in order to enhance retention overall. Also in November, an article in the South African *Sunday Times* reported misinformation about the study. Following a quick, coordinated, and accurate response to the newspaper and relevant stakeholders based on previously constructed key messages, the story was not picked up further. Site management staff received media training and established study guidelines for media interaction.

January–June 2006: To maximize the amount of available data, but avoid extending the trial end date, recruitment was extended again by three months, to June 30, 2006. A total of 6,299 women were enrolled by this date. Based on the number of seroconversions observed so far, it is anticipated that the number required for sufficient power will easily be reached with this sample. Since the end date of the study will remain March 31, 2007, the last women enrolled will be in the study for 9 months, rather than the previously planned 12 months. Despite this change, the planned evaluation of long-term safety will still be feasible based on the thousands of women who will have participated for more than 12 months.

In January, PharmaLinkFHI, Inc. and Family Health International (FHI) were chosen to provide regulatory and statistical support in finalizing the draft statistical analysis plan (SAP) and the final report to the FDA. The SAP, a detailed narrative which documents the methods for analysis and presentation of study data, was completed in early June and will be submitted to the FDA before the end of that month.

In March, a second DSMB meeting for safety was held via teleconference, and the DSMB recommended that the study continue.

During Year Two, testing of all returned applicators continued. Two main measures of adherence were established. The primary measure of adherence will be a ratio comparing the estimated average weekly applicator insertions (based on the applicator test) to the estimated average weekly sex acts (based on self-reported data). A value close to one indicates that most or all sex acts involved gel use; a value close to zero indicates poor gel coverage for most sex acts. The secondary measure of adherence will be the percentage of applicators that were inserted, out of those that were returned opened, indicating which participants are squeezing gel out but not using it in their vaginas. It was decided that rules for determining inclusion in the per-protocol analysis should be established once all the data have been collected and reviewed, but before the trial is unblinded.

The possibility of conducting additional behavioral research on gel use dynamics and acceptability was explored. As a result, several activities came to fruition. A case report form was being finalized in June for an exit interview, which will be administered to a subset of the trial population to capture information about acceptability and reasons for non-adherence (see “Informed Consent and Behavioral Aspects of Carraguard Trials”). Additionally, in April, co-funding from the International Partnership for Microbicides was secured for three qualitative assessment sub-studies within the trial, which will continue with PCPD funding during Year Three (see “Social Science Research in Population Council Microbicide Trials”). And, USAID agreed to allocate Year Three PCPD funds for a gel use study, outside the trial, comparing applicator usage test results with results from participant interviews conducted either face-to-face or by ACASI (audio computer-assisted self-interviewing).

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

Contractor(s): B. Gerard Lindeque
Claude Ware
Clindev (Pty.) Ltd. (cost share)
DF/Net Research, Inc.
Gary Maartens
James Trussell
Juhani Tuominen
Lancet Laboratories (USAID and cost share)
MRP Solutions
PharmalinkFHI, Inc.
Stephen Hardiman

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Carraguard® Nonclinical Development

Project Number/s: 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. 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. 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 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) during Year One, 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 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 for submission to the FDA in 2008.

Report of Year Two:

Production and supply of study gels to trial sites

July–December 2005: Two batches of each gel were produced in August and two more batches of each gel were produced in September. Gel was shipped to study sites in December. Product liability insurance was paid on the study gels in December.

January–June 2006: Gel was shipped to all three sites in April and May. Production of additional batches of each gel began in March and continued into June.

Control testing of each production batch of gel

July–December 2005: All eight batches of gel successfully passed control testing.

January–June 2006: Control testing began on batches of gels produced March–June 2006.

Stability testing of gels

July–December 2005: The 18-month samples of Carraguard and methyl cellulose were evaluated and remained within the specified limits for chemical, physical, and biological activity.

January–June 2006: In April, evaluation began on the 24-month samples of Carraguard and methyl cellulose to determine if they have remained within the specified limits for chemical, physical and biological activity. Results are expected by the end of June.

Patent protection and trademark rights for Carraguard

July–December 2005: In July, the inventor's declaration was submitted to the USPTO by PC legal counsel. According to the USPTO, the application was dispatched from the Office of Initial Patent Examination in August, and was docketed to an examiner and electronically published in November (Publication No. US-2005-0261240-A1).

January–June 2006: No activity, as PC staff were awaiting the decision of the USPTO patent examiner.

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

July–December 2005: No activity.

January–June 2006: Due to a change in personnel in the microbicide team's chemistry department, the assembling and formatting of the submission was not initiated. Work on the submission will instead commence in Year Four, after analysis of the Phase 3 results.

Preparation of a New Drug Application to the FDA

July–December 2005: No activity.

January–June 2006: No activity. Conversion of the regulatory file for Carraguard to an electronic Common Technical Document, planned for Year Two, was delayed until preparation of the rest of the NDA, in Year Four.

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

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, 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 International Development Cooperation Agency will be used to help support this activity in Years Two and Three, and the Council expects to continue seeking support for this activity.

Report of Year Two:

July–December 2005: At the end of Year One, the lab had developed three different strength formulations of PC-815. For the first clinical studies, in caution it was decided that until more safety information is gathered, the low-strength formulation of PC-815 should be used. Although it is not expected that

MIV-150 will be systemically absorbed through vaginal application, since it has poor systemic absorption via oral intake, the matter is still uncertain. In addition, doubts exist regarding whether HIV can adapt to become resistant to an anti-retroviral applied vaginally.

Submission of the IND and IB to the U.S. Food and Drug Administration (FDA), expected in June 2005, was delayed to accommodate two amendments to the first Phase 1 study protocol. The lab's discovery of how to radiolabel MIV-150 made the second amendment—inclusion of the pharmacokinetic absorption of MIV-150—possible. The Nonclinical team also managed the Spanish translations of the protocol, its amendments, and the IB, which were required to comply with a new Dominican Republic law (see activity "PC-815 Clinical Development" for information about the study).

In the lab, the high-strength PC-815 formulation continued to be produced and control tested as needed for the Robbiani lab's monkey studies (see activity "PC-815 Nonclinical Development: Robbiani [Pope] Laboratory"). Several assays were completed on the low- and high-strength PC-815 formulations: 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. Regarding production methodology, concerns arose that the method of formulating PC-815 (using ethanol as a solvent) might facilitate precipitation of MIV-150, and so efforts were begun to find a more optimal methodology for formulation, focusing on the chosen solvent and preservative.

January–June 2006: The PC-815 IND and IB were submitted to the FDA early in February and the FDA responded with a request for additional data from pharmacology and toxicology studies in animals and humans previously conducted by the Medivir and Chiron corporations. Consulting with the FDA in early March, it was mutually agreed to put PC-815 on a "pre-IND track." This FDA program allows communication so that the agency can work with the sponsor in the selection of the IND contents. During June, the Nonclinical team was preparing to supply the full study reports, including raw data, of the requested studies.

Due to the delay in submission of the IND, scale-up of PC-815 production at Clean Chemical Sweden planned for Year Two will instead begin in Year Three.

Results from stability tests at the 10-month point, during Year One, showed that the low-strength PC-815 formulation is stable. During Year Two, since the lab was making efforts to find a more optimal methodology for formulation, only limited stability tests continued on the low-strength ethanol-solvent formulation, for two parameters whose acceptable limits were not anticipated to vary in a newly optimized formulation, that is, MIV-150 concentrations and activity against HIV-1. Stability testing for pH and viscosity parameters was discontinued, as these acceptable limits are likely to vary with any formulation changes.

Regarding the formulation, the lab began investigating the use of other solvents, besides ethanol, and other additives that might ensure that MIV-150 does not precipitate out of the formulations over time, while reducing the likelihood of interactions with the preservative. Benzyl alcohol was found to be suitable as both solvent and preservative for these purposes. In the process of testing progressive changes in the formulation, the lab used the standard stability parameters: pH, viscosity, MIV-150 concentration, and HIV activity. A more appropriate measurement technique for MIV-150 concentration is also being developed

for use on the newly optimized formulation(s).

Since the medium- and high-strength formulations will not be used in the first clinical trials, rabbit vaginal irritation tests were not conducted on them. Toxicity and pharmacokinetic tests in rats, originally planned for Year Two, will instead be made with the optimized formulation in Year Three.

Also in the lab, the activity of the low-strength formulation against 12 clinical Clade C isolates was compared to that of Carraguard using peripheral blood mononuclear cells and a reverse transcriptase assay. PC-815 was found to be more efficacious by an average of an order of magnitude. Activity against free virus was also compared, using Centriprep YM-30 filtration columns. It was found that MIV-150 can inactivate free virus and is active against HIV-2. Results from these assays also indicated that neither seminal fluid nor vaginal secretions had an effect on the activity of PC-815.

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

Project Number/s: 09303

Country/ies: United States

Technical Coord.: Melissa Robbiani (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 Robbiani (Pope).

Activity Description:

The Robbiani laboratory will employ *in vitro* and *in vivo* systems to test the ability of PC-815 (the combination of Carraguard® and the anti-viral MIV-150) to block the transmission of HIV and/or SHIV-RT by dendritic cells (DCs) across the mucosa. (SHIV-RT is a chimera virus utilizing the SIV backbone paired with the HIV reverse transcriptase.) Agents like PC-815 act in a general manner to block virus and cell interactions, and potentially to inactivate immunodeficiency virus independent of the receptors involved. Such approaches that block the complex interactions of pathogens with DCs and other target cells represent extremely attractive microbicide strategies. In *in vitro* assays, DCs or DC-T cell mixtures will encounter HIV or SHIV-RT alone or in combination with model STIs (e.g., herpes simplex virus type 2, 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 provide necessary data to support the extensive *in vivo* studies, which are the primary focus of this activity.

The *in vivo* studies, contracted to the Tulane National Primate Research Center (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-exposure. In addition to providing valuable data on PC-815's efficacy, these studies will allow us to seek future funding to test new-generation carrageenan-based formulations in these settings.

All *in vivo* studies will involve the use of formulations provided by the Phillips laboratory. The PC-815 formulation being used in the macaque studies comprises Carraguard with the high dose of MIV-150 (500µM MIV-150). We chose to perform the first macaque studies with this dose to give the best chance to measure the MIV-150 effect. This approach might be especially critical when PC-815 is added at longer times before virus exposure or after virus exposure. If we decide to move product development forward with a formulation containing a lower MIV-150 dose, future macaque studies should be performed to verify its activity. It seems most appropriate that those dosing experiments be done after we have completed the timing studies using the high-dose formulation.

Report of Year Two:

July–December 2005:

Efforts continued to determine the challenge dose of the virus isolate SHIV-RT, substituted as the target virus during Year One, and to give initial insight into the activity of PC-815 and Carraguard against this virus isolate. Data was collected and analyzed on the 10 animals that had been challenged in April 2005 with 10^3 TCID₅₀ of SHIV-RT after treatment with PC-815, Carraguard, or MC gel. (The 10 animals

comprised 6 non-PCPD-funded and 4 of those from the Year One budget.) All animals pretreated with PC-815 (4 animals) or Carraguard (3 animals) were protected from infection, while all 3 MC-treated animals became infected.

In a further dosing study, in November the 7 uninfected animals were recycled and challenged with 10^4 TCID₅₀ of SHIV-RT in the presence of the same gels that each animal received in the previous experiment. At two weeks post-challenge, the microbicide-treated groups still appeared to resist infection.

January–June 2006:

Since the 7 animals challenged with 10^4 TCID₅₀ of SHIV-RT in the November 2005 dosing study remained uninfected, that higher dose was also used on the remaining 8 animals from the Year One budget. These animals came out of quarantine at the end of February. During March and April baseline bleeds were gathered, the animals were treated with Depo-Provera, and either PC-815 or the MC placebo was administered. They were then challenged, with 10^4 TCID₅₀ of SHIV-RT, late in April. Blood samples taken before and after challenge are being monitored for viral load (RNA PCR) and SHIV-specific immune responses (presence of antibodies in plasma and cellular responses to *in vitro* stimulation). These data are being combined with the initial data obtained from the earlier two sets of animals followed in Year One and early Year Two, in order to fully evaluate the ability of PC-815 (vs. MC and Carraguard) to prevent vaginal SHIV-RT infection in healthy macaques. Once all data have been studied, we will determine and report on efficiency of PC-815 to prevent vaginal SHIV-RT infection in these animals.

For the study of PC-815's effect in a setting of pre-infection with HSV-2 and subsequent SHIV-RT challenge, there were inevitable delays in acquiring the six animals from the Year Two budget. These animals also came out of quarantine at the end of February, and baseline data were gathered. However, before these animals can be infected with HSV-2, the HSV-2 infection model must be finalized in the TNPRC Pilot study. As the Pilot study's last four animals also were quarantined until February, the infection model is now expected to be optimized by July. At that time, the model will be applied to pre-infect the six Year Two animals with HSV-2, and the study will proceed into Year Three.

To support the *in vivo* work, important *in vitro* analyses on the immune cells, with and without PC-815 exposure, are being carried out during the last four months of Year Two (with other donor funding). These studies focus on dendritic cells' capture and transmission of virus when in the presence of either PC-815, one of its separate components (Carraguard or MIV-150), or MC. These *in vitro* observations are expected to lead to a better understanding of the mode of action *in vivo*. Results from preliminary data, using indicator cell lines to test the ability of titrated doses of Carraguard and MIV-150 to block virus infection, indicate that Carraguard was most efficient against X4 HIV, with blocking of R5 HIV and SHIV-RT occurring only when very high doses were used. In fact, at low doses ($\sim 2\mu\text{g/ml}$, much lower than those that would be used *in vivo*) Carraguard exhibited enhancing effects on R5 HIV, and more so on SHIV RT. Meanwhile, MIV-150 was observed to effectively block X4 HIV, R5 HIV, and SHIV-RT, and, when MIV-150 and Carraguard were applied together, MIV-150 was also able to overcome the enhancing effects of Carraguard. Similar results were observed when each substance was tested for its ability to block transmission of virus by virus-loaded mature dendritic cells.

Contractor(s): Tulane National Primate Research Center (TNPRC)

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 – December 2011
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 second-generation microbicide. Carraguard serves as the vehicle base for MIV-150 and as an active ingredient. Clinical testing on the second-generation microbicide PC-815 contributes to the overall development of female-initiated HIV prevention technologies.

The PC-815 clinical development plan includes three 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, is planned to be conducted in mid-2006 under the direction of International Committee for Contraception Research member Vivian Brache at the Asociación Dominicana Pro-Bienestar de la Familia (Profamilia/DR) clinic in the Dominican Republic. Assuming success, two additional Phase 1 trials will be conducted to further assess product safety. The second Phase 1 trial will assess safety in men, and the third will evaluate lavages taken from HIV-positive women after vaginal exposure to PC-815 to examine if the gel affects the survival of HIV in the vaginas of HIV-positive women post-use. The study with men and the study with HIV-positive women will take place at the Setshaba Research Center, managed by the University of Limpopo/Medunsa Campus, one of the Carraguard Phase 3 trial sites.

While the expanded 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 mid-2008, 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 International Development Cooperation Agency (SIDA) 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 Two:

July–December 2005: Although the first Phase 1 study protocol (Protocol 362) was intended to begin at the end of Year One, the Profamilia/DR IRB made requests that delayed approval of the protocol. Due to changes in the regulatory requirements of the Dominican Republic, the IRB requested a Spanish translation of the protocol and the Investigator’s Brochure, which was managed by the Nonclinical (Phillips lab) team in late 2005. The IRB also requested a protocol amendment to clarify the HIV testing procedures within the trial. The amendment was drawn up, translated into Spanish, and submitted to the PC and Profamilia/DR IRBs. The PC IRB approved the amendment during this reporting period. While these additional tasks were being completed, the Nonclinical team discovered how to radiolabel MIV-150. This advance enabled the pharmacokinetic absorption of MIV-150 to be included within Protocol 362, and obviated the need for a follow-up Phase 1 study for that purpose. A second amendment adding this preliminary pharmacokinetic component was drawn up and submitted to the PC IRB.

In December, the protocol for the expanded Phase 1 “infectivity” study planned at Medunsa with HIV-positive women (Protocol 366) was submitted to the Medicines Control Council (MCC), South Africa’s medicines regulatory agency. PC-Johannesburg staff found a local laboratory, Synexa Life Sciences in Cape Town, to process samples for this study.

January–June 2006: Amendment 1 to Protocol 362 (the first Phase 1 study at Profamilia/DR), already approved by the PC IRB, was approved by the Profamilia/DR IRB in January and subsequently by the National Council of Bioethics in Health (CONABIOS), the Dominican Republic’s regulatory agency. Amendment 2 to Protocol 362, adding the preliminary pharmacokinetic component, was also approved by the PC IRB. Amendment 2 was translated into Spanish, and submitted to the Profamilia/DR IRB in June. This trial will be initiated following local IRB approval and approval of the IND by the FDA (see activity “PC-815 Nonclinical Development: Phillips Laboratory” for information about the IND).

In January a male safety study was proposed. A protocol for this study was drafted in June.

In the expanded Phase 1 “infectivity” study (Protocol 366), vaginal lavage samples will be collected after administration of the study gel to HIV-positive women, and analyzed to determine whether gel use could reduce the infectiousness of vaginal fluid. A protocol amendment which restricts eligibility to include only women who have normal Pap smears and are free from sexually transmitted infections (STIs) at screening was approved by the Medunsa IRB in January and the Council IRB in April. (Otherwise-eligible women who test positive for an STI at screening will be treated and can be enrolled at a later date.) In February, the Population Council responded to the South African MCC’s queries on the original protocol (submitted in December 2005), and included Amendment 1 in the response. The MCC granted approval for the final, amended protocol in June.

During the ethical and regulatory reviews of Protocol 366, Synexa Life Sciences worked with samples of PC-815 and Carraguard and was able to optimize the lavage analysis to ensure that the presence of gel would not mask true levels of infectivity. The study will be implemented upon favorable results from Protocol 362 indicating that MIV-150 cannot be detected in the bloodstream following vaginal administration of PC-815.

For the Phase 2/3 trial, development continued during Year Two. At the end of the program year, the

possibility of having sites in countries in addition to South Africa was being investigated, and in particular, discussions were ongoing with a site in Malawi.

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

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

Developing Informed Consent and Recruitment Materials for Population Council Microbicide Trials

The entry for this activity (known by its short name “IC Materials”) can be found in the following pages, under the activity entries “Informed Consent and Behavioral Aspects of Carraguard[®] Trials” (“Carraguard IC”), “Informed Consent and Behavioral Aspects of PC-815 Trials” (“PC-815 IC”), and “Social Science Research in Population Council Microbicide Trials” (“Microbicide Social Science”).

In the Year Three Workplan, published in August 2006, the IC Materials activity was split into two activities, one for efforts related to the Carraguard trial (Carraguard IC), and one for efforts related to PC-815 trials (PC-815 IC). This document follows the same format.

Also beginning in Year Three, one component planned under the IC Materials activity—a qualitative evaluation of the informed consent process in the Carraguard Phase 3 trial—was moved under the new activity “Social Science Research in Population Council Microbicide Trials.” The report for this component is therefore included in the Microbicide Social Science report following the Carraguard IC and PC-815 IC reports.

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:

Note: Beginning with Year Three, the activity "Developing Informed Consent and Recruitment Materials for Population Council Microbicide Trials" ("IC Materials," project #44211) is replaced by two separate activities, one for Carraguard and one for PC-815. The Carraguard activity, "Informed Consent and Behavioral Aspects of Carraguard Trials" ("Carraguard IC") retains project #44211, and the PC-815 activity, "Informed Consent and Behavioral Aspects of PC-815 Trials" ("PC-815 IC") is assigned project #44214. Further, the qualitative evaluation of the informed consent process in the Carraguard trial, included under "IC Materials" in the Year Two Workplan, is now moved to the new activity, "Social Science Research in Population Council Microbicide Trials" (project #44213). (For administrative reasons, the quantitative IC evaluation, mostly completed under the Population Council Program III [PCP3], USAID cooperative agreement HRN-A-00-99-00010, and finished under the PCPD, will remain in "Carraguard IC".)

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. 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 microbicide Phase 3 efficacy trial, have been at the forefront of research on informed consent and efforts to improve standard of care for microbicide trial participants. 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

Ensuring truly informed consent and voluntary participation is one of the most difficult aspects of conducting any clinical trial. In addition to being 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 devoted considerable resources to developing and evaluating the informed consent process in the Phase 2 and 3 trials of Carraguard. Based on the experiences in Phase 2, the study booklet was adapted and a recruitment video was developed for use in Phase 3. Under this

activity, a quantitative evaluation of the effect of the 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 of appropriate trial participants is essential to ensure that a clinical study has sufficient power to determine the test product's effect. As part of the scale-up process, Council staff collaborated with local researchers at the study sites—the Medical Research Council (MRC) in Durban, the University of Limpopo/Medunsa Campus (Medunsa), and the University of Cape Town (UCT)—to develop standard operating procedures (SOPs) for recruitment and retention. Recruitment and retention strategies included identifying partners in the community to facilitate recruitment from local clinics, NGOs, women's groups, and other organizations (also see Community Relations below). Under this activity, 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

Safer sex and HIV counseling are important aspects of HIV prevention trials. In microbicide trials, the efficacy of the product is unknown, so it is important for study staff to counsel women on the best ways to reduce their risk for HIV infection (abstinence, mutual monogamy, condom use) and to reinforce the fact that we do not yet know that the test product works. A standardized counseling manual was developed during scale-up for the Phase 3 trial. Under this activity, 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

Strategies for care and support for HIV-positive women were developed while the protocol was being written, as part of the scale-up process. Because anti-retroviral treatments (ARVs) are available through the public health service in South Africa, women who are HIV-positive at screening or who seroconvert are referred to existing services in the trial communities. In recognition that the local services may experience an influx of many more patients with the large number of women being screened for the trial, the Population Council provides funding in the subawards to trial sites to help support the local referral centers. Under the subject activity, 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

As part of the scale-up process under the PCP3, the Population Council and the South African study sites worked to create links with the national and local communities to prepare for the Phase 3 Carraguard trial. Government and health officials were informed about the trial, and in some areas were called upon to assist in the identification of available clinic space. Meetings were held in all three study communities, and community advisory groups (CAGs) were established at the UCT and Medunsa sites. The CAGs comprise volunteers who, prior to the trial, met regularly to review the protocol, informed consent procedures, language used, and recruitment strategies. During the trial, CAG meetings are held on an *ad hoc* basis, and can be called by the study teams or by the CAG members to provide or request progress reports, discuss media attention, or address other study-related issues that may arise. At the MRC site, the political

structure of the surrounding community was not conducive to the creation of a CAG, so ongoing, individual contact with various community leaders and regular community meetings ensure that relevant stakeholders are involved and informed about the trial. Under this activity, Population Council staff monitor these community relations and review CAG meeting minutes and community meeting reports.

Report of Year Two:

Summary

July–December 2005: During this period, the behavioral group focused on implementing a quantitative evaluation of the informed consent process, revising the recruitment strategies, developing a procedure to evaluate the counseling process, and updating communication guidelines. Also during this period, a proposal was submitted to the International Partnership for Microbicides (IPM) to supplement USAID funding for the qualitative evaluation of the informed consent process, as well as for two other ancillary studies: an evaluation of the referrals for HIV-positive women and a qualitative study to explore sexual norms and practices related to microbicide use (see activity “Social Science Research in Population Council Microbicide Trials” for more information on these studies).

January–June 2006: During this period, we made progress on the data cleaning and analysis of the quantitative informed consent evaluation, organized and held a recruitment workshop, and continued counseling monitoring and evaluation activities. The proposal submitted to IPM earlier in the year for the three studies ancillary to the Carraguard Phase 3 trial received initial funding. (The PCPD will pick up continued funding for these studies beginning in Year Three under the activity “Social Science Research in Population Council Microbicide Trials”.) In addition, an exit interview case report form was developed to capture acceptability and adherence data. A random sample of women (500 per site) will be asked as they exit the study to respond to questions about gel and condom use, gel acceptability, partner’s perceptions about the gel, barriers to use, and how much they would be willing to pay for Carraguard if it were shown to be effective. These interviews will provide important information on acceptability and adherence that will help to interpret the Phase 3 data, and inform the design of behavioral questionnaires in future trials.

Informed consent

July–December 2005: For the quantitative evaluation of the informed consent process in the Carraguard Phase 3 trial begun under the PCP3 cooperative agreement, data collection was not complete by the close of the PCP3 in August. Therefore, the Council issued a subaward under the PCPD to the Community Agency for Social Enquiry (CASE), the social science research organization based in Johannesburg which had begun the work, to complete data collection. CASE conducted the evaluation between July and December at the UCT and Medunsa sites. Four hundred women (200 per site) were interviewed before and after attending recruitment sessions with or without the Carraguard Phase 3 video in order to assess the video’s impact on comprehension and willingness to participate. An additional 300 women (150 per site) were interviewed at the completion of their enrollment visit in order to assess the overall level of comprehension for women who had completed the screening and enrollment process. Double data entry was completed and data cleaning was begun.

January–June 2006: Data cleaning and preliminary analysis of the quantitative informed consent evaluation continued during this period. However, the final analysis and write-up were not completed as originally anticipated, since staff time had to be shifted to developing the qualitative informed consent study and the two other ancillary studies, which must be carried out while the Phase 3 trial is ongoing. (These studies received initial IPM funding, and the PCPD will pick up continued funding for these studies

in Year Three. See “Social Science Research in Population Council Microbicide Trials” for more information on these studies.) Two new staff members were hired at the Population Council to facilitate the completion of the quantitative informed consent study as well as the implementation of the three ancillary studies.

Recruitment and retention

July–December 2005: Recruitment strategies were developed to enroll a greater number of women under 25, as they are at the greatest risk of HIV infection. To address issues of adherence, the recruitment script was revised to include more specific messages about the gel at the beginning of the recruitment sessions—including an emphasis on using only the gel issued by the study staff, to prevent gel sharing among participants. Regarding retention, the team worked to develop strategies to address early withdrawal due to pregnancy, such as providing contraceptives on site, in order to reduce the number of women who withdraw for that reason. In addition, weekend and extended clinic hours, increased contact between visits, continuing education on study goals, and the provision of activities in the waiting room were employed in order to enhance retention overall.

January–June 2006: By the end of March, over 5,500 participants had been enrolled in the study. The enrollment target goal had been to enroll 6,639 women by the end of June 2006. Initially enrollment had been rapid and consistent across the sites, but as each site neared its enrollment target, the pace of enrollment slowed. To address this challenge, the MRC team in Durban hosted a workshop to enable the team members from the three sites to meet and discuss challenges and strategies to ensure optimal enrollment and retention of participants for the trial in the final three months of enrollment. The workshop was fruitful and enabled us to achieve a total enrollment number of 6,299 women by the end of June, providing enough statistical power to evaluate Carraguard’s efficacy based on seroconversion rates to date.

Counseling

July–December 2005: A formal procedure was developed for evaluating the counseling process in the Phase 3 Carraguard trial. The goal of the evaluation is to ensure that the counseling process adheres to the study protocol and that the participants are benefiting from the counseling process in the research context as much as possible. An SOP for this bi-annual evaluation was developed by Population Council staff and colleagues at the study sites. The evaluation involves a two-part approach: (1) the evaluator observes counseling sessions conducted by each counselor, and (2) the evaluator meets with each counselor to solicit and provide feedback. The first set of evaluations was conducted in December 2005.

Care and support for HIV-positive women

January–June 2006: At the suggestion of USAID, Population Council staff contacted PEPFAR staff at the USAID mission in Johannesburg to discuss potential opportunities for linking with PEPFAR funding. A meeting between PEPFAR and Population Council staff was held in January, and the PEPFAR staff recommended working with BroadReach Healthcare, an organization already receiving PEPFAR funding. Through BroadReach, women who test positive at screening or during the trial will be offered ongoing monitoring in order to facilitate earlier ARV introduction. Since many women are not eligible for ARVs when they first test positive for HIV, it is imperative that women receive ongoing care and support so that they can enroll in an ARV program as soon as they do become eligible. Additionally, it is important for women to receive guidance on nutrition in order to remain healthy for as long as possible. At the end of the program year, specific logistics were being worked out at each site for the program.

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

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, recruitment and retention, counseling, care and support for HIV-positive women, and community relations.

Activity Description:

Note: Beginning with Year Three, the activity "Developing Informed Consent and Recruitment Materials for Population Council Microbicide Trials" ("IC Materials," project #44211) is replaced by two separate activities, one for Carraguard® and one for PC-815. The Carraguard activity, "Informed Consent and Behavioral Aspects of Carraguard Trials" ("Carraguard IC") retains project #44211, and this PC-815 activity, "Informed Consent and Behavioral Aspects of PC-815 Trials" ("PC-815 IC"), is assigned project #44214.

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. 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 microbicide Phase 3 efficacy trial, have been at the forefront of research on informed consent and efforts to improve standard of care for microbicide trial participants. 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 three 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. Therefore, the subject activity focuses on the subsequent Phase 1 trials to be conducted in South Africa (one among HIV-negative men and a second among HIV-positive women) and 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 Two:

July–December 2005: No activity.

January–June 2006: During this period, the behavioral coordinator participated in the development of the informed consent forms to be used in the Phase 1 “infectivity” study (Protocol 366) to be conducted at the University of Limpopo/Medunsa Campus site. The protocol was approved by the Population Council and Medunsa IRBs, and the South African Medicines Control Council.

We had originally planned to write the protocol for the Phase 2/3 trial during Year Two; however, delays in obtaining regulatory approvals to begin clinical testing of PC-815 slowed the product development process. Because of these delays, the Phase 1 trials were not conducted during Year Two, which led to a delay in the timeline for carrying out the IC activities originally planned to take place in Year Two, and for implementing the Phase 2/3 trial itself.

Nevertheless, the behavioral coordinator participated in ongoing discussions about the protocol design and site selection for the Phase 2/3 trial, and helped begin planning the feasibility studies which will take place prior to the conduct of this next large-scale trial. In particular, planning began for a study comparing face-to-face interviewing with audio computer-assisted self-interviewing (ACASI), using the applicator test as a biological marker. Results of this study will have an impact on the types of questions and interview methodology used for the PC-815 large-scale effectiveness trial.

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 microbicide trials.

Activity Description:

Note: This activity, “Social Science Research in Population Council Microbicide Trials” (project #44213) is launched beginning with Year Three. One study under this activity, the qualitative evaluation of the informed consent process in the Carraguard® trial, was previously planned under the activity “Developing Informed Consent and Recruitment Materials for Population Council Microbicide Trials” (project #44211, now renamed “Informed Consent and Behavioral Aspects of Carraguard Trials”). Beginning in Year Three, the qualitative IC evaluation is moved under this Microbicide Social Science activity. (For administrative reasons, the quantitative component of the evaluation, mostly completed under the Population Council Program III [PCP3], USAID cooperative agreement HRN-A-00-99-00010, and finished under the PCPD, will remain under project #44211.)

Council researchers have been involved in a wide range of activities related to microbicide development, including involving local communities in microbicide research, building clinical trial capacity in developing countries, conducting behavioral research to inform clinical trials, and improving clinical trial methodology. Under this activity, Council researchers are collaborating with Population Council microbicide trial sites to conduct social science studies ancillary to the trials that will further these objectives. Three studies are planned at the Carraguard Phase 3 trial sites (Medical Research Council, University of Limpopo/Medunsa Campus, and University of Cape Town, all in South Africa), with co-funding from the International Partnership for Microbicides. This research includes a qualitative evaluation of the informed consent process, an evaluation of the referral networks available for HIV-infected women, and an exploration of the range of factors influencing microbicide gel acceptability in local communities. 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 process in the Phase 3 Carraguard trial

Recognizing the importance of the informed consent process, Population Council researchers have devoted considerable resources to developing and evaluating the informed consent process in Phase 2 and 3 trials of Carraguard. The research conducted during the Phase 2 trial served as the foundation for the production of a recruitment video and study booklet to be used in the Phase 3 efficacy trial of Carraguard. A quantitative evaluation of the video, begun under the PCP3 and completed under the activity “Informed Consent and Behavioral Aspects of Carraguard Trials” (formerly “Developing Informed Consent and Recruitment Materials for Population Council Microbicide Trials”), will be complemented by a qualitative evaluation of the overall informed consent process, to be conducted under this activity. This qualitative study will involve in-depth interviews and focus group discussions 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 specific materials such as the booklet, video, and informed consent form. Study counselors and recruiters will also be interviewed to gain their insights into how the informed consent process can be improved in further trials. Results will be submitted for publication in a peer-reviewed journal.

Evaluation of referrals in the Carraguard Phase 3 trial

At each Carraguard Phase 3 trial site, the investigators have developed specific strategies to 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. In addition to counseling sessions at the study clinics, all women are also referred to existing services in the trial communities. Services are provided by a “referral network” which includes non-governmental organizations (NGOs), public hospitals and clinics, and private physicians. During May 2006 to February 2007, we are conducting a study to assess whether the care and support strategies established within the referral networks are meeting the needs of women diagnosed with HIV during their screening visits. The study involves 20 in-depth interviews with women who test positive for HIV at screening or who seroconvert. The interviews, which will be conducted four to six weeks after women receive an HIV-positive test result, will explore whether or not women have accessed any of the services and, if so, their experiences. In addition, we are conducting a survey of healthcare providers (including doctors, nurses, and counselors) at facilities in the established “referral network” to determine how women referred from the Phase 3 trial contribute to the center’s caseload, and to gather suggestions for improving the referral system. Results of this study will be used to improve the referral network system for the PC-815 Phase 2/3 trial.

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

Acceptability research has featured prominently in the Population Council’s microbicide program, both in the context of clinical trials and in freestanding studies. Council researchers have conducted a number of studies to evaluate the potential acceptability of a microbicide product, including a feasibility study with women who participated in the expanded safety trial, and an exploratory study on practices and preferences related to lubrication during sex and the implications for microbicide use. In an effort to further explore the complexity of microbicide acceptability, Council researchers and colleagues from the University of Cape Town (UCT) have developed a study to examine sexual norms and practices as they influence gel use. Using qualitative methodology, researchers will interview Carraguard trial participants about their direct experiences with gel use, exploring issues of communication, lubrication, sexual activities, vaginal practices (e.g., intravaginal cleansing), and the logistics of gel use and storage. We will also conduct additional in-depth interviews with participants who withdrew early to elicit their attitudes toward the gel, and with Phase 3 trial staff members. With participants’ permission, we will also interview male partners to learn about their direct experiences with the gel. Results of the evaluation will be submitted for publication in a peer-reviewed journal. This information will be used to improve data collection instruments and educational materials related to behavioral aspects of the PC-815 Phase 2/3 trial, and to inform messages for eventual introduction of a PC microbicide.

Report of Year Two:

July–December 2005: Although the Microbicide Social Science activity was not funded during this period, related tasks were completed under the activity “Developing Informed Consent and Recruitment Materials

for Population Council Microbicide Trials” (now renamed “Informed Consent and Behavioral Aspects of Carraguard Trials”). Data collection and data entry were completed for the quantitative analysis of the informed consent process in the Phase 3 trial, which focused on evaluation of the video; and a proposal was submitted to the International Partnership for Microbicides (IPM) to provide initial support for these Microbicide Social Science studies.

January–June 2006:

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

This study was co-funded during Year Two under the activity “Developing Informed Consent and Recruitment Materials for Population Council Microbicide Trials” (now renamed “Informed Consent and Behavioral Aspects of Carraguard Trials”) and by IPM, and is reported on here. The study protocol was developed by Population Council staff in April and May and was approved by the Population Council’s IRB in June. The development of a moderator’s guide was underway at the end of the program year. Although the original intent was to complete both the quantitative and qualitative evaluations in early 2006, the two other Microbicide Social Science studies were launched during this period (with IPM funding) (see below), leaving limited staff to complete the informed consent evaluation as originally anticipated. At the end of the program year, the quantitative study was in the analysis phase, and both it and the qualitative study will be completed during Year Three.

Evaluation of referrals in the Carraguard Phase 3 trial

The Evaluation of Referrals study was funded by IPM in Year Two. The protocol, which was an amended version of the pilot study implemented at the Medunsa site in 2005 (funded by the Hewlett Foundation), was approved by the University of Cape Town ethics committee in January and by the Medunsa ethics committee in February. The Population Council Institutional Review Board approved the amended protocol in March; and the protocol was submitted to the Medical Research Council (MRC) ethics committee by the end of the program year. A training meeting was held in May at the UCT, led by the principal investigator, Jane Harries. The study began at the UCT and Medunsa sites shortly thereafter, and by the end of June, ten interviews had been conducted at UCT and the instrument had been pilot tested at the Medunsa site.

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

The Exploration of Sexual Norms and Practices study was funded by IPM in Year Two. The protocol was developed by the principal investigators, Alana de Kock and Phyllis Orner at UCT, with input from co-investigators at the Population Council, the MRC, and Medunsa. The protocol was approved by the UCT ethics committee and Population Council IRB. By the end of the program year, the protocol had been submitted for review to the Medunsa and the MRC ethics committees, and the interview guides were under development.

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

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 continue to improve the informed consent process in microbicide 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, microbicide 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 condom use or increase their numbers of partners).

Recognizing its importance, Population Council researchers devoted considerable resources to developing and evaluating the informed consent process in the 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 gel), 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 of this activity is to identify the terms and concepts that have not yet been successfully communicated and explore alternatives for explaining them better. As described below, we will continue to investigate the best ways to explain difficult concepts to trial participants by assessing current methods used in ongoing microbicide trials as well as exploring new methods for informing participants and assessing comprehension.

Workshop on Informed Consent in HIV Prevention Trials

Researchers at the Population Council and Family Health International (FHI) have been engaged in ongoing efforts to improve the informed consent process in their own organizations' microbicide trials. Through these efforts, the researchers and their colleagues have recognized that there is a need for broader research and dialogue on the practical aspects of how to improve the informed consent process. While previous meetings have touched on informed consent within the larger context of ethical issues in HIV prevention trials, this workshop will be the first to focus entirely on informed consent. The objective of the workshop, which will be held in the spring of 2005, is to provide an opportunity for researchers to share experiences, review informed consent materials, identify ways to improve communication of difficult words and concepts, explore evaluation of the consent process, identify areas for further research, and disseminate information and recommendations from the workshop. Researchers, clinical trial sponsors, donors, ethicists, and experts in the related fields of risk perception and adult learning, from the United States and from countries in Africa, Latin America, Asia, and Europe, will participate in this workshop. Colleagues from FHI will co-host the meeting and will work with Council staff to develop the agenda and participant list and to produce a meeting report. A small meeting grant (\$6,000) received from the National Institutes of Health 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. The recommendations from 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/guide for explaining difficult concepts

One of the most difficult aspects of conducting microbicide trials is the complexity of language and translation, particularly in international settings. Language barriers can have an enormous impact on all aspects of microbicide trials including community interactions, recruitment, informed consent, data collection, and dissemination of study results. In order to ensure informed consent, researchers must ensure that difficult concepts and study procedures are explained as simply as possible using words and analogies that are meaningful in the local context. This is particularly important for populations that are unfamiliar with medical research. During data collection, which often involves questions about sexual behavior and other sensitive issues, it is crucial that participants and researchers are using the same language to describe partnerships and types of sexual practices in order to capture the most accurate information possible. Recognizing these issues, researchers at the Population Council developed a lexicon to be used for translating difficult concepts in the Council's Carraguard trials in South Africa. The lexicon includes research terms and concepts, as well as sexual and reproductive health terminology. The development of the lexicon was important for identifying ways to explain terms in a culturally relevant manner in several South African communities, as well as for ensuring that all terms were translated consistently across study documents. In collaboration with colleagues from FHI, we will expand our lexicon into a handbook by including terminology and colloquialisms that can be used in microbicide trials in various countries and regions. This lexicon will build on the wealth of information gleaned during qualitative studies from previous and ongoing trials conducted by the Population Council and FHI. A database of these terms will be created so that the information is easily accessible by researchers conducting HIV prevention trials around the globe. In addition, we will develop an elicitation tool for researchers to use when developing translations in research naïve settings.

Report of Year Two:

July–December 2005: In the first half of Year Two, a short article was written for *The Microbicide Quarterly* summarizing the main discussion points from the Informed Consent Workshop held in May 2005. The complete meeting report which summarizes the meeting proceedings was drafted by the rapporteur (Elizabeth McGrory) in the fall of 2005. Specific recommendations for follow-up actions that emerged from the meeting included: (1) to form a working group focused on informed consent in HIV prevention trials to identify specific research priorities and strategies, to exchange information and ideas, to look closely at comprehension assessments, and to continue to develop research design and advocacy strategies for conducting overall evaluations of informed consent processes in ongoing trials; (2) to convene a follow-up workshop for local clinic study staff and researchers in order to address informed consent with activists and community members; and (3) to advocate for formative research to be analyzed and disseminated more widely. We had intended to include a CD-ROM with examples of materials used in various clinical trials (such as videos, flip charts, and booklets) as part of the workshop report. However, the meeting organizers ultimately decided against this since we did not have full information on how each of the materials had been tested. Instead, we included only sample illustrations within the text of the report to illustrate how difficult concepts had been explained in various trials.

Because of the scarcity of USAID funds, other work under this activity could not be funded during Year Two. Therefore, Council researchers sought support from other donors to continue their efforts to improve the informed consent process. Specifically, we were successful in obtaining a grant from IPM to produce a generic video which could be used as an educational tool in a range of microbicide trials.

January–June 2006: The text of the IC Workshop report was completed and reviewed by the co-authors and relevant presenters in February and March. Layout and design were developed simultaneously, and the report was printed in April, in time to be disseminated at the Microbicides 2006 conference in Cape Town, South Africa (held in April 2006), both at the Population Council's booth and at a symposium on informed consent in clinical trials. The Microbicides 2006 conference organizers requested that the Population Council and FHI hold this symposium on informed consent as a way to continue the dialogue that had been started at the May 2005 Informed Consent Workshop. Council planning for the symposium was carried out under this activity, although the event itself was funded by another donor. At the symposium, representatives from four ongoing trials gave updates on the informed consent process in their trials. Dr. Morenike Ukpong, a pediatric dentist who heads the Nigeria HIV Vaccine and Microbicide Advocacy Group, gave the keynote speech, "Informed consent: A community perspective." Dr. Ukpong shared her perspectives on community involvement in the informed consent process, which had emerged as a key issue at the May 2005 workshop.

The IC Workshop report, available on the Council's Web site as a PDF file (<http://www.popcouncil.org/pdfs/ICWorkshop.pdf>), has been generating a great deal of interest from researchers around the world. As a result, we plan to develop a short brief on the key points from the workshop and to translate it into multiple languages so that it can be accessible to a broader audience.

Subawardee(s): TBD

Contractor(s): Elizabeth McGrory
Others TBD

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: 07902, 07600

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 150/15 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, package, and ship the rings, 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 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 (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 (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 12 sites in its Contraceptive Clinical Trials Network (CCTN).

A total of 2,200 women at 22 sites 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. Enrollment will begin first in Protocol 300B, the 10 sites managed by the Population Council (8 funded by the PCPD and 2 by the World Health Organization), and afterward in Protocol 300A, the 12 NICHD CCTN sites.

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 (ADME) 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 Years Three and Four of the PCPD, a 26-week carcinogenicity study of NES in mice will be made.

Report of Year Two:

July–December 2005: An amendment to the Council's investigational new drug (IND) application, which included the Phase 3 protocol, was sent to the FDA on June 27, 2005. Based on recommendations received from the FDA in 2002, this protocol called for inclusion of 1,280 subjects to obtain 10,000 cycles with at least 200 women completing one year of use. The package sent to the FDA also included the investigators brochure and the study synopses for three Phase 1 and 2 protocols.

The FDA customarily requires 90 days to review IND amendments prior to studies proceeding. Accordingly, Council staff contacted the FDA on October 7 to determine the FDA's position on proceeding with the Phase 3 trial. At that time, FDA staff indicated there were no comments on their part and that the trial could proceed. Plans then progressed to identify and qualify the remaining 13 clinical sites to participate in the large Phase 3 safety and efficacy trial. All sites were identified and qualifying visits were begun.

Regarding study product manufacture, Crystal Pharma, a manufacturing contract organization, completed the development of a synthetic chemical process for the manufacture of NES. However, there were delays associated with the scale-up process to produce the validated material. For this reason, and in order to avoid further delaying the initiation of the Phase 3 trial, the remaining NES available in-house was used in the rings manufactured by QPharma. A new source of NES was necessary in any case, as we need a backup

if there are problems with the Phase 3 trial; we also require a new drug master file, since the previous manufacturer is no longer interested in manufacturing NES.

At QPharma, mass manufacturer of the ring, completion of the rings for the nested PK segment of the trial was delayed until December, when they were shipped directly to the three participating ICCR clinics.

Concurrent with NES and ring manufacture, process development and validation of the LCMS/MS assay method to be used in the nested PK segment of the trial were completed. Enrollment for the nested PK trial commenced after receipt by clinics of the manufactured rings in December, all three sites having already received local and national ethics committee approvals. The Los Angeles clinic enrolled several subjects and the Santiago (Chile) and Santo Domingo (Dominican Republic) clinics began screening volunteers.

For the core Phase 3 study, Council staff planned two investigators' meetings, one in New York for the U.S. sites and one in Geneva for the non-U.S. sites, to be held later in Year Two in order to adequately prepare sites for the upcoming trial.

Contracts were let with three European contract research organizations (CROs), to write the European equivalent of an IND, the Investigational Medicinal Product Dossier (IMPD), and to assist in Europe with other aspects of the core Phase 3 study. FGK Clinical Research GmbH (Munich, Germany) is the Council's legal and pharmacovigilance-qualified representative in Europe, and the Council's liaison with the EMEA, handling interactions with the European clinics and regulatory authorities as required by new European Union regulations. FGK will work on the clinical portion of the IMPD. CRID Pharma (Saint Gély du Fesc, France) (formerly known as CRID Pharma-CLIPA) will be the qualified pharmaceutical representative in Europe and will be responsible for the packaging (including printing of labels) and shipment of the rings to the clinical sites in Year Three. During this period, CRID Pharma wrote the quality, manufacture, and control section of the IMPD. Voisin Consulting (Paris, France) will write the pre-clinical (toxicology and pharmacology) sections of the IMPD.

Although the FDA indicated in October that there were no comments concerning the study on their part and that the trial could therefore proceed, on December 28 the FDA faxed a letter to the Population Council with numerous additional recommendations based on their review of the IND submitted in June 2005. Based on the need to harmonize with the EMEA, in terms of approval of a new contraceptive containing a new chemical entity, the FDA doubled the requirements for the number of cycles and for women completing one year of use. The agency is now requiring data on 20,000 cycles with at least 400 women using the ring for one year. The FDA also requested additional laboratory chemistries. Furthermore, they requested a series of substudies: a microbiological study to determine if use of the ring would increase the risk of infection; a hepatic factors study to determine whether use of the ring may be associated with an increased risk of thromboembolism; and an endometrial safety study to determine whether use of the ring would induce changes in the lining of the uterus that could lead to endometrial cancers.

January–June 2006: In order to meet the challenge of conducting the greatly expanded Phase 3 study, USAID/PRH staff, in consultation with the Population Council, contacted the NICHD, which agreed to fund participation in the study by 12 sites in its Contraceptive Clinical Trials Network (CCTN). The CCTN will also have responsibility for conducting the microbiological, hepatic factors, and endometrial safety substudies.

Qualifying visits to 13 Phase 3 clinical sites (the original core study sites not also in the PK study) were completed by mid-January. (The 6 additional sites are among the CCTN sites, and therefore did not require qualifying visits from the Council.) Clinics selected for participation had the protocol reviewed by the relevant local and national ethics review committees. Where appropriate, the protocol, informed consent form, and label for the ring packaging were translated into local languages. Two investigators' meetings were held, one in New York on April 3 for the U.S. sites, and one in Geneva on May 8 for the non-U.S. sites. The protocol and study procedures were reviewed at these meetings, and the principal investigators and their staffs were trained on good clinical practices, serious adverse events reporting, and completion of case record forms. Additional changes were made to the protocol, which were approved by the Council's IRB as Amendment 5.

Packaging and labeling activities took place at CRID Pharma in anticipation of receiving rings shipped from QPharma on June 30. FGK Clinical Research worked on the clinical portion of the IMPD, in close collaboration with Council staff, and Voisin Consulting completed the pre-clinical (toxicology and pharmacology) sections.

Enrollment of 39 participants for the nested PK segment of the study, commenced in December, was close to complete by June 30. Each participant undergoes a three-month treatment period. In cycles 1 and 3, and in cycle 13 (when each participant will have continued into the core Phase 3 study), serum estradiol and progesterone levels are being tested twice per week, and pharmacokinetics of NES and EE are being determined using the LCMS/MS assay method. The purpose of these evaluations is to compare the efficacy on ovulation suppression, and the drug release, of the mass-manufactured rings with that of rings manufactured manually in CBR laboratories and tested previously in Phase 2 studies. The pharmacokinetic data are also documenting the burst effect of the steroids, with the expectation that the burst in cycle 3 will be less dramatic than that in cycle 1, and measuring clearance of the study drugs in cycle 13, following ring removal. Preliminary results of these studies indicate that the QPharma-manufactured rings are performing as well as the rings used in the Phase 2 studies. The PK study is scheduled to be completed by September 2006.

Finally, a nonclinical study was conducted over the course of Year Two to determine the ADME of NES following administration of a single subcutaneous dose of ^3H -NES to female rats. Radioactivity was excreted primarily in the feces of female rats given a single subcutaneous dose of ^3H -Nestorone. The large percentage of radioactive dose recovered in feces after subcutaneous administration indicates biliary excretion as a major elimination route for ^3H -Nestorone-derived radioactivity. ^3H -Nestorone-derived radioactivity was widely distributed throughout all tissues following subcutaneous administration by the first collection time point (0.5 hours). The highest concentration of radioactivity was detected in adrenal glands at 2 hours post-dose. The highest amount of radioactive dose was recovered in the contents and wash of the small intestine (33.8%) at 4 hours post-dose. Unchanged parent drug was a major component in profiled plasma samples. The major metabolite present in plasma was 4,5-dihydro-17 α -deacetyl-Nestorone. Most of the radioactivity excreted in urine and fecal homogenates was associated with 4, 5-dihydro-17 α -deacetyl-Nestorone. The results of this study showed that there is no accumulation of NES in any of the target or non-target tissues, allowing us to proceed with the human mass balance study planned for Year Three.

Subawardee(s): Chilean Institute of Reproductive Medicine (ICMER) (CB05.123A)
Dominican Association for the Well-Being of the Family (Profamilia/DR)
(CB05.122A)
Health Research Associates, LAC/USC (CB05.121A)
Family Planning Association of New South Wales, Australia
Karolinska Institutet, Sweden
University of California San Francisco
University of Campinas, Brazil
University of Chicago Hospitals

Contractor(s): Contractalents
Covance
CRID Pharma
Crystal Pharma, SA
DF/Net Research, Inc.
FGK Clinical Research GmbH
Lerner, David, Littenberg, Krumholz & Mentlik, LLP
Lisa Rarick
Micron Technologies
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: 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 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 infection 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, 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 Two:

Norplant

July–December 2005: An annual report was submitted to the FDA in November. Also in November, the final data became available for a postmarketing commitment, made in August 1999, 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 data were submitted to the FDA in November in a final report for the commitment.

January–June 2006: Another annual report was submitted in April to cover the period of October 2005 through February 2006. (This report covers a period of less than a year in order to coincide with the anniversary date of the initial approval of the NDA.) Amended labeling information, requested by the FDA in Year One in response to the Council's submission of an amendment to the NDA related to extending Norplant's use life from five to seven years, was not yet submitted. It will be submitted during Year Three. Near the end of the program year, the Council was still awaiting a response from the FDA regarding whether *in vitro* studies on the release rate of levonorgestrel from implants removed from subjects after seven years of use will be required, as part of the effort to extend Norplant's approved use-life to seven years.

Jadelle

July–December 2005: Information for two manufacturing supplements was received from the manufacturer, Schering Oy, very late in Year One. The first supplement provides for the extension of the product shelf life from three to five years. The Council submitted the supplement in June 2005, with amendments filed in July and August, and the FDA gave their approval in November. The second manufacturing supplement, to provide an alternative batch size in the manufacture of the drug product, was submitted to the FDA in August, amended in November, and approved by the FDA in November.

January–June 2006: Information for a third manufacturing supplement was received from Schering Oy in December and January. This supplement, which relates to the change in *in vitro* release/dissolution test medium and test method, and revised dissolution test specification, which Schering planned to implement in May, was submitted to the FDA in January. On June 1, the FDA found the supplement "approvable", with approval dependent on amending the supplement to respond to listed deficiencies. The Council notified the FDA on June 6 of its intent to file this amendment, and will continue to interact with the manufacturer and the FDA to prepare the amendment. The manufacturer's clinical pharmacology and biopharmaceutics study commitment to collect five years of *in vitro* release rate data from commercial production lots continued, also requiring Council staff interaction with the manufacturer and the FDA. Additionally, an annual report for Jadelle was submitted to the FDA in April.

Copper T 380A IUD

July–December 2005: Based on FEI Women's Health (FEI)'s submission of responses to FDA safety and effectiveness queries during Year One, the FDA responded regarding extending the use-life beyond ten

years: The FDA did not approve the use-life extension. The FDA did however accept other revisions to the prescribing label for ParaGard® (ParaGard is the IUD's commercial name in the U.S.), approving it in September for women in all stages of reproductive life, from age 16 to menopause, who are in stable relationships and therefore not at high risk of sexually transmitted diseases or HIV. In recent years, ParaGard had been recommended only for women with at least one child, in mutually monogamous relationships. Council staff assisted FEI with its submissions to the FDA. In November, Duramed Pharmaceuticals, a subsidiary of Barr Pharmaceuticals, acquired FEI Women's Health and the ParaGard NDA.

January–June 2006: The Council contacted Barr Pharmaceuticals to inquire as to their interest in continuing use-life extension efforts, but Barr has been unresponsive. No consultation with USAID PRH/RTU staff was requested during Year Two.

Activity Funding: Pop Core

Contribution to Results Framework: IR 2.4

Intellectual Asset Management

Part of project Number/s: 99503

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

Activity Description:

The Intellectual Asset Management (IAM) group is carrying out activities to locate and reach suitable agreements with partners who will commercially manufacture and market the products supported by the Population Council Product Development cooperative agreement. A Population Council microbicide would provide women with a female-controlled way to reduce the chance of HIV transmission during sexual intercourse. The NES/EE contraceptive vaginal ring would serve as a female-controlled contraceptive for women. Based on the manufacturing and distribution requirements for each product, the Council seeks partners for the microbicide in the developing world and partners for the ring in the developed and/or developing world. Although the marketing rights can be licensed at any point, the Council plans to license the products during the Phase 3 efficacy studies to minimize the time to product availability. The Phase 3 study for the microbicide Carraguard is scheduled to end in 2007, and the Phase 3 study for the ring is scheduled to end in 2009.

To find partners who will successfully bring products to market, IAM staff begin by conducting research to identify manufacturing and marketing companies that may be appropriate for the tasks. This research consists of networking with Population Council, USAID, and other colleagues, and with professionals at pharmaceutical, licensing, and public health meetings attended in the course of business, and it is supplemented by review of appropriate publications and directories. Each prospective company is then approached, contacts made and conversations begun, by e-mail, phone, or in person, to determine whether the company has an interest in exploring the possibility further. For companies that express a serious interest, confidentiality agreements must be negotiated and signed, and IAM staff meet with company principals in person. At a first or second meeting, the Council discloses additional technical information, and initiates a preliminary discussion of license agreement terms. For companies that reach this level of involvement, IAM staff must conduct due diligence: the research and analysis to evaluate the company thoroughly for potential partnership. If the relationship continues, the Council and the company will negotiate a Material Transfer Agreement, enabling research materials to be transferred to the company so that it can further evaluate its capabilities and interest to proceed. After both parties assess and confirm their interest, abilities, and compatibility, the IAM group negotiates and crafts actual license terms. IAM negotiates low pricing and requires favorable provisions for the public sector. License terms may be negotiated with as many companies as have passed through the earlier stages in the process, but typically with not more than three. Based on the public sector pricing and many other factors, IAM selects one or more manufacturers and marketers. After a licensing agreement is in place, the IAM group continues to manage the relationships with the manufacturers and distributors, and monitors production and distribution in order to ensure that the products get to the people who need them.

The IAM group provides staff support for the Council's Patent Committee, which oversees all important issues related to the patent process in accordance with the Council's patent policy. The committee, currently chaired by Sandra Arnold and Elof Johansson, advises the Council's president regarding patent strategy and progress. IAM staff coordinate the patent process by acting as the central liaison among external patent counsel, inventors, the product development teams, other consultants as needed, and the committee.

In addition to arranging for products to get to market and coordinating patent prosecution, IAM manages relationships with other important business partners: with the Swedish manufacturers of the microbicide gel (Clean Chemical Sweden) and of the NES/EE ring (QPharma), in order to ensure supplies for the clinical studies; and with the U.S. producer of the carrageenan combination that is Carraguard's active ingredient. IAM is also seeking additional sources of the active ingredient, to provide manufacturers with the raw material needed to produce Carraguard.

The IAM group is located in the Council's Corporate Affairs Division, and consists of Vice President Sandra Arnold, Senior Director James Sailer, General Counsel Patricia Vaughan, Senior Business Analyst George Young, and two staff assistants. The group works in close coordination with key staff in the Council's Center for Biomedical Research: Vice President Elof Johansson, Executive Director Régine Sitruk-Ware, and the product development teams. Through the PCPD, USAID provides partial funding for IAM staff time and travel, with microbicide funds supporting efforts on behalf of the microbicide beginning in Year Two, and population funds supporting about half of the budget for efforts on behalf of the NES/EE ring beginning in Year Three.

Report of Year Two:

July–December 2005: IAM continued networking, particularly with Population Council colleagues in South Africa, to gain additional leads on partners for manufacturing and distribution of the microbicide. In December, representatives of three South African pharmaceutical companies were contacted, generating interest from all of them. E-mail correspondence with them continued, with the aim of planning in-person meetings, and Web research was undertaken to make preliminary evaluations of these companies. In India, two of the three companies visited by IAM staff in November 2004 completed confidentiality agreements in September, but only one of the companies proved appropriate, and the relationship with that company moved forward with plans for a second visit, to take place early in Year Three.

IAM continued their staff support for the Council's Patent Committee.

January–June 2006: IAM continued correspondence with the three new South African leads, to arrange in-person meetings with them during the April Microbicides 2006 conference. Confidentiality agreements were drawn up for each company. Council staff members concerned with IAM attended the Microbicides 2006 conference in Cape Town, where they gained useful information and made new contacts, including with another South African pharmaceutical company interested in a formal meeting. IAM met with representatives of this company, and with the three companies identified earlier in the year. Together with members of the Council's microbicide development team, IAM staff provided the companies with background information on the Council, the trial status, and the product licensing strategy. All four companies expressed substantial interest in licensing Carraguard. One company completed its confidentiality agreement, with the rest expected to be negotiated and executed early in Year Three.

Meeting company representatives in person served to dramatically accelerate the relationship-building process. Prior to meeting, representatives had been slow to respond to repeated phone calls and e-mails, and even arranging the meetings proved to be a challenge. However, the meetings greatly facilitated the mutual introduction process, and communication with these contacts since those meetings has been more frequent.

IAM also moved forward in its efforts to find another manufacturer for the carrageenan combination that is Carraguard's active ingredient. Using a source list previously compiled, IAM staff contacted 40 refiners and manufacturers around the world. Nine of those—in the U.S., Chile, the Philippines, Canada, and Europe—expressed interest, as did an additional unsolicited company in Turkey. Discussions and arrangements for confidentiality proceeded with each company, and it is expected that most will have signed confidentiality agreements by the end of the program year. A number of these companies have agreed to send samples of their carrageenan to the Council for testing.

The current manufacturer of Carraguard, Clean Chemical Sweden, avoided a potential destabilizing buyout, which lowered the priority of exploring further relations with a potential backup manufacturer in Sweden. That partnership was therefore put on hold, although contact is being maintained.

IAM continued its staff support for the Council's Patent Committee.

Activity Funding: HIV/AIDS Core

Contribution to Results Framework: SO4

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