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PROJECT STATEMENT

9320537004902

Date: December 10, 1976

A. PROJECT SUMMARY

1. Statistical

Project Title: International Fertility Research Program (IFRP)

New or Extension: Extension

Contractor and Address: Primary Contractor - International Fertility Research Programme, Inc. Research Triangle Park, North Carolina

Contract AID/csd-2979

Principal Investigator: Dr. Elton Kessel

Duration:

RAC authorized duration:	6 years (6/71 - 6/77)
RAC authorized funding:	6 years (6/71 - 6/77)
Additional funding requested:	5 years (6/77 - 6/82)
Extension or duration requested:	5 year (6/77 - 6/82)

Total Estimated Cost: $51,069,973

Amount Requested for RAC Approval: 38,969,363

Funding by Fiscal Years:

FY 71	$3,106,000	TQ	0
FY 72	1,800,000	FY 77	6,346,095
FY 73	0	FY 78	7,697,670
FY 74	1,499,610	FY 79	7,683,514
FY 75	2,695,000	FY 80	8,348,316
FY 76	3,000,000	FY 81	8,893,668

Project Managers: PHA/POP/R, J.J. Speidel/M. I. Dobrovir

2. Narrative

The International Fertility Research Program (IFRP) has been established to conduct comparative field trials on new means of fertility control in the less developed countries. Since the inception, collaborating investigators have joined this program, and studies have been developed, initiated and completed relating to six major fertility control modalities. Considerable scientific data relating to the performance of several means of fertility control is now available from the IFRP to guide family planning program administrators.

B. Expanded Narrative Statement

1. Project Description, Background and Progress Report

a. Description and Background

The International Fertility Research Program was established July 1, 1971, to allow rapid high quality clinical trials of new means of fertility control on a comparative basis under use conditions in a spectrum of countries and cultures. Objectivity and comparability are sought by use of statistical and epidemiological techniques employing standard data collection formats and central analysis of data. There are now numerous fertility control techniques not yet in clinical usage in developing countries which have the potential of marked advances in ease of use, reliability and acceptability. Particularly, the newer IUDs, improved sterilization techniques, prostaglandins and various steroidal contraceptives urgently require comparative clinical testing. In addition, the program supports special studies to bring promising methods to the field trials stage and selected in depth studies of the success of certain methods. The most important result of this project is the rapid evaluation of various means of fertility control, a process either impossible or requiring years of experience if directly comparable clinical field trials are not available.

During its five and one-half years of existence, IFRP developed standardized data collection instruments, study protocols, instruction manuals and computer programs to rapidly analyze research data in six major study areas: pregnancy termination, menstrual regulation, intrauterine contraceptive devices, male and female sterilization, and systemic contraceptives, including oral contraceptives. IFRP has developed an international network of more than 250 Contributor physicians in more than 30 countries, primarily LDCs, conducting clinical trials according to IFRP study protocols. IFRP headquarters in Research Triangle Park, North Carolina, manages the program by continuous dialogue with the contributing physicians, by organized training programs, by site visits, and by selected contributor conferences. As IFRP research methodology has attracted the interest of national groups in LDCs, several national and regional semi-autonomous fertility research programs have been organized using IFRP standard forms and computer systems.

The research efforts of IFRP add significantly to the body of scientific knowledge related to fertility control technology. Rich feedback from IFRP to its Contributors in the form of computer generated standard tables and special analyses enable leading clinicians in LDCs to write high quality research reports. In addition, the IFRP staff prepare reports of pooled data from many parts of the world. Information about methods which have proven safer, more effective, and more acceptable is

disseminated widely through scientific conferences and publications including the International Journal of Gynaecology and Obstetrics which is now the official organ of the IFRP as well as of the International Federation of Gynecology and Obstetrics (FIGO).

A Medical Advisory Committee has been organized to help determine research priorities among the many drugs, devices, and procedures proposed for study through the IFRP. A Protection of Human Subjects Committee approves each new method and study design and periodically reviews study results to assure that the benefits derived from these studies outweigh the risks to volunteers in the studies.

Continuation of this program is sought to provide an effective international mechanism for field testing fertility control methods, techniques, and devices so as to provide data relating to safety, effectiveness, and acceptability of these methods. The institutionalization of family planning in a large number of countries has heightened interest on the part of government officials, administrators, and clinicians in the means of achieving fertility control. Hence scientifically designed and carefully monitored studies at the clinics and hospitals under use conditions offer the best opportunity for impartial evaluation of the methods. It has now become clear that the present and projected computer data base of IFRP can be an important source of information to guide both AID and LDC policy decisions related to contraceptive technology, commodity procurement, and service delivery systems.

The IFRP will continue to conduct rigorous clinical trials of both promising new methods and many accepted methods of fertility regulation. Clinical trials in the six general study areas cited above will continue to be the major emphasis of the program. IFRP also will support research needed to bring promising methods of fertility control to the point where clinical studies are appropriate. The IFRP international network of contributors will continue to be the final common path to field trials, under use conditions in the LDCs, of new and improved fertility control technology developed at IFRP, under other AID projects, and through other public and private agencies.

Continuation of the program will provide for training of collaborating investigators in the newer techniques of fertility control so that clinical trials can be initiated in the overseas setting. This is only a part of the total training effort which includes establishing a records dialogue on standard data collection instruments and introducing comparative study protocols in an international network of study Contributors. Aspects of training more recently include interpretation of computer programmed standard tables, which impose a form of quality control in scientific reports.

During the last few years of the program, the level of expertise has been

developed to such a degree among contributors in several LDCs that semi-autonomous research programs have been organized utilizing IFRP research methodology in India, Bangladesh, Colombia and the Sudan. Further transfer of technology and responsibility to national and regional fertility research programs will be an objective of the continued program. Also in response to requests from Contributors, the program will be further broadened to include the development of record systems to evaluate both clinic-based and community-based family planning programs, including postpartum programs. To accelerate the introduction of improved surgical technology in family planning services, IFRP's efforts will be expanded to include a small program of physician training and support, principally of selected clinical services provided by collaborating research centers.

IFRP was organized on July 1, 1971. The initial contract period was for a total of five years, to June 30, 1976, with initial funding for three years, to June 30, 1974. Subsequently, authorization was provided to extend both the period of services and funding to June 30, 1977, a total of six years. By the end of 1974, IFRP had developed into a large international field trial center with its own administration. It was then decided by mutual agreement of the University, AID, and IFRP that the program could operate as an independent non-profit institution. On February 14, 1975, the IFRP officially separated from the University and is now located in Research Triangle Park, North Carolina. The current proposal requests continued support of the program for an additional five years, effective July 1, 1977 when the present funding authority expires.

b. Progress Report

The International Fertility Research Program (IFRP) was initiated July 1, 1971. A detailed report of progress made during the first three years of the program was presented to the Research Advisory Committee May 6-7, 1974 when the program was reviewed and approved for extension of services and funding through June 30, 1977.

In the first three years of the program, an organization was developed capable of initiating studies in six study areas: pregnancy termination, menstrual regulation, IUDs, female sterilization male sterilization, and systemic contraceptives. Significant findings from clinical field testing in each of these areas were described in detail. Review mechanisms were established to screen new methods for study, including review by the IFRP Medical Advisory Committee and the University of North Carolina's Committee on Human Experimentation. Standard data collection instruments were developed. Computer assisted data management, editing and analysis became well advanced. Study protocols were developed and straight and comparative studies of new methods of fertility control were initiated. Study results were disseminated by papers in appropriate scientific journals, at scientific conferences and meetings, and by consultant reports prepared by IFRP personnel.

Over the total five and one-half years of the program, the primary objective and accomplishment of IFRP has been the development of a research system which provides rapid evaluation of methods of fertility control through clinical field trials to identify those which are desirable for program use, i.e. safe, effective and acceptable. Through this system, important findings have been made in each of the six main study areas which will be described in some detail later in this section. Important supporting accomplishments over the life of the program are noted as follows:

- Straight and Comparative clinical study protocols and data collection instruments have been designed, pretested, refined and placed into wide field use in the major study areas, i.e. pregnancy termination, menstrual regulation, IUDs, male and female sterilization, and systemic contraceptives including orals.

- Data processing and analysis have reached a high degree of sophistication, reliability and efficiency.

- IFRP has developed in international network of more than 250 contributors in over 30 countries who are now actively engaged in IFRP research activities. These clinical investigators have been trained in IFRP research methodology and medical procedures, and are able to conduct standardized clinical trials resulting in reliable, high quality data.

- Several national and regional fertility research programs are in the process of being organized to coordinate the research activities, including data collection management, in their geographic areas. Semi-autonomous programs are now functioning in India, Bangladesh, Colombia and the Sudan.

- The computer capabilities have been employed to provide data on field use of new means of fertility control in the program context through a Family Planning Clinic Record system, a Maternity Record system, and record systems for Community-Based Distribution of Contraceptives.

- In collaboration with its Contributors, IFRP has played a major role in developing improved techniques of fertility regulation, recent notable examples being female sterilization by laparoscopy and the simpler mini-laparotomy procedure.

- Research data on approximately 200,000 cases in the six study areas have been processed and loaded into the IFRP data bank.

- In excess of 288 scientific papers have been prepared by IFRP staff and Contributors to disseminate research findings. Presently, about 100 scientific papers are prepared each year.

- The recent formal association with the International Federation of Gynecology and Obstetrics (FIGO) and its standing committees promises to broaden the international network of clinicians through which population research can be conducted and to promote the effective dissemination of research information by publication in the FIGO Journal which has now become the official organ of IFRP as well.

Significant findings in the six major study areas are summarized as follows:

Pregnancy Termination

Vacuum aspiration (VA) has become the most frequently used procedure for performing induced first trimester abortions. Many institutions now perform the procedure on an outpatient basis without the use of general anesthesia. The complication rate for the procedure is low. Important findings include:

1) With respect to all criteria of performance (rates of specific complications, blood loss, frequency of cannula reinsertion, amount of retained tissue), there are no significant differences between the metal and flexible plastic (Karman type) cannulae for terminating pregnancies of 7 to 10 weeks' gestation by vacuum aspiration.

2) The vented and nonvented cannulae result in similar rates of effectiveness and complications when used for terminating pregnancies at 7 to 12 weeks' gestation.

3) VA compared to dilitation and curettage (D&C) when performed in gravidas at 13 to 15 weeks' gestation is associated with significantly higher rates of complications.

4) Performing D&C at 13 to 15 weeks' gestation appears to be safer than waiting until after 15 weeks' gestation and administering intra-amniotic hypertonic saline.

5) The incidence of complications for saline abortion increases with the duration of placental retention, while the hourly rates of spontaneous expulsion of the placenta decrease. Surgical removal of the placenta appears indicated if it is not spontaneously expelled within two hours of delivery of the fetus.

6) Intra-amniotic hypertonic saline augmented with intravenous oxytocin is associated with shortened instillation-to-abortion times (median, 25.5 hours) compared to intra-amniotic hypertonic saline without supplemental oxytocin (median, 33.3 hours). The instillation-to-abortion time does not depend on the rate of oxytocin administration (17-64 mIU/min), but does depend on the time of administration. Oxytocin

initiated within 8 hours after saline instillation decreases the instillation-to-abortion time.

7) Instillation-to-abortion times for intra-amniotic saline are not dependent on the patient's gestation age (16-24 weeks), age, race, or parity.

8) There were no apparent advantages to the removal of amniotic fluid (in various amounts--100 ml or 150 ml) prior to the instillation of 200 ml of 20 percent hypertonic saline. Success (in terms of incomplete abortion rates), safety (specific complication rates), and speed (time from instillation to abortion of the fetus) were criteria considered.

9) Since the interval from intra-amniotic administration of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) to abortion has been reported to depend on the time of day $PGF_{2\alpha}$ was instilled, a study was undertaken to determine if there was a periodicity in response to the intra-amniotic instillation of 200 ml of 20 percent hypertonic saline. In this study of 4,000 hypertonic saline abortion cases, no significant differences in instillation-to-abortion times were found after controlling for the known effect of oxytocin infusion.

10) Controllable risk factors associated with infection after saline abortion are: prolonged instillation-to-abortion time, repeat instillations, and the techniques used by the physician performing the instillation. The only controllable risk factor associated with hemorrhage is placental retention beyond one hour's duration.

11) Compared to the single intra-amniotic 50 mg $PGF_{2\alpha}$ dose schedule, the 25 mg multiple dose schedule (additional 25 mg $PFG_{2\alpha}$ injected at 6, 24, and 30 hours if abortion has not yet occurred), results in shortened median instillation-to-abortion times (17.4 vs. 20.8 hours), but it has similar rates of complications and side effects except for reduced vomiting.

12) Both the 50 mg and repeated 25 mg $PGF_{2\alpha}$ dose schedules have shorter instillation-to-abortion times than 200 ml of 20 percent hypertonic saline (median, 26.3 hours), but they have higher rates of incomplete abortion, and higher rates of gastrointestinal side effects.

13) Sterilization via laparotomy with a Pomeroy ligation of the tubes does not significantly increase the complication rates after terminating pregnancies at 15-20 weeks' gestation with either intra-amniotic $PGF_{2\alpha}$ (single or multiple dose schedule) or intra-amniotic hypertonic saline.

14) Studies of incomplete abortion demonstrate complication rates which are significantly higher for women who probably had an illegally induced

abortion compared to women who probably had a spontaneous abortion. Rates of serious complications and death from spontaneous (including illegally induced) abortions are significantly higher than for legally induced abortion.

15) A comparison of septic and non-septic incomplete, inevitable and threatened abortion (IIT) cases was conducted at four centers and the analysis controlled for location. Septic cases were more likely than IIT cases to have previous histories of induced abortion, to be admitted for treatment at later gestational ages, to have higher rates of immediate complications (after controlling for method of treatment), especially fever, excessive blood loss and uterine perforation, and to require longer hospitalization.

16) Several studies were conducted to establish baselines of routine treatment of abortion in countries with legal restrictions on abortion. Large institutions were more likely to provide induced abortions than smaller ones. Each institution used one treatment method (usually D&C or VA) routinely, and complication rates were significantly lower for patients requesting treatment in the first trimester instead of the second trimester.

Menstrual Regulation

IFRP has played a leading role in demonstrating the increased safety of early termination of a suspected pregnancy by vacuum aspiration. The IFRP has developed the major data bank for menstrual regulation (MR) which permits analysis of vacuum source, cannula size, length of amenorrhea and equipment durability as well as safety, effectiveness and acceptability. Dissemination of research results by the IFRP staff and Contributors appears to have had a significant impact on knowledge regarding this procedure worldwide as a method for terminating a suspected pregnancy. Important research findings include:

1) The Pregnosticon Dri-Dot pregnancy test is not a very reliable test for the diagnosis of pregnancy for amenorrheic women who are within 14 days of a missed menstrual period; however, only 8.0 percent of positive results are false, but about 41.2 percent of negative results are false. As the number of days delay in onset of menstruation increases the false-positive and the false-negative rates of the test decrease.

2) The probability of complications with an MR procedure increases slightly as days delay in onset of menstruation increases; however, the probability of an unnecessary procedure (i.e. an MR procedure performed on a patient who is not pregnant) decreases rapidly offsetting the increased risk of complications.

3) The proportion of patients documented to be pregnant increases from about 30 percent for patients at less than 32 days of amenorrhea to over 80 percent for patients at 46-49 days of amenorrhea.

4) Regardless of the size of cannula (4, 5, or 6 mm), vacuum source (50 cc syringe, electric pump), or length of amenorrhea, rates of significant complications are low--less than 3 percent in most of the studies reported by IFRP. In fact, the variation in complication rates among Centers does not appear to be related to the equipment used but does appear to be related to the training and experience of the physicians performing the procedures.

5) Complication rates are higher for patients documented to be pregnant than for patients who are not pregnant at the time of the MR.

6) Higher rates of complications have been reported for MRs performed in countries where artificial abortion is illegal than in countries where it is legal.

7) The overall failure rate of MR to terminate pregnancy is about 2 percent, but failure rates decline with increased experience of operators.

8) Some studies have reported lower failure rates for MRs performed with the larger diameter (6 mm) cannulae than MRs performed with the smaller diameter (4 mm) cannula. Also, the failure rate of MR appears to decrease with increasing duration of amenorrhea.

9) One study has demonstrated that nurse-midwives can be trained to perform MRs, and that their complication and failure rates are no different than those of physicians who performed the procedures. However, in one study where nurse-midwives have been inadequately trained, high rates of complications and failures were initially obtained.

10) The intramuscular administration of an estrogen/progesterone preparation (50 mg progesterone and 3 mg estradiol benzoate in oil) was found to be ineffective in inducing bleeding in non-pregnant women. Two-thirds of non-pregnant patients began menstruation within one week of first requesting MR independent of whether they received intramuscular estrogen or no treatment.

11) There appear to be no significant advantages to the intrauterine administration of 5 mg $PGF_{2\alpha}$ for MR when compared to vacuum aspiration procedure. All $PGF_{2\alpha}$ treated patients need to be premedicated with tranquilizers and analgesics. Over 30 percent of the PG treated patients had one or more episodes of vomiting and all had prolonged durations of uterine bleeding (9-18 days) following the PG administration.

Intrauterine Devices

IFRP evaluation of IUD performance has focused on pregnancy and expulsion rates, and more recently on reduction of IUD related bleeding, particularly that which leads to removal. Bleeding/pain removal rates currently range from 4 to 15 per 100 women at the end of one year. Specific findings include:

1) The near zero one year pregnancy rate previously reported in Cairo with the Spring Coil IUD was reported in two additional studies involving over 1,500 women. Bleeding/pain removal rates were high in each study.

2) The long term use effectiveness of the Cu-7 200 indicated that the yearly rates of pregnancy did not increase with duration of use. The study was based on 514 Cu-7 users followed for a period of up to 63 months. Though five year bleeding/pain removal rates were significantly lower than corresponding rates of Loop C and D cases, pregnancy rates were significantly higher.

3) In a retrospective study of the LEM device it was found that the performance of the device was suboptimal relative to pregnancy. One year pregnancy rates may have been elevated by possible structural problems which caused the device to lose its memory over time and to be displaced in the lower uterine segment.

4) In a study of over 400 women using a zinc-copper 7-device, it was found that the addition of zinc significantly lowered the pregnancy rate of the 7-device relative to the Cu-7. Biopsies taken at various time intervals in the study suggest that early abnormal histopathological findings may be transitory.

5) In another study of the small Cu-7 it was found that expulsion rates were significantly lower for this device relative to the standard Cu-7. Bleeding removal rates were not different, however.

6) In a follow-up study of 841 users of the M-device, it was found that the five year expulsion rate of this device was less than one per 100 acceptors. Embedding of the device has been advanced as the most probable cause of this high retention rate.

7) One year expulsion rates were found to be uniform among five centers using the Dalkon Shield. The high level of pregnancy protection originally reported for this device was not reported in any of these five studies. The studies involved over 5,100 users of the Dalkon Shield.

8) In studies in which bleeding was the primary parameter of interest, it was found that U-Coil IUDs loaded with tranexamic acid (200 cases) were superior to copper-loaded U-Coils (250 cases) in reducing bleeding problems. A heavy menstrual flow and increase in duration of flow was

experienced more often by users of the Copper U-Coil than by users of the medicated device. The six month bleeding removal rates were 9.9 and 1.1 for the two devices respectively.

9) In another study of bleeding involving the Spring Coil as a carrier for copper, progesterone, and mestranol, it was found that mestranol and progesterone were associated with less bleeding than were copper and the inert Coils. Progesterone did cause an increase in the length of menstrual flow, but bleeding leading to a removal of the device was comparable to that of the mestranol loaded device.

10) Early findings with the Pleated Membrane IUD (IUM) indicated that this device was associated with heavy bleeding though some improvement was noted when the device was used in the immediate post-abortion period. Modifications designed to decrease this bleeding included a hydron coated IUM, one made with a soft material and one with a decreased wishbone supporting the device. Findings from the study of these modifications suggested that bleeding was reduced with the smaller wishbone IUM, but slightly increased with the hydron coated device. The soft material device was too rapidly expelled.

11) The fluid-filled Tecna device was designed to decrease bleeding and pain. The performance of this device was suboptimal in preventing pregnancy, in retention, and was associated with a high incidence of bleeding. Additionally, it was reported that a foul smell was associated with the use of this device. This report along with that from a study of the Anderson Leaf IUD suggests that not only these two silastic devices, but all, may be unuseable in conjunction with intrauterine devices.

12) A prescriptive approach to the use of an IUD was tested with the Weiss device. This pliable device was to conform to the shape of the uterus. In two separate studies, use of the device was associated with a high level of bleeding and most devices were ultimately expelled. Both studies were terminated in the early stages.

13) There were no significant differences in the pregnancy, expulsion or bleeding/pain removal rates for IUDs inserted by midwives (252) or by physicians (646) in a study of the Copper-T IUD. IUD continuation rates were, however, significantly lower among women who had the IUD inserted by midwives.

Female Sterilization

IFRP has been instrumental in developing and testing improved methods of surgical contraception for women over the last five years. Female sterilization has evolved from a procedure requiring general anesthesia and hospitalization to one which may be performed on an outpatient basis with the use of local anesthesia.

1) The following results were obtained from a pooled study of 8,568 laparoscopic sterilization procedures performed in 16 countries and including 4,928 electrocoagulation, 1,696 spring-loaded clip, and 1,944 tubal ring procedures. Nearly 84 percent of the laparoscopies were performed as interval precedures.

a) Problems with equipment occasionally caused difficulties with all three methods of tubal occlusion, but problems were most frequent with prototype spring-loaded clip equipment. Failure to complete the planned procedure occurred less frequently among electrocoagulation cases (0.2%) than among spring-loaded clip (0.8%) or tubal ring (0.6%) cases.

b) Laparotomy, for various reasons, was required for five cases (0.1%). Bowel injuries occurred in five patients (0.1% of electrocoagulation cases), four of whom did not require surgical treatment. Bleeding of the tubes and/or mesosalpinx was reported for a higher proportion of electrocoagulation (1.0%) and tubal ring (1.2%) patients than spring-loaded clip (0.2%) patients.

c) The pregnancy rates, at six months, were 0.4 percent for cautery, 1.2 percent for clip, and 0.2 percent for tubal ring cases. Cumulative 12-month rates were 0.7 percent for cautery and 2.5 percent for clips. Not enough data were available at the time of this analysis to determine reliable 12-month rates for the tubal ring.

2) In an analysis of follow-up data on 8,483 women sterilized by laparoscopic electrocoagulation (5,097 cases) or application of spring-loaded clips (1,466 cases) or tubal rings (1,920 cases), the results were as follows:

a) The 12-month pregnancy rates in interval patients were significantly higher for clip (2.7 per 100 women) than for cautery (0.4) or ring (0.6). Among postabortion patients the 6-month rates were also significantly higher for clip (2.6) than for cautery (0.7) or ring (0.0).

b) Based on this analysis, the three currently available techniques of laparoscopic tubal occlusion are similarly free of significant gynecologic effects for the first year after surgery. Rates of gynecologic surgery were low (less than one percent) for all techniques and pregnancy status patient groups.

c) No consistent changes in menstrual patterns were observed and the majority of the women reported no change in menstrual cycle parameters.

3) Comparative studies of interval sterilization via laparoscopy with electrocoagulation and division of the tubes or the application of spring-loaded clips, in which the technique of tubal occlusion was randomly assigned to a total of 600 subjects, indicated:

a) Technical difficulties were more frequent with the spring-loaded clip (7.3%) than electrocoagulation (4.1%) primarily as a result of mechanical problems with the laparoscope.

b) Rates of surgical and early postoperative complications were similar for the two techniques.

c) Moderate or severe pain during the procedure was reported by a significantly higher proportion of the cautery (19.6%) than clip (7.3%) patients. However, postoperative pain was more frequent after the application of spring-loaded clips than after cautery both before discharge (33.2% and 22.4%, respectively) and between discharge and the 7-21 day follow-up visit (15.6% and 9.0% respectively).

4) Pregnancy rates in pooled data of comparative and straight studies of laparoscopy at the same centers were significantly higher for the spring-loaded clip than for electrocoagulation and the tubal ring. The six-month rates were 1.3 per 100 women for clip patients, 0.2 for cautery, and 0.2 for ring; twelve-month rates were 2.1, 0.2, and 0.3, respectively.

5) In studies of laparoscopic tubal ring (797 cases) and electrocoagulation (816 cases) conducted at the same institution (Kwak, Korea), the rates of surgical difficulties were 1.9 percent for tubal ring and 2.6 percent for electrocoagulation, and the rates of surgical complications were 1.3 and 1.4 percent, respectively.

6) In a study of 200 patients undergoing laparoscopic sterilization within five days of an uncomplicated term delivery, the following results were obtained:

a) Technical difficulties were encountered in two (1.0%) patients.

b) Operative and early postoperative complications were reported for 9.5 percent of the subjects. Two complications were serious; in one patient, laparotomy was performed because of a suspected bowel burn, and in another, the small intestine was punctured during placement of the Tuohy needle.

7) An analysis was performed on follow-up data from 14 Asian institutions on 2,925 women sterilized by laparoscopic electrocoagulation (1,526 cases), laparoscopic application of spring-loaded clips (286 cases) or tubal rings (422 cases), laparotomy with Pomeroy tubal ligation (342 cases), and culdoscopy with Pomeroy ligation (349 cases). The results were:

a) The incidence of menstrual irregularities within six months of sterilization and the incidence of gynecological abnormalities and

the need for pelvic surgery within 12 months of sterilization were infrequent for all procedures.

b) Some changes in menstrual cycle parameters were reported for all sterilization procedures evaluated. For each of the procedures, similar proportions of women reported an increase or a decrease in the severity of dysmenorrhea and duration and amount of menstrual flow.

8) The results of an analysis of the first 2,820 minilaparotomy cases recorded by the IFRP are as follows:

a) Varying degrees of surgical difficulties were encountered in approximately ten percent of the procedures. No procedure was a complete failure and in just five cases was it possible to occlude only one tube.

b) Surgical complications were reported for 1.6 percent of the cases, including eight cases (0.3%) of bowel/bladder injury and seven cases (0.2%) of uterine perforation. The rate of bleeding of the tubes during surgery was 0.9%.

c) During the immediate postoperative period, before discharge, complications were noted for fewer than one percent of the patients.

d) Fever requiring antibiotics and/or wound infection were each reported for 2.6 percent of the 2,686 patients observed at the 7-21 day follow-up visit.

9) In a study of culdoscopy in an outpatient setting at three institutions involving 525 patients:

a) The procedure could not be completed in seven (1.3%) patients. In 16.6 percent of the procedures technical difficulties which did not require a change in the planned technique were encountered.

b) Complications at the time of surgery were reported for 2.1 percent of the patients.

10) Infundibulectomy (fimbriectomy) via laparotomy was performed in 310 women who were sterilized within 10 days of a vaginal term delivery (88.4%) or abortion (11.6%).

a) Difficulties at surgery which prevented infundibulectomy were encountered in three cases (1.1%).

b) Infection and other incision problems were the primary complications. At the time of the first follow-up visit, 7-21 days after

sterilization, this complication was noted in eight postpartum patients (3.1%) and one postabortion patient.

c) No pregnancies were reported among the 169 patients who had been observed at the six-month visit.

Male Sterilization

The first studies planned for this area involved bipolar electrocoagulation of the vas but were delayed due to problems in equipment development and the higher priority placed on other study areas. Consequently, there are no significant research results for this study area. Computer programs have been developed for data management.

Systemic Contraceptives

This study area is the last and most complex to be developed by IFRP. Two studies have been completed in Seattle, Washington. In the first study (pretest), patients were given either Ovral or Norinyl 1/50 for three cycles and were switched to Norlestrin 1 for the next three cycles. Symptom grids were completed for all the six cycles by contacting women by telephone twice in a cycle. In the second study, three oral contraceptives (OCs)--Ovral, Norinyl 1/50, and Norlestrin 1--were compared during the first three cycles and then women were crossed over to any of the three cycles forming nine study groups. Again symptom grids were completed during the study period. The patients on these studies were young (90% below age 25), white (90%), and never married (85%). The following are important findings.

Comparison of Ovral, Norinyl and Norlestrin:

1) The incidence of various side-effects in the two Seattle studies were higher than generally reported in the literature. The incidence of break-through bleeding (excluding spotting), for instance, obtained in this study was 18 to 26 percent compared to about 11 percent reported in the literature. This difference is likely attributable to the method in which information was collected, i.e. women in these studies were contacted every two weeks by telephone and were specifically probed about various signs and symptoms related to the use of the OC.

2) Changes in the amount of menstrual flow (either an increase or decrease compared to prior pill use) were reported by most women during the study. Of Ovral, Norinyl and Norlestrin users, 60, 80, and 90 percent had reported changes in the menstrual flow.

3) The incidence of breast discomfort was higher for Norinyl users (43.0%) than for Ovral (25.8%) or Norlestrin users (28.6%).

4) The incidence of breakthrough bleeding was lower for Ovral users than for Norinyl and Norlestrin users.

5) The incidence of nausea was higher for Ovral users than the other OC's.

6) The side-effects of Ovral were generally of longer duration compared to Norinyl or Norlestrin users.

7) Withdrawal bleeding occurred about one day later for Ovral users compared to Norinyl or Norlestrin users.

Effect of Crossover:

1) A switch from Ovral to Norinyl or vice versa resulted in an increased incidence of nausea. The Norlestrin users, when switched to Ovral, reported a higher incidence of nausea; no significant changes were reported when the switch was made to Norinyl (from Norlestrin).

2) There was significant increase in the incidence of abdominal bloating when Norlestrin users switched to Ovral.

3) The Norlestrin users when switched to Norinyl reported a higher incidence of acne.

4) The incidence of breakthrough bleeding increased significantly when Ovral users switched to either Norinyl or Norlestrin. When Norinyl or Norlestrin users switched to Ovral, the incidence of breakthrough bleeding declined.

Another study is being undertaken in Seattle in which women using either Ovral or Norinyl 1/50, are switched to either Lo-ovral or Brecivon. The data on side-effects are being collected for comparison with the earlier comparative study at Seattle. This study will evaluate the results of crossover in the following four groups: Ovral to Lo-ovral, Ovral to Brevicon, Norinyl to Lo-ovral and Norinyl to Brevicon. The data collection for this study is scheduled to be completed in 1977.

2. Significance to AID Objectives

As AID continues to extend assistance to countries who wish to regulate their population growth, AID and these countries will wish to employ the safest and most cost-effective means to achieve their goals.

It is clear from study of fertility patterns and family planning programs that success of efforts to control fertility is highly dependent upon availablity of and technical advances in fertility control methods. It is also clear that the most successful programs have offered a variety of techniques, including post-conceptive means of fertility control. It is auspicious for the success of family planning programs that there are now a number of very promising new fertility control techniques which are ready or will soon be ready for clinical trials.

The IFRP has demonstrated its ability to carry out trials of diverse new methods under actual use conditions in a wide variety of countries and cultures particularly in LDCs. The IFRP worldwide network has evolved into the clinical testing resource for new and improved fertility control technology developed through IFRP, under other AID supported projects, and through other public and private agencies. Some of these methods of fertility control require long term follow-up of large numbers of cases to evaluate the risks and benefits in various LDC settings. IFRP is conducting the follow-up of these cases, which will extend into the continued program.

The IFRP permits high quality comparative clinical trials of new means of fertility control with maximum involvement of local contributors in LDCs whose institutions may assume increasing increments of responsibility for conduct of studies as experience is gained. Clinicians have been trained to be skilled investigators, and in several countries semi-autonomous fertility research programs have been developed to coordinate research in fertility control, a significant step in the transfer of technology.

Most contraceptive development work is focused in the more advanced countries with drug regulatory boards, patent protection and often in places which fit into the marketing strategy of pharmaceutical firms. For these reasons, methods which are potentially the simplest, safest, least expensive and most appropriate for LDC settings are frequently not pursued, and LDCs are relatively ignored as test sites.

In addition to continuing evaluation of improved fertility control methods, a smaller allied initiative will be pursued to develop and evaluate innovative delivery schemes to make these methods available and to increase user acceptability.

LDC studies of new means of fertility control are important for:

a. Determination of the value of new fertility control methods under use conditions in the countries where they must eventually be employed.

b. Determination if there are problems specific to the LDC setting which require developmental work. This work could go on concomitantly with that in the U.S. and Europe--rather than after the method is widely used or marketed.

c. AID to be able to satisfy the desires of major research elements in leading LDCs to begin work with the most advanced new fertility control techniques such as prostaglandins.

d. LDC participation in the research and developmental work on a new drug or method can be expected to greatly enhance the speed with which it can become accepted and operational in a national family planning

program. Any research effort which can speed up the acceptance timetable for a new means of fertility control is highly important.

e. If new fertility control technology results in a major shift in family planning strategy for delivery systems in LDCs, the sooner this new pattern emerges the better able to make long term plans and meet the needs of these new program requirements.

The IFRP has identified safe and effective methods for use in LDC family planning programs and disseminated information about these methods to promote their early utilization. Continued use of the demonstrated capabilities of IFRP will provide a cost-effective means of assuring a continued flow of information to AID and LDCs which may be used to make programmatic decisions. The conduct and evaluation of clinical trials, the dissemination of information, distribution of commodities, and the training which can be effected throughout the IFRP international network can play an integral role in implementing these decisions.

3. Relation to Existing Knowledge

Studies sponsored by AID and other agencies have resulted in a number of new means of fertility control. However, evaluation of their worth in the LDC setting is necessary and requires vigorous field testing under use conditions.

Contraceptive development depends upon three steps: (1) fundamental research in reproductive biology, (2) new product development including small scale, carefully controlled clinical trials for efficacy and safety, animal toxicology, drug formulation, establishment of manufacturing methods and standards, quality control and dealing with drug regulatory agencies, (3) broad scale clinical trials to prove acceptability and evaluate safety and efficacy. The IFRP concentrates on the third step in this procedure. This is frequently neglected by drug companies--they have no interest in seeking the best drug, just in marketing their own. Furthermore, in the second step, that of product development, there are many leads which deserve exploration which may not fit in with corporate policy of drug firms; for example, non-clinically based methods on which there is little chance of profit may not interest them; or, the clinical trials which this study will carry out may seem too expensive to warrant the investment. This is particularly true because of the intense scrutiny and additional testing required by the FDA for contraceptives compared to other drugs.

Therefore, this program serves the dual purpose of testing new methods of fertility control of little interest to manufacturers and accelerating the development of specific methods and compounds which are controlled by industry. Finally, it will provide objective comparisons between methods under LDC conditions--data which would otherwise be unavailable.

A brief discussion of the status of the six modalities of fertility control being studied is as follows:

A. Abortion. Considerable information now exists with respect to risks of first trimester surgical abortion; however, a number of new techniques for use in the second trimester including urea, new prostaglandin analogs and dilatation and evacuation require additional evaluation. New mechanical and pharmacologic means of cervical dilatation are, or will soon be, available which require testing. Pharmacologic means of later first trimester abortion do not appear to be promising.

B. Menstrual Regulation. Practically all of the presently available data on surgical menstrual regulation (i.e., termination of pregnancy at or close to the time of the missed menses) has been established by the IFRP. The efficacy and safety of various techniques of surgical menstrual regulation such as the mini-suction syringe is now reasonably well established. Menstrual regulation with

prostaglandins remains promising and additional studies of the method are needed. Pregnancy tests for use at the time of the first missed menses need testing.

C. Female Sterilization. Relative risk and complication rate of various procedures and surgical techniques in the LDC setting need study. Laparoscopic sterilization allows use of local anesthesia on an outpatient basis. Its major drawback is thermal trauma to abdominal structures when the tubes are occluded by electrocautery. The spring loaded (Hulka) clip and the Falope (Yoon) ring show great promise in surmounting this infrequent but serious side effect. These new methods need some additional testing in the LDC clinical setting. A number of new methods of tubal occlusion including sclerosing agents, cryosurgery, and plugs are likely to be ready for testing during the proposed continuation of this program.

D. Male Sterilization. Several new techniques of male sterilization, including sealing the ends of the vas with clips and fulgarization, and chemical injection of the vas, need comparative trial with the routine surgical techniques now in use.

E. IUDs. There are now a great variety of IUDs in existence and under development, both inert and containing active agents such as hormones and metals. Most of these IUDs need clinical testing on a small population (less than 1000 subjects) to obtain a preliminary assessment of their worth. Promising designs can then be entered into comparative trials. Additional clinical data on a variety of IUDs is needed to allow analysis to discover which design parameters are related to performance. Early removal for pain, bleeding, or a combination thereof is the single most important problem to solve. A number of bioactive IUDs containing, for example, anti-bleeding agents, hormones, or metals show promise in this regard and will be available for testing.

F. Systemic Contraceptives. AID assisted programs have reported great variations in the side effects and acceptability of various preparations provided to LDC family planning programs. There is a most urgent need for additional comparative studies to establish the rate of subjective side effects for different preparations in LDCs. Studies of other systemic contraceptives such as injectables are needed.

4. Relation to Other Research

The IFRP serves as the field trials network for a number of AID-sponsored research projects which have developed new or improved means of fertility control which are appropriate for clinical testing. These AID funded contractors and studies include the following:

Battelle Memorial Institute: Cooperation in early and in full scale clinical trials for:

a. Vas cautery, the Schmidt Technique and portable cautery unit

b. Evaluation of improved versions of the 50 cc menstrual regulation syringe with vacuum lock and accompanying cannulae

c. Evaluation of the new mechanical cervical dilatation device.

Cooperation with and feedback to Battelle on newly designed equipment and devices includes monitoring data at early trials, and site selection for full scale clinical experience and the analysis of data submitted on standard IFRP data collection instruments.

PARFR (Program for Applied Research on Fertility Regulation - Northwestern University): Close collaborative relationships exist between PARFR and IFRP. When a technique developed by PARFR is ready for broadscale trials, it is entered into the IFRP system. Current and planned studies of this nature include studies of IUDs and bleeding in Cairo and Germany, studies of the copper clad Lippes Loop IUD. A number of additional techniques may be to the point of requiring clinical trials in the near future.

Johns Hopkins University: Abortion studies involving new equipment and methods are recorded on IFRP forms to facilitate analysis and contribute to the IFRP data base.

Population Information Program (PIP - George Washington University): To date, IFRP research staff have cooperated with the PIP in reviewing selected reports and preparing subject area information. The production of IFRP Research Findings is very great, and close cooperation with the PIP will be continued to enhance the dissemination of these findings.

At present, the IFRP is the only large scale network for international comparative clinical studies involving LDCs. Other organizations have established clinical trial networks for individual method studies, including IUD studies sponsored by the Population Council and WHO-sponsored studies for prostaglandin injectables, and hysteroscopic sterilization. Drug companies continue to sponsor multi-center clinical trials but they are not comparative trials which would allow the selection of the best among several similar drugs or techniques.

5. Proposed Work Plan and Methodology

During the period covered by the current contract, IFRP has developed an international network of over 250 contributors who are knowledgeable,

closely linked, and skilled in the IFRP research system. These clinical investigators have been trained in research methodology and medical procedures, and are able to conduct standardized clinical trials resulting in reliable, high quality data. Several national and regional fertility research programs are in the process of being organized to coordinate the research activities, including the data collection management, in their geographic areas. Through this established network of individuals and institutions, IFRP proposes to continue research in newer methods of fertility regulation and in closely related activities which contribute to the objectives of AID.

Through previous support from AID, the Program has developed standard data collection instruments in six study areas: Pregnancy Termination, Menstrual Regulation, Female Sterilization, Male Sterilization, IUDs and Systemic Contraceptives. Computer programs have been developed for management of data in each study area and for editing data collected. In addition, standard tables have been developed to assist in analysis of data. These are in two parts; one set for patient characteristics which are similar across all study areas and a second set for the clinical findings in each study area. Instruction manuals for completion of each data collection instrument have been written. The instruments have been approved by the Medical Advisory Committee of IFRP., the AID Project Manager, and the IFRP Human Subject Committee.

IFRP will continue to utilize these standard forms to collect baseline data from new centers chosen as Contributors to the IFRP. This provides a learning period through a records dialogue during which the meaning of questions on the forms become understood. The data are useful for comparison of present fertility control methods with those introduced in straight (non-comparative) studies.

Straight studies of newer developments in fertility control will be initiated utilizing the same data collection instruments in centers that can assure a high level of follow-up and accurate recording of information. New methods are suggested by staff of IFRP, IFRP Contributors, PARFR, Battelle, pharmaceutical companies and other research and development centers. The methods are screened by the IFRP Medical Advisory Committee and the AID Project Manager.

When results of straight studies are not definitive, the method field tested will be placed in an IFRP comparative protocol. These protocols provide random allocation of method to patient and, as far as possible, separation of operator doing the procedure or providing the method and the evaluator or person providing for the patient's follow-up care. In this way, bias is reduced and study results can be relied upon. All comparative study protocols are approved by the IFRP Human Subjects Committee.

Major elements which are now considered to be the most significant program undertakings in the next contract period are:

(1) Continuing clinical studies of fertility control methods.

(2) Evaluation of impact fertility control methods

(3) Support of surgical contraception (sterilization) research and services

(4) Commodity procurement and distribution

(5) Information services.

A Clinical Studies

The bulk of the continuing program effort will continue to be clinical trials under LDC conditions in the following six areas:

(1) Pregnancy Termination: Over the last five years, abortion has gained increasing official acceptance as a method of fertility control. Documenting the safety and effectiveness of pregnancy termination methods when offered in a health care system continues to be of significant importance. New procedures which may be associated with lower morbidity and shorter procedure times must be tested. Additional study is needed to determine methods of cervical dilation which will reduce the trauma associated with this aspect of the procedure. Surgical methods such as dilation and evacuation for second trimester abortion should be further evaluated since early findings indicate that these procedures may be associated with less morbidity than pharmacologic procedures.

Comparative studies should be conducted to evaluate new developments in first trimester abortion, whenever they are ready for field testing. For example, the safety and efficacy of using prostaglandin analogs for the termination of first trimester pregnancies should be evaluated when satisfactory dose schedules and routes of administration have been defined.

It appears that cervical dilatation can be accomplished with vaginally administered prostaglandin. Comparative studies which evaluate mechanical methods, the use of hydrophyllic laminaria, and the use of prostaglandins for cervical dilatation should be conducted to determine the least traumatic methods.

Comparative studies to evaluate D&C, vacuum aspiration, or a combination of these two procedures, and prostaglandin analogs (intramuscular, vaginal or extraamniotic administration using various dose schedules) for terminating pregnancies at 13-15

weeks' gestation should be conducted. Also, studies should be initiated to evaluate whether it is safer to terminate pregnancies at 13 to 15 weeks' gestation by the above methods, or postpone the procedure until 16 weeks' gestation when intraamniotic procedures can be performed.

Straight and comparative studies should be conducted to evaluate the safety and effectiveness of first and second trimester abortifacients that appear to be safer and more effective than available procedures.

It has been documented that widespread availability of induced abortion is associated with declining rates of maternal morbidity and mortality. The long term effects of abortion on fertility and subsequent reproductive outcomes need to be studied more completely.

Studies to evaluate the management of second trimester abortion failures, and the optimum procedures for management of incomplete second trimester abortions should be initiated. The IFRP is currently developing a form to record the appropriate information in order to evaluate the management of second trimester abortion failures.

Initial reports by some investigators have indicated that dilatation and evacuation (D&E) procedures may result in fewer side effects for second trimester abortions than the pharmacologic termination procedures. IFRP plans limited studies to document comparative morbidity rates.

(2) Menstrual Regulation: Early trials of vaginal suppositories containing the prostaglandin analog 15(S)-15 Methyl $PGF_{2\alpha}$, appear promising in menstrual regulation. This proposal provides for the continuation of these studies. Research is now underway to produce a silastic wafer and melting vaginal suppositories as releasing mechanisms for the analog. As these devices have the potential of becoming a self-administered method, IFRP plans to introduce them into clinical trials for controlled evaluation. Other prostaglandins and their analogs should be evaluated for early abortion ($\leq$ 8 menstrual weeks' gestation) when practicable doses and routes of administration have been defined, especially those that may be self-administered.

The incidence of repeated MR procedures and their effects on subsequent reproductive history should be evaluated.

There is still a need for large (at least 1000 cases) surveillance MR 302 Studies ($\leq$ 2 weeks delayed menses). These studies may be

used to 1) evaluate changes in complication and failure rates over time, 2) document the incidence of specific complications, and 3) evaluate complication and failure rates in terms of various independent variables such as the patients' age, parity, length of amenorrhea, and vacuum source and cannula size. Three such studies would be desirable. A few large studies are preferred to many small studies, since there appears to be more variation in the inter-Center complication and failure rates than in the intra-Center complication and failure rates when type of vacuum source, cannula type and size, length of amenorrhea, etc., are controlled.

Comparative studies to evaluate the safety and efficacy of performing MR with different vacuum sources, and types and sizes of cannulae should be conducted whenever necessary. Each of these studies would have to be replicated 3-4 times to obtain adequate amounts of data for evaluation.

Additional studies in which progestins are administered for the induction of menstruation in non-pregnant patients are warranted. The number of these studies will depend upon the number of drugs to be evaluated. All studies should be replicated, preferably 2-3 times.

(3) Intrauterine Devices

Intrauterine devices (IUDs) are unique in that they offer an effective method of contraception that is easily reversible and coitus independent. In the decade of the sixties, lower pregnancy and expulsion rates were the main focus of attention in the development of new intrauterine devices. While still lower pregnancy and expulsion rates are desirable, the current focus has been in the reduction of IUD related pain and bleeding. Recently new IUDs have been developed which appear to be associated with less bleeding than previously marketed devices.

IFRP is currently engaged in the development of IUDs to reduce bleeding and for the early postpartum acceptor to prevent expulsion. Beginning with devices which have generally produced the least side effects and modifying them to achieve the desired effects, the prototypes have been placed in limited trials to determine the results of the modifications. These include (a) a medicated Lippes Loop designed to inhibit excessive IUD related bleeding, (b) a Lippes Loop with a soft flexible extension that enables the IUD to resist expulsion when inserted immediately postpartum, and (c) a tapered Lippes Loop and a reduced size Lippes Loop whose structural modifications are expected to improve both pregnancy and bleeding removal rates. Clinical evaluation of these IUDs

(their development funded under contract AID/pha-C-1111), and commercially developed devices which show promise of improved performance are provided for in this proposal.

Studies of excessive bleeding, the fundamental cause for the discontinuation of use, and its solution are a high priority investigation. Anti-metrorrhagic agents which could be incorporated into an IUD, can extend to many theoretic substances from steroidal hormones, catecolamines, vasoactive polypeptids, oxytocics, etc. to the antifibrinolytic agents

In many parts of the world, a woman's primary contact with medical personnel occurs with childbirth. Additionally, at this time, the woman is usually more highly motivated to accept some family planning method than at subsequent time periods. Unfortunately, because of the recently enlarged uterus, retention of IUDs is poor The device is either completely expelled or displaced away from the fundus. For this reason, methods of maximizing retention of IUDs should be explored. These include:

(a) Use of biodegradable extensions on the upper crossarm of the device

(b) A determination of the best techniques of inserting and positioning IUDs in the uterine cavity

(c) Use of biodegradable anchors

A further important role for the IFPF is the continued international surveillance of all new IUDs.

(4) Female Sterilization: IFRP proposes to continue its contribution to the development and clinical testing of surgical sterilization procedures.

Bipolar electrocoagulation equipment and the Waters Low Voltage Fallopian Tube Coagulator are available for testing. The use of bipolar equipment can be expected to reduce the incidence of bowel burns experienced with monopolar probes, but because the incidence of this complication is so low (5 in 5000 electrocoagulation cases reported to the IFRP) any statistically significant differences could only be demonstrated with a very large number of cases.

The Waters Low Voltage unit and the Wolf Endotherm-Coagulation instrument employ heat rather than electrical current to burn and sever the tube. Several studies of this equipment are recommended. New prototypes of clips and rings and of applicators for these devices should also continue to be tested and evaluated.

Additional development work is needed on methods of tubal occlusion suitable for application via the needlescope. Use of the prototype bipolar forceps for needlescope resulted in an unacceptably high pregnancy rate. Hopefully, within the next year other occlusive methods will be modified for use with the needlescope, but small scale Phase II studies will be required before such methods will be ready for large-scale field testing. The Olympus 4 mm laparoscope with a 2 mm operating channel and bipolar cautery forceps will be evaluated in future trials.

The IFRP is presently committed to the analysis of approximately 14,000 cases of minilaparotomy, involving both standard ligation techniques and tubal ring application as the occlusive methods. In addition to these studies utilizing standard IFRP forms, other studies are being initiated which utilize a special abbreviated form, primarily for evaluation of the AID minilap kits. Various ingenious modifications of the "minilap" procedure continue to be proposed. The particular type of procedure a physician selects will probably be based as much on personal preference as on the associated rates of difficulties and complications, but continued study will be needed to determine if there are significant differences in these rates among procedures. Additional studies, particularly on new modifications of the technique and preferably of a comparative nature, may be useful. Comparative studies of minilaparotomy and laparoscopy would also be of interest.

The IFRP is accumulating some data on vaginal procedures, both culdoscopy and colpotomy, with approximately 6000 cases involved. As many of these cases are in planned studies, few additional studies should be proposed until the results of these studies begin to come in. The only possible exception among straight studies would be tubal ring application via culdoscopy and colpotomy. There are several planned comparative studies of two or three occlusive techniques via culdoscopy or colpotomy, but comparative studies of culdoscopy vs colpotomy and of vaginal vs abdominal approaches are also suggested. Although such studies are not double-blind, they have all the other advantages of comparative studies.

Retrospective and prospective data on hysteroscopic electrocoagulation procedures are being collected on IFRP forms from Dr. Quinones. Evaluation of these data will determine whether additional studies of this procedure are warranted. Instillation of quinacrine hydrochloride, on various time and dose schedules, is also being evaluated on a limited basis. No other chemical/non-surgical methods for transcervical applications which are ready for field testing are known with the exception of methyl cyanoacrylate.

Protocols and method lists have also been developed for studies to evaluate different anesthetics for use with female sterilization

procedures. One such series of studies will be conducted through the Intergovernmental Coordinating Committee (IGCC) for evaluating the relative safety and effectiveness of various analgesia/anesthesia combinations in several types of sterilization procedures. The other involves study of intrauterine anesthetics in tubal ring application and possibly other procedures.

Studies to evaluate the long-term (2 years or more) sequelae of sterilization procedures, particularly pregnancy rates, the need for subsequent pelvic surgery, and menstrual pattern changes are needed.

(5) Male Sterilization: Improvement of techniques used in vasectomy, assessment of the safety and reliability of new equipment, and the development of chemical methods as adjuncts for contraception are aspects of male sterilization proposed for study. New equipment has been developed to cauterize the vas deferens and to produce effective and rapid occlusion.

Though use of chemical methods will require early phase development, a small number of studies suggest that antiandrogens, progestagens, and combinations of these compounds may be successful in suppressing fertility while maintaining libido. Vas flushing studies will be performed to accelerate reduction of viable sperm.

Several studies using ligation techniques are active and others are planned. These studies may be sufficient for their primary purpose, i.e., to collect baseline data and to test the data collection and processing systems.

Plans are underway to evaluate the Battelle Vaseal bipolar electrocoagulation unit, employing the Schmidt technique. These studies were delayed because of problems with the prototype equipment, but studies at several centers in the U. S. have now been initiated.

The IFRP plans to test the Vasector penlight unit, which employs a hot wire to thermocoagulate the vas.

Irrigation of the vas after vasectomy will be included in later studies. This technique could be important in programs in which it is difficult to perform subsequent semen tests and where men cannot be expected to use contraception until all sperm in the vas have been ejaculated.

One large (1000 case) retrospective study of ligation techniques with prospective follow-up is to be initiated soon. Other such studies should be considered to document the safety, effectiveness, and acceptability of male sterilization in geographic areas that have been slow to incorporate vasectomy in their family planning programs.

(6) Systemic Contraceptives: Oral contraceptives (OCs) continue to be a popular method of contraception in spite of side effects coincident with their use. This study area, the last and most complex to be developed by IFRP, includes several aspects which merit further investigation.

The continuation of comparative studies of OCs containing less than 50 µg estrogen with higher dose pills are important. The results would indicate whether the lower dose pills do cause less and less severe side effects, and thus would increase acceptability and prolong use of OCs.

Continuation of studies to measure the results of crossover from OCs containing 50 µg ethinyl estradiol or mestranol to those containing 35 µg ethinyl estradiol or less are important to determine side effects in Asian women. This will provide AID with research data on which it can base future commodity procurement.

Retrospective studies in England and the United States have established an association between OC usage and thromboembolic disorders. IFRP proposes to conduct case-control studies on usage of OCs in Asia where their use in family planning programs is quite prevalent. Feasibility of this type of study will be first tested by epidemiologic surveillance on hospitalized cases with thromboembolic disorders.

New compounds and types of systemic contraceptives are now in various stages of development. These include new long-acting injectables and non-hormonal oral contraceptives. These new formulations will need to be evaluated in terms of efficacy and associated side effects. IFRP is planning to introduce these types into clinical field trials as they become available. IFRP proposes a study to measure side effects and efficacy of Depo-Provera.

B. IFRP Evaluation Unit

IFRP proposes to employ several evaluation tools which compliment each other when used together or used individually to measure program effectiveness. The expertise in data collection and management which is available at IFRP can effectively be employed to develop reporting and analysis systems for population program evaluation. IFRP's family planning record systems involve three interrelated components. These are the Family Planning Clinic Record (FPCR) and record systems for the Community Based Distribution of Contraceptives (CBDC) and the study of feasibility of Household Distribution of Contraceptives. A pretest of the Family Planning Clinic Record is now in progress in Honduras and El Salvador. The IFRP Household Distribution Study has been under way for some months in Tunis and is being considered for use in other countries.

At the request of the Population Officer in El Salvador, IFRP has designed a system to collect data on the performance of the Rural Health

Penetration Project being conducted there. In this project, rural health aides have been trained to provide both health services and distribution of pills and condoms. The evaluation system will provide for compilation of performance indicators of the rural health worker as well as the incidence of treatment of specific conditions or clinic referral in a community. This system could act as an early warning system for an abnormal incidence of a given ailment in a community.

The Maternity Record, originally developed to collect denominator data for postpartum family planning programs has been expanded into a system which can determine not only the need for and acceptance of family planning services but can provide information on the quality of maternity care. As such it too can serve as an integral part of a health and family planning service. The Maternity Record form has been adopted by The International Federation of Gynecology and Obstetrics (FIGO) as its standard international form for the collection of data in affiliate member's hospitals.

C. Surgicenters

The IFRP now has established a close research relationship with over 250 Contributors who conduct quality field trials of newer development in fertility control. National groupings of Contributors are in the process of development. Almost all of the present Contributors work in the premier medical centers of their country which are already recognized as Research and Training Centers (RTCs). Affiliated with each RTC are several medical institutions--mostly urban, but some rural--that deliver fertility control services to the public.

In order to accelerate the introduction of improved techniques of surgical contraception, especially male and female sterilization, into national service programs, it is proposed that networks of Surgicenters be established around the RTCs. Training for the improved techniques, such as the tubal ring for female sterilization, or provision of a visiting surgical team, would be the responsibility of the RTCs, as would be the monitoring of performance of the Surgicenters.

It is proposed that IFRP have resources for a flexible program of support for the development of Surgicenters. In most cases, support will be based on performance in terms of expansion of services. Priority will be given to establishment of Surgicenters in rural health centers affiliated with the RTCs.

The Surgicenters will be used to study acceptability of various methods of surgical contraception under a variety of cultural settings. A protocol has been developed for such studies. They may also be used to expand numbers in effectiveness studies of methods of surgical contraception. A simplified sterilization report form designed for audit of Surgicenter services has also been designed.

D. Commodity Procurement and Distribution

As has been noted throughout this proposal, IFRP conducts research through clinical field trials conducted by its Contributors. When trials are initiated, needed equipment is placed on loan to the Contributor with sufficient supplies to complete the number of cases stipulated in the study design.

The Contributor recruits patients to participate in the study, frequently creating a demand for the procedure being tested. Study protocols often dictate particular patient characteristics for those to be entered into the study; sufficient supplies are made available for research patients only; those persons who do not fall within the study requirements must often be denied service due to a lack of supplies.

Upon completion of the study, the supplies provided by IFRP are usually depleted. If there is no justification for continued research, the clinician is placed in the unfortunate situation of receiving requests for a procedure which he can no longer provide.

When new methods are determined to be improvements over existing practice, they are developed commercially and/or placed into AID's commodity distribution system. As this process may take one to two years, there is frequently a long interval during which time Contributors must resort to methods which may produce greater side effects or less efficacy.

In the past few years, IFRP has observed the lack of equipment and/or supplies for proven techniques during the period of time required to develop normal distribution through existing channels. Approval and funding are sought through this proposal to provide supplies and equipment to Contributors and the Surgicenter networks to continue the availability of the new methods tested. This can prove to be the most effective method of dissemination of new fertility control methods, i.e., making them immediately available for service purposes.

E. Information Services

The Technical Information Service (TIS) is currently a part of the Carolina Population Center (CPC), the University of North Carolina at Chapel Hill. Among the major accomplishments of TIS have been the development of: (1) an automated bibliographic storage and retrieval system; (2) a thesaurus covering social science aspects of population studies; (3) a training program for LDC information specialists; (4) a technical assistance capability for development of information facilities in developing countries; and (5) a publications program which includes a quarterly journal, an international directory, and a library manual. While other organizations have undertaken similar individual projects, no other organization has done so many, at such a uniformly high level of quality, and in so coordinated an attempt to build an information-handling capacity in the information-poor countries of the developing world.

This accomplishment was made possible by the development of TIS as a unique type of information project, one not defined only in terms of information gathering. A TIS-type information project is one which identifies and evaluates certain information problems and then designs and implements solutions. This is done through the interaction of two distinct components: (1) an information gathering and organizing unit (i.e., a library system/information service); and (2) a problem-solving and project development unit, made up of people expert in analysis and design and supplemented by other technical personnel as appropriate. Funding for TIS is proposed for a three-year period during which time other avenues of support will be sought.

As it currently exists, TIS will not receive a level of funding which will allow it to continue to function at more than a minimal level after July 1, 1977. A program developed through an investment of approximately two million dollars from AID could become dismantled and thereby become non-functional.

IFRP has realized a need to provide technical assistance and information retrieval services to its network of Contributors. National and regional Fertility Research Programs now being established are particularly in need of the capabilities which could be extended by TIS. The recently established relationship between FIGO and IFRP opens communication channels to approximately 20,000 gynecologists and obstetricians throughout the world who could receive benefits or stimulation in population efforts through services extended by TIS.

It is proposed that selected elements of TIS be transferred to IFRP and that the data base be expanded to include biomedical materials which pertain to the field of population. The following elements of TIS can be successfully and usefully relocated to IFRP:

1. TIS data base and associated software
2. Selected relevant documents from the TIS library collection
3. TIS expertise and experience and appropriate materials and methodology
4. TIS familiarity with and leadership role in population information activities.

The CPC has agreed in principle with the transfer of TIS. It would continue to input materials to the data base providing continuity though it has been relocated. Information service and technical assistance will continue to be provided to the individuals and institutions previously served by CPC.

6. Researcher Competence

In the first five and one-half years of the IFRP the necessary facilities and staffing structure have been developed and personnel appointments made to carry the program forward.

Listed below are the professional personnel of IFRP, their titles and percent time working in the Program. Their place in the Organization Chart of IFRP can be seen in the Figure at the back of this project statement.

Name	Title	% of Time
ADMINISTRATION		
Elton Kessel, M.D.,M.P.H.	Director and Principal Investigator	75
Margaret Morrow	Studies Manager	100
Linda Lewis, M.A.	Editor	100
Robert McDowell	Assistant Editor	100
FIELD DEVELOPMENT		
Roger Bernard, M.D.,M.S.P.H.	Director for Field Epidemiology	90
George Stathes, M.S.P.H.	Associate Director	90
Dale Flexner	Assistant to the Associate Director	50
RESEARCH AND TRAINING		
Leonard Laufe, M.D.	Director	50
Gary Berger,M.D.,M.S.P.H.	Associate Director	50
Robert Wheeler	Staff Engineer	20
DESIGN AND ANALYSIS		
David Edelman, Ph.D.	Head	100
I-cheng Chi, M.B., Dr.P.H.	Epidemiologist	100
Judith Fortney, Ph.D.	Research Associate	100
Prem Talwar, Ph.D	Research Associate	100
Robert Taylor, M.P.H.	Research Associate	100
Michael Thomas, M.A.	Research Associate	100
Lynda Cole, M.A.	Research Associate	100
Alan Kay, M.A.	Research Assistant	100
Mary Jo Levinski, R.P.N.	Research Assistant	100
Margaret McCann, M.A.	Research Assistant	100
Meera Mitra, M.A.	Research Assistant	100
Sharon Page, M.S.P.H.	Research Assistant	100
Joy Wood, M.S.	Research Assistant	100

FIELD STUDIES

Alfredo Goldsmith, M.D.,M.P.H.	Acting Head and Area Coordinator	100
Pouru Bhiwandiwala, M.D.,FCPS DGO	Staff Gynecologist	100
Helen Compton Jensen	Field Studies Coordinator	100
Khairia Omran, M.D.,Dr.P.H.	Area Coordinator	100
Anjali Saha, M.D., M.P.H.	Area Coordinator	100
Javad Vakilzadeh,D.V.M.,M.P.H.	Area Coordinator	100
Christine Colven	Assistant Area Coordinator	100
Betsy Taylor	Data Collection Coordinator	100

DATA PROCESSING

Peter Harkins	Head	90
David Terwey	Deputy Head	100
Karen Ulberg	Lead Programmer	100
Samuel Gilbert	Computer Programmer	100
Frances LaPier	Supervisor of Data Processing	100
Catherine Roraff	Computer Programmer	100
James Smith	Computer Programmer	100
John Pittman	Computer Programmer	100
David Tolley	Data Processing Coordinator	100
Christopher Whitener	Systems Manager	100

The qualifications and duties of the key personnel from the above list are summarized as follows:

Dr. Elton Kessel has been the overall project director since the beginning of the program in 1971. He is a Public Health physician with many years of experience in field work. Prior to directing the IFRP, he was President of the Pathfinder Fund and Director of International Programs at the Carolina Population Center.

Dr. Roger Bernard, Director for Field Epidemiology, has also been with the program since its beginning. Previously he was project director of Pathfinder International IUD Program. Dr. Bernard will participate in the analysis of data and presentation of research findings. A significant portion of his time will be devoted to the initiation and monitoring of field trials. He will play a major role in introducing new areas of research through his contacts with government representatives of LDCs.

Dr. Leonard Laufe joined IFRP as Director of Research and Training in 1975. He is responsible for the direction of three divisions of IFRP-Field Studies Division, Design and Analysis Division and the Data Processing Division. Prior to joining IFRP, Dr. Laufe was Chief, Division of Obstetrics & Gynecology at Western Pennsylvania Hospital, Pittsburgh.

He also was Clinical Director of the AID-supported Advanced Technology Fertility Management Program at that hospital, providing practical training in latest fertility control methods to physicians from developing countries. Throughout his career he has been active in innovative medical equipment design and evaluation.

Dr. Gary Berger was recently appointed Associate Director for Research and Training, assuming the in-house responsibilities of the Director for Research and Training in his absence. He recently completed his residency in obstetrics and gynecology and has been appointed assistant professor of that department at the University of North Carolina. His professional experience includes two years as Epidemic Intelligence Service Officer, Family Planning Evaluation Division, Center for Disease Control, Atlanta. This experience will be beneficial in developing study designs, analysis of data and preparation of research reports. Dr. Berger will provide valuable input in research directions and procedures based upon his gynecologic training.

David A. Edelman, Head, Design and Analysis Division, is responsible for the development of study designs, protocols, and manuals. Upon completion of studies, staff within this division analyze study data, prepare Consultancy Reports which highlight significant findings, and write scientific articles on pooled data. Mr. Edelman, who has a Ph.D. in Biostatistics, joined IFRP as Staff Biostatistician in 1972, rising to his present position.

Dr. Alfredo Goldsmith is acting head of the Field Studies Division, which has responsibility for maintaining a continuous dialogue between IFRP North Carolina and the IFRP Contributor Network in the field. In addition, he will continue to function as Area Coordinator for Latin America. Before joining IFRP in 1973, Dr. Goldsmith had extensive experience in obstetrics and gynecology practice and population program evaluation in his native country, Chile, and subsequently served as Director of Medical Research and Development at the Pathfinder Fund and as lecturer and consultant in Population and Health Planning at Harvard University.

Mr. Peter Harkins as head, Data Processing Division, and Mr. George Stathes, as Associate Director for Field Development, have been key individuals under the Program. Both are well experienced, having joined IFRP in 1972, and will continue in these positions.

7. Contribution to Institution Building

The availability of an international group of experts to provide assistance and consultation will greatly enhance the development of institutional capabilities in the cooperating LDCs. Another important contribution to institution building will result from the stimulation of early clinical research work in LDCs with new means of fertility control. It is hoped that by including investigators from a

number of LDCs in these trials that their institutional strengths will be enhanced and the acceptability of this new modality increased so that if it proves valuable to LDC programs it will be incorporated in such programs early on.

Findings are always provided to the cooperating investigators for their own use and publications. This stimulates LDC publication and use of findings as does the involvement of LDC investigators in the program. A series of publications will receive wide distribution to maximize availability and utility of the trials.

An ultimate objective of IFRP is to transfer method development and field trial capability to LDCs. Considerable progress in this regard has occurred. Several autonomous or semi-autonomous country programs have been established and efforts to continue their development and assist with the establishment of additional country programs continue.

At present there are four established and operational country fertility research programs: the India Fertility Research Programme, the Sudan Fertility Control Association, the Bangladesh Fertility Research Programme, and the Programa Regional de Investigaciones en Fecundidad (PRIF) which was formed in Colombia. Other regional collaborative programs being considered are in the Middle East (Islamic Fertility Research Program), Korea, Thailand, the Philippines, Sri Lanka and Nigeria.

The Asia Fertility Research Programme (AFRP) is an active affiliation of IFRP contributors in the six member countries of the Inter-governmental Coordinating Committee of Southeast Asia (IGCC). Contributors in three of the IGCC countries (Thailand, Indonesia, Philippines) are moving forward plans for individual country programs which will be affiliated with the IGCC/AFRP.

An important contribution to institutional development results from IFRP training programs. The IFRP provides training in the areas of improved research techniques, data collection, and analysis of data to further develop the field testing and reporting skills of contributors. The IFRP also provides clinical training in the newer methods of fertility control and in the methodology to conduct clinical trials.

As promising methods and techniques become evident, IFRP will conduct conferences to provide training and discuss in depth the new developments in the area of fertility control. These conferences are anticipated to be held in conjunction with other population programs.

8. Utilization Plans

In some sense the entire project is structured to ensure early acceptability and utilization in LDCs as well as test the value of this means in the LDC setting. It is probably fair to say that results of research carried out by leading LDC investigators in the LDCs will be translated into action sooner than if all research were confined to the U.S. and Europe.

Early dissemination of research results from IFRP and its affiliated national fertility research programs will continue to be accomplished through reports to conferences and publications in scientific journals including the International Journal of Gynaecology and Obstetrics which is now the official organ of IFRP as well as FIGO.

IFRP will also continue to participate in dissemination of research findings by contributing both current data and information for articles in the Population Report Series of The Population Information Program at George Washington University. The cooperative efforts of these two organizations are expected to lead to the publication of the most current information on fertility control techniques, methods and devices.

9. Budget Analysis

A recent Ford Foundation sponsored report estimates costs for developing a single new fertility control method have about tripled in the past 15 years--now totaling $5-15 million per method.

In the scheme of contraceptive development, clinical trials are usually the most expensive step. Dr. Djerassi, former director of Syntex Research, writing in Science estimated a cost of about $800,000 to complete clinical trials on a single method. Over the three years, 1969-1971, AID spent approximately $1.5 million to thoroughly evaluate less than a dozen IUDs in the International IUD Program.

The present program uses the same backup group for data processing and analysis for each of the methods tested. This is considerably more economical than using a separate analytic group for each method, and of course it is more economical to provide centralized data processing for the network of collaborating clinics at a single point. Therefore, there is no provision made for clinical studies in other AID-sponsored contraceptive development contracts; the IFRP provides this support. Considering the great expense of contraceptive clinical trials, the budget proposed is not excessive. The additional special studies, when integrated into this program, will be completed at considerably less than it would ordinarily cost.

The IFRP has requested funds for a larger program than AID may be able to support. While the proposing office supports and requests RAC approval of the proposed level of funding, it recognizes that a smaller scope of work may be necessary with reductions of as much as $1 million annually a distinct possibility.

A summary of the budget follows:

INTERNATIONAL FERTILITY RESEARCH PROGRAM
CONTINUING CONTRACT PROPOSAL
7/1/77 to 6/30/82
(RESEARCH AND SERVICE)

	7/1/77-6/30/78	7/1/78-6/30/79	7/1/79-6/30/80	7/1/80-6/30/81	7/1/81-6/30/82	Total
Salaries	**$1,874,020**	$2,084,988	$2,333,803	$2,576,575	$2,794,844	**$11,664,230**
Fringe Benefits	402,914	448,272	501,768	553,964	600,391	2,507,809
Total	**$2,276,934**	$2,533,260	$2,835,571	$3,130,539	$3,395,735	**$14,172,039**
Overhead	1,265,046	1,416,220	1,543,453	1,676,892	1,817,288	7,718,899
Consultants	43,400	46,100	60,600	60,600	50,900	261,600
Trainee Travel	19,140	13,520	7,900	10,210	13,520	64,290
Domestic Travel	38,950	41,320	43,990	46,750	49,700	220,710
Foreign Travel	225,452	231,900	249,000	262,900	277,500	1,249,752
Equipment	45,600	43,400	49,500	69,800	66,700	275,000
Supplies	43,260	45,900	48,600	51,100	54,300	243,160
Data Processing	225,000	247,500	272,250	299,475	329,425	1,373,650
Equipment Rental	31,233	25,800	27,000	28,300	29,500	141,833
Telephone - Long Distance	25,000	27,500	30,000	32,500	35,000	150,000
Miscellaneous	32,900	34,700	36,500	31,800	33,400	169,300
Data Purchases	555,780	532,800	481,500	494,500	507,000	2,571,580
Subcontracts	55,000	55,000	55,000	55,000	30,000	250,000
Printing and Binding	62,000	68,000	73,000	75,000	70,000	348,000
New Drugs and Devices	51,000	54,500	58,500	62,500	67,000	293,500
Business Meeting Expenses	2,800	3,350	3,750	4,150	4,600	18,650
Commodities	500,000	550,000	600,000	650,000	700,000	3,000,000
Technical Information Services	106,000	112,700	119,500	131,300	137,100	606,600
Surgi-centers	641,600	1,511,200	988,000	1,025,000	1,075,000	5,240,800
Subtotal	6,246,095	7,597,670	7,583,514	8,198,316	8,743,668	38,369,363
Fixed Fee	100,000	100,000	100,000	150,000	150,000	600,000
Total	$6,346,095	$7,697,670	$7,683,614	$8,348,316	$8,893,668	$38,969,363

10. Internal and External Review

These reviews are in process and will be reported on when completed.

A formal AID evaluation of the program was carried out in the fall of 1975 by a four person team. It was the general concensus of findings by that evaluation team that

"1. IFRP has made a distinctive and unique contribution toward international comparative studies of advanced techniques of human fertility management.

"2. The primary objectives of the project have been met with an overall high degree of effectiveness--these being:

a. Scientifically field testing promising developments in fertility regulation.

b. Shortening the time between development of new methods of fertility regulation and their implementation into general clinical practice.

c. Disseminating information on research findings internationally.

Some flaws, mostly administrative in nature, were noted by the evaluation team during its examination of the project activities. Measures have been initiated to correct these instances through procedural changes on the part of the contractor and AID monitorship. For the most part, these problems, relatively minor, have been satisfactorily remedied.

11. General Evaluation

The proposing office considers this program to be one of its most successful. It is the largest single population research program supported by AID--a reflection of Agency priority and evaluation of performance of the program. Its continuation is strongly urged.

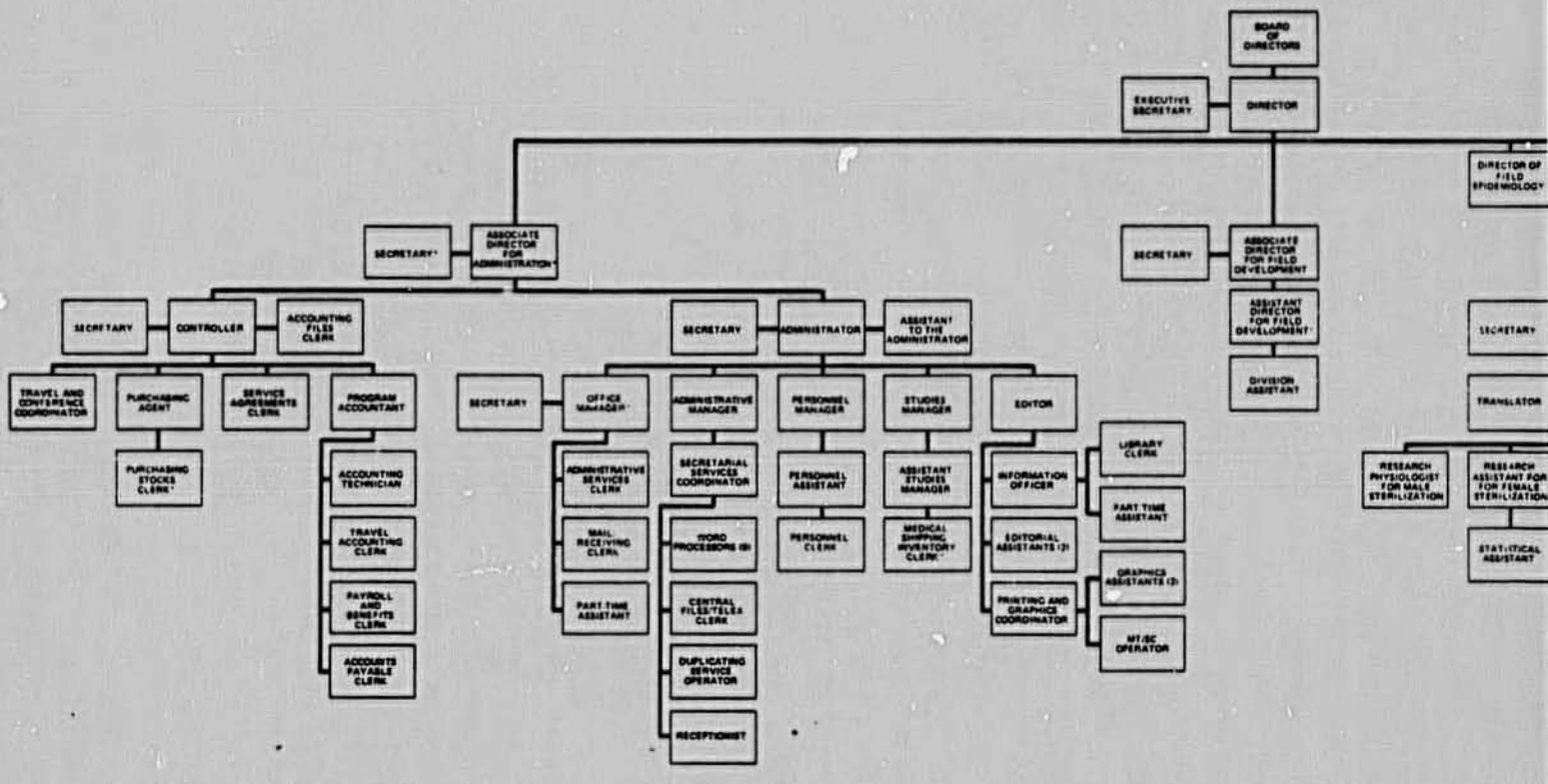
J. J. Speidel 12-14-76
Signature of Monitor - J. J. Speidel

Signature of R. T. Ravenholt
Director, Office of Population

M. I. Dobrovir
Signature of Monitor - M. I. Dobrovir

Signature of Fred O. Pinkham
Assistant Administrator for PHA

INTERNATIONAL FERTILITY RESEARCH PROGRAM
ORGANIZATION CHART



INTERNATIONAL FERTILITY RESEARCH PROGRAM
ORGANIZATION CHART