

9320537-①

PD-AAA-273-F1 PROJECT STATEMENT

Date: January 15, 1981

A. PROJECT SUMMARY

1. Statistical

Project Title: International Fertility Research Program (IFRP)

New or Extension: Extension

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

Principal Investigator: Dr. Malcolm Potts

Duration: 15 years, 5-year extension requested

Total Estimated Cost: \$46,294,605

Amount Requested for RAC Approval: \$21,003,729

Funding by Fiscal Years:

FY 71	3,106,000	FY 78	3,200,000
FY 72	1,800,000	FY 79	3,400,000
FY 73	0	FY 80	3,000,000
FY 74	1,499,610	FY 81	3,629,093
FY 75	2,695,000	FY 82	3,902,320
FY 76	3,000,000	FY 83	4,180,291
TQ	0	FY 84	4,482,114
FY 77	3,590,266	FY 85	4,809,911

Project Officers: James D. Shelton, DS/POP/R
Maria E. Mamlouk, DS/POP/R

B. EXPANDED NARRATIVE STATEMENT

1. Introduction and Background

The International Fertility Research Program (IFRP) is a nonprofit corporation, incorporated under the laws of North Carolina and located in the Research Triangle Park, North Carolina. The IFRP was founded in July 1971 to continue the work of the Pathfinder Fund in the international evaluation and testing of contraceptive methods. In 1971, the IFRP was administratively attached to the Carolina Population Center, University of North Carolina at Chapel Hill. The sole support for the IFRP came from a five-year research Contract (AID/csd-C-2979) from the Agency for International Development (AID). Under this contract the work of the IFRP expanded, and within two years the IFRP had developed into one of the world's foremost research organizations to evaluate contraceptive effectiveness and safety. By mid-1974 it became apparent to both the IFRP and the University of North Carolina that the administrative needs of a dynamic research organization, such as the IFRP, could not be met by the University of North Carolina. The IFRP, AID and the University of North Carolina mutually agreed that the IFRP should become an independent organization, separate from the University of North Carolina. The IFRP began to function as an independent nonprofit organization in February 1975 under an independent Board of Directors.

The IFRP's five-year Contract (AID/csd-C-2979) was extended for one year and, in 1977, the IFRP received from AID a one-year Contract (AID/pha-C-1172) later extended for three additional years. This contract will expire on 31 July 1981.

The primary research objectives of the IFRP have been to:

- a. conduct clinical field trials of various existing, new or improved contraceptive methods in order to evaluate their

safety and efficacy under actual use conditions in different cultural and clinical settings;

- b. conduct the necessary clinical studies required for the development of new contraceptive methods that are likely to be appropriate for developing countries;
- c. analyze existing data to evaluate issues related to contraceptive safety and use;
- d. conduct the necessary studies to evaluate the relative risks and benefits of different contraceptive methods and their safety;
- e. aid in the development of fertility control related equipment that may prove to be useful in the provision of contraceptive services;
- f. evaluate contraceptive methods that might significantly increase user and provider acceptability; and
- g. disseminate information and technology on new and improved methods of contraception.

Recognizing that the IFRP's research objectives were not necessarily the same as those of its associated investigators, in 1977 the IFRP sought and was awarded a grant by AID (AID/pha-G-1198) to develop and fund work that fell outside the scope of its research contract with AID. The grant provided funds for some work that was initially performed under the AID research contract, including the development of national fertility research programs and the conduct of studies that have programmatic rather than research significance. The grant has also enabled the IFRP to transfer the knowledge and skills it has acquired relating to contraceptive research to developing country individuals and institutions. Some of these programs now have the capability for conducting all aspects of the research necessary to meet their needs as well as those of the IFRP's research program. The addition of the grant to

the IFRP's sources of funding has allowed the organization to provide a sharper focus to its program of clinical research.

In September 1977, a comprehensive evaluation of the IFRP program was made by the Research Division of the Office of Population and by a subcommittee of the Research Advisory Committee (RAC) to AID. Recommendations made by both groups resulted in a restructuring of the IFRP's scope of activities and its research goals and the changes recommended by these evaluation teams have been implemented. In March 1978, a major reorganization of the IFRP occurred. The IFRP staff was reduced from 135 to 106; its administrative, support and research components were restructured to increase operating efficiency, the internal committee structures and approval mechanisms were revised, research efforts no longer pertinent to the objectives of AID were cancelled, and the IFRP's activities funded by the AID contract and grant were separated administratively. Additional changes continue to be made to the IFRP's organizational structure and operating procedures to increase efficiency and to make maximum use of the skills and professional expertise of its staff. These changes have significantly increased the scientific outputs of the IFRP and reduced overhead expenses.

In 1979 the program audit team from the Office of the Auditor General reviewed the IFRP's operations. The findings and recommendations made by the program audit team are contained in a report (number 80-39) from the Office of the Auditor General. Recommendations made by the audit team have been reviewed and followed up.

The IFRP is a nonprofit organization registered in the State of North Carolina. The Board of Directors currently consists of seven individuals of four nationalities and has both an Executive and Audit Committee (Appendix A). A Technical Advisory Committee exists to review IFRP's overall research program (Appendix B). The membership and function of this committee are currently being updated. All research proposals and all voluntary consent forms

used by the IFRP are carefully reviewed by its Protection of Human Subjects Committee (Appendix C).

The IFRP is now the leading specialist organization in the world working in the field of clinical research relating to contraceptive use and development. It receives numerous requests from around the world for data and information relating to the safety and efficacy of contraceptive methods, requests to participate in IFRP research projects and requests for the funding of projects. The expertise and efficiency of the IFRP in conducting clinical contraceptive research is also attested to by the fact that it has conducted research for major drug companies and has been awarded contracts by NIH to conduct clinical trials of two new barrier contraceptive methods. The IFRP has also solicited and received support from philanthropic organizations interested in family planning.

At the present time, the IFRP is conducting, under its contract to AID, studies in the following contraceptive-related areas:

- a. Female sterilization
- b. Intrauterine device contraception
- c. Steroidal contraception
- d. Male sterilization
- e. Barrier contraception
- f. Menstrual regulation/pregnancy termination

Within each of the areas listed above, a diversity of studies are conducted. Some studies cut across all areas. The IFRP conducts clinical trials of a single contraceptive method and comparative studies of two or more methods. The IFRP also conducts epidemiologic investigations into the short and long-term safety of contraceptive methods currently in use based on data previously collected by the IFRP and by others.

This proposal requests support for the IFRP to:

- a. continue research work currently supported by Contract AID/pha-C-1172;

- b. develop and conduct appropriate clinical studies to evaluate the safety and efficacy of existing and new contraceptive methods;
- c. support epidemiologic investigations of events that potentially limit the use of particular contraceptive methods or raise questions regarding their safety;
- d. support the development of new and improved contraceptive methods;
- e. investigate the effects of local cultural and medical practices, taboos or laws that might limit the use of contraceptive methods or make them unavailable to those who most want them;
- f. conduct phase IV (postmarketing) trials to further evaluate long-term contraceptive safety; and
- g. conduct other studies to investigate issues related to contraceptive safety, efficacy and acceptability.

These studies will be conducted within the present administrative and scientific framework of the IFRP, with the available equipment and facilities and with the existing level of staffing. The IFRP will place particular emphasis on the transfer of technology overseas and the reinforcement of national research activities.

The IFRP keeps abreast of ongoing work in the proposed areas of research and will not duplicate the work of other organizations. In particular, it will work closely with other AID-funded organizations to conduct studies that are most pertinent to the overall objectives of AID. The work of the IFRP will continue to advance current knowledge related to the safety and efficacy of contraceptive methods. It is expected that the proposed work of the IFRP will have significant impact on the contraceptive-related policies of developing countries, on the provision of safe and effective contraceptive methods in these countries and on the overall well-being and betterment of women and their families.

2. Research Accomplishments Under Contract AID/pha-C-1172

Research conducted by the IFRP through its contract from AID has contributed to significant improvements in the provision of safe, effective, acceptable and less costly contraceptive methods and the development of improved methods of fertility regulation. The IFRP has built-up an international network of collaborators that is one of the most important and irreplaceable assets of the organization. The IFRP has worked with over 267 investigators in 47 countries. At the present time the IFRP conducts research with 78 investigators including medical school deans, chairmen of large obstetrics and gynecology departments, doctors working in peripheral health centers and doctors in private practice in large cities and rural areas. Special efforts have been made to involve collaborators who have access to and who work with paramedical workers and traditional health personnel.

The IFRP's research efforts to evaluate new and improved techniques of female sterilization have significantly reduced the time required before these improved methods become widely used. The IFRP has one of the largest bodies of data on female sterilization (over 50,000 cases) and is thus in a unique position to answer questions relating to the short- and long-term effects of different methods of tubal occlusion. The IFRP's extensive evaluations of the tubal ring, applied either by laparoscopy or minilaparotomy, have considerably reduced the time required for this method to be widely used around the world, thereby providing a safer method of sterilization compared to the use of electrocoagulation for tubal occlusion.

The IFRP has made major strides toward the development of a nonsurgical procedure for female sterilization through the intrauterine placement of quinacrine hydrochloride. The IFRP hopes that it will soon have a practical nonsurgical sterilization procedure that will be suitable for wide-scale phase III clinical trials and eventual use by paramedical personnel.

Recognizing that all commercially available IUDs are associated with high expulsion rates when inserted in the puerperium, the IFRP has devoted considerable resources to the development and evaluation of modified IUDs suitable for immediate postpartum use. Trials of these IUDs--the Delta-Loop and Delta T--indicate that their use significantly reduces the high expulsion rates of the standard Lippes Loop and TCU-220C, without significantly affecting the rates of other events associated with the use of IUDs.

The IFRP has documented the safety and effectiveness of the menstrual regulation (MR) procedure (a procedure to evacuate the uterus of a woman suspected of being pregnant). The MR procedure is now accepted and performed widely throughout the developed and developing world. The IFRP's research demonstrated that MR is safer and often more acceptable than abortion at a later gestational age.

The following sections summarize some of the research findings from completed work supported by Contract AID/pha-C-1172.

Voluntary Female Sterilization (FS)

On a world level, voluntary sterilization is now the single most common method of family planning. However, it continues to be technically difficult to make current methods of female sterilization available in certain areas where demand is great. The IFRP has worked hard, and continues to strive, to simplify and increase the safety of voluntary sterilization.

As of September 1980, data on 52,407 female sterilization procedures have been collected by the IFRP; 31,626 were interval sterilizations; 13,819 were postpartum sterilizations; and 6,962 were postabortion sterilizations. These figures represent the largest data bank on voluntary sterilization in the world and it is being intensively exploited. Table 2.1 gives the type of procedure performed by patient category. Many of the studies collected baseline data on various approaches and techniques.

TABLE 2.1

Number of Female Sterilization Cases
October 1, 1980

	Interval	Postabortion	Postpartum	Total
Culdoscopy				
Ligation	1,372	111	36	1,519
Tantalum Clip	734	74	38	846
Tubal Ring	110	0	0	110
Other*	178	27	3	208
Total	2,394	212	77	2,683
Colpotomy				
Ligation	1,111	1,061	54	2,226
Other*	72	23	2	97
Total	1,183	1,084	56	2,323
Laparoscopy				
Electrocoagulation	10,450	1,282	592	12,324
Thermocoagulation	283	35	1	319
Hulka Spring-Loaded Clip	1,553	568	171	2,292
Rocket Spring-Loaded Clip	648	39	7	694
Tubal Ring	5,496	1,482	760	7,738
Other*	299	56	14	369
Total	18,729	3,462	1,545	23,736
Laparotomy/Minilaparotomy				
Ligation	5,679	1,732	10,120	17,531
Tubal Ring	2,270	318	1,739	4,327
Other*	369	142	227	738
Total	8,318	2,192	12,086	22,596
Open Laparoscopy				
Tubal Ring	917	10	54	981
Other*	6	0	0	6
Total	923	10	54	987
Suprapubic Endoscopy				
Tubal Ring	79	2	1	82
Total	31,626	6,962	13,819	52,407

*Includes technical failures.

Of these studies, 57 have been completed, 9 are active, and 25 will begin within the next year. Other studies were part of clinical trials in which approaches and/or techniques were randomly assigned to women requesting a sterilization procedure. Of these comparative studies, 39 are complete, 10 are active and 6 will be implemented in 1981.

Since August 1977, the IFRP has developed new research admission and follow-up forms on which to collect sterilization data. Baseline data have been collected on various procedures and techniques, including laparotomy, colpotomy, laparoscopy, culdoscopy, and minilaparotomy approaches, and Pomeroy, electrocoagulation, tubal ring and spring-loaded clip techniques of tubal occlusion. The following summarizes results from female sterilization studies:

Procedure Evaluations

1. Laparoscopy: Prototype Spring-loaded Clip vs KLI Tubal Ring. The ease of performance, safety and effectiveness of these techniques was evaluated in a comparative study of interval patients. The technical failure rates were low (<1% of the procedures). The pregnancy rate for the prototype spring-loaded clip was significantly higher than that of the tubal ring. Rates of difficulties at surgery were similar for both groups of patients. Tubal transection occurred in 2% of the tubal ring patients. The severity of pain reported by patients during sterilization was significantly higher for the tubal ring procedures.
2. Laparoscopy: El-Kady vs KLI Tubal Ring. Technical failure, complication and pregnancy rates were similar for the two techniques.
3. Culdoscopy: Weck Clip vs KLI Tubal Ring. The Weck clip was associated with a significantly higher pregnancy rate than the KLI tubal ring. Rates of other events were similar.

4. Minilaparotomy: KLI Tubal Ring vs Modified Pomeroy. Technical failure, complication and pregnancy rates were similar for the two techniques when performed in interval, postabortion and postpartum patients.
5. Minilaparotomy: Rocket Spring-loaded Clip vs KLI Tubal Ring. In one comparative study, the tubal ring had a significantly higher rate of technical failures than the spring-loaded clip in interval patients; in a second study, the rates for the two techniques were similar.
6. Minilaparotomy vs Culdoscopy: Modified Pomeroy. In a comparative study of interval patients, the rate of surgical difficulties was significantly higher for culdoscopy than minilaparotomy. Surgical and follow-up complication rates were similar for the two procedures. No pregnancies were reported for either group.
7. Open vs Closed Laparoscopy with the KLI Tubal Ring. In a comparative study of these two approaches in interval patients, technical failure, complication and pregnancy rates were similar.
8. Laparoscopy vs Minilaparotomy: Rocket Spring-loaded Clip. A study with random allocation of study procedures to subjects showed no difference in technical failure, complication and pregnancy rates between the two approaches. In an analysis of pooled data both laparoscopy and minilaparotomy were demonstrated to be safe, effective and efficient procedures that can be performed on outpatients under local anesthesia.

In most clinical settings, minilaparotomy with the ligation method of tubal occlusion is superior to laparoscopy and to minilaparotomy with the application of mechanical occlusive devices.

The IFRP's research suggests that laparoscopic sterilization should be performed only in institutions where the number of

laparoscopic procedures (including diagnostic laparoscopy, laparoscopic sterilization and other operative laparoscopic procedures) is sufficient to make the purchase and maintenance of equipment cost-effective and to ensure that the laparoscopic surgeon and auxiliary personnel maintain a high level of skill. Even in institutions that meet these conditions, minilaparotomy may be preferred by the medical personnel or the patients because it minimizes the risk of major complications. If laparoscopy is performed, the mechanical occlusive devices are preferred for tubal occlusion because of the potential hazards of electrocoagulation.

9. Room Air Insufflation. The use of room air insufflation during laparoscopic sterilization considerably simplifies the equipment needed for the procedure, making it more appropriate for use in the developing world. Preliminary results in interval patients showed that the complication rate using room air is the same as with high-pressure gas.
10. Topical Anesthesia. Two comparative studies evaluated pain associated with or without the application of topical anesthesia to the fallopian tubes during sterilization. Preliminary results indicate that the use of topical anesthesia significantly reduces the incidence of pain as perceived by both patient and physician during the procedure and in the recovery period.

Equipment Evaluation

1. Tubal Rings. KLI and Dyonics tubal rings were applied in interval patients via minilaparotomy in a comparative study. Rates of surgical difficulties and surgical complications were similar for the two ring groups.
2. Water's Thermocoagulation Unit. The equipment functioned properly during the procedures and no equipment-related surgical complications were reported. The heating of the tissues

impaired the surgeon's vision briefly. Thermocoagulation performance was satisfactory in all cases. There were few postoperative complications.

3. KLI Laprocator. Ten studies were conducted to evaluate the laprocator, a simplified laparoscope designed by KLI. Some investigators participating in the laprocator studies reported equipment problems to the IFRP. As a result, modifications were made and it was sent to the field for further study. Because of complaints that the original grasping tongs were not completely in the field of vision, the angle of the tongs was changed to permit direct vision by the surgeon throughout the whole procedure. A longer laprocator was evaluated and found to be as easy to use as the standard instrument in normal cases, but to have advantages for obese women.

Sequelae of Sterilization

1. Timing of Postabortion Sterilization. Patients who underwent sterilization immediately after a first trimester abortion had similar rates of complications as women sterilized one or more days postabortion.
2. Incidence of Pain. Data from five comparative studies show a relationship between the technique of tubal occlusion and pain experienced by patients both at the time of the procedure and during the recovery period. During the procedure, the spring-loaded clip is the technique least likely and the tubal ring the technique most likely to be associated with pain. During the recovery period, both of these occlusive devices are associated with higher rates of abdominal and/or pelvic pain than is electrocoagulation. Differences in pain that occurred during the recovery period did not persist to the early follow-up visit.
3. Technical Failures. The tubal ring is associated with a higher incidence of technical failures (cases in which the procedure

cannot be completed as planned) than electrocoagulation, the Rocket clip or the modified Pomeroy techniques. The risk factors for technical failure include obesity, previous IUD use and previous abdominal surgery.

4. Risk and Outcome of Pregnancy after Sterilization. Women who are sterilized in the early phases of a service program, who are young or who delivered a child at the time of sterilization, have a higher risk of sterilization failure. Laparoscopic electrocoagulation has a reduced risk of pregnancy when compared to the mechanical occlusive devices but has a risk of ectopic pregnancy, among women who become pregnant, at least nine times higher than that of other techniques. Operator error was the major reason for sterilization failures.
5. Menstrual Pattern Changes. Changes in menstrual cycle length, duration and amount appear to be associated primarily with the contraceptive method used before sterilization and not with the sterilization procedures per se. Women who had used IUDs were more likely than others to have a decreased amount of flow two years following sterilization. Conversely, more women who had used orals were more likely than users of other methods to change from a regular to an irregular cycle length by two years poststerilization. No significant changes were detected among patients using conventional contraceptives or no contraceptive method.

Nonsurgical Sterilization with Quinacrine Hydrochloride

While simplifying surgical sterilization, the IFRP has also given priority to the study of a nonsurgical method of female sterilization, which, if perfected, may be more acceptable to women, may be associated with less risk than surgery and should be appropriate for use by trained auxiliary workers.

As of September 1980, the IFRP had obtained data on 460 female sterilizations by the transcervical insertion of quinacrine

hydrochloride. The following summarizes the IFRP's considerable work on nonsurgical female sterilization that has been accomplished since August 1977:

Since the late 1960s, Dr. Zipper in Chile has experimented with the passage of quinacrine solutions through the cervix in an effort to achieve tubal occlusion. However, there was a high failure rate with a need for repeated applications and some volunteers suffered a transient toxic psychosis.

From January 1977 through June 1978, 139 women at an outpatient clinic in Santiago, Chile, received transvaginal insertions of quinacrine pellets preceded by a single pellet of 20 mg of sodium thiopenthal as their only means of contraception. The results obtained from this study indicate that the pellet method of quinacrine insertion was more acceptable than the solution and the high pregnancy rate associated with the quinacrine solution instillation procedure that occurred in the month between the first and second instillation was greatly reduced with no toxic psychoses reported.

The IFRP is currently evaluating the safety and effectiveness of the transcervical insertion of quinacrine hydrochloride pellets without the added sodium thiopenthal pellet as a method of nonsurgical female sterilization.

As a first step, twenty-three volunteers who were scheduled for hysterectomies due to uterine prolapse voluntarily accepted the intrauterine insertion of 250 mg quinacrine pellets.

Hysterectomies were performed one month postinsertion, and the intramural portions of the tubes were examined. In more than 50% of the tubes, a definite sclerosing lesion of the tubal lumen was identified. As a second step, a regimen of three insertions at monthly intervals was devised and 262 volunteers seeking permanent sterilization were recruited at three clinics. Five pregnancies have been reported; three before completion of the insertion schedule and two after completion of the insertion schedule.

Blood and saliva samples were obtained from 11 women who underwent pellet insertion; samples are being analyzed to determine the amount of quinacrine in the saliva and blood within 48 hours following insertion of the pellets.

In an effort to further simplify nonsurgical sterilization and occlude the tubes with a single procedure, the IFRP developed a method of adding a quinacrine mixture to the arms of a plastic IUD in order to localize the effect, reduce the total dose and attempt to secure tubal occlusion by a single procedure. The quinacrine mixture dissolves within four hours. A number of studies on quinacrine-loaded IUDs inserted in menstruating women awaiting hysterectomy for uterine prolapse are now being carried out. The extirpated uteri are being examined to determine the presence of sclerosing lesions in the intramural portion of the tubes. In the first series of eight cases, 50%-60% of the tubes were occluded. Modifications were then made in a further 17 cases and in the most recent (November 1980) series of 16 specimens, 90% tubal occlusion has been achieved. Further modifications of the vector are under study, which should lead to a still higher success rate.

With support from the IFRP, investigators at the Johns Hopkins University are currently studying the toxicology and teratology of quinacrine. The studies will provide information necessary to obtain a Claimed Investigational Exemption for a New Drug (IND) for the use of quinacrine hydrochloride as a sclerosing agent. A related subcontract was awarded to the University of North Carolina School of Pharmacy to prepare quinacrine pellets with varying dissolution rates.

The data obtained from toxicologic and teratologic work will be used in the preparation of the IND for submission to the US Food and Drug Administration so that the IFRP may continue this most important piece of coordinated research to its next state in the United States and other countries.

Intrauterine Contraception

Although intrauterine devices (IUDs) have many advantages in family planning, results from studies on their use on a large scale have been uneven and the IFRP is pursuing several complementary lines of research to measure acceptability, document possible risks and improve IUD performance.

As of September 1980, data on 66,769 IUD insertions have been collected in IFRP studies; 45,845 were interval, 8,677 were postabortion and 12,247 were postpartum insertions (Table 2.2). Many of the studies collected baseline data on various IUDs; of these, 139 have been completed, 10 are active and 31 will be implemented in 1981. Other studies were part of clinical trials in which IUDs were randomly assigned to women; 41 have been completed, 33 are active and 30 will be implemented in 1981.

TABLE 2.2

Number of Intrauterine Device Cases
October 1, 1980

IUDs of Past Research Interest	Interval	Post Abortion	Post Partum	Total
Antigon	414	15	15	444
Dalkon Shield	5,413	509	366	6,288
Ghorbani	228	1	71	300
Grafenberg Ring	169	8	14	191
Latex Leaf (plain and Cu-Zn)	696	148	229	1,073
IUM (various materials and designs)	990	1,098	224	2,312
LEM	0	101	1,394	1,495
Monterrey	4 ^a	2	488	494
M-device	2,689	96	97	2,882
Quadracoil (plain and Cu)	700	0	0	770
Spring Coil (various materials)	1,030	1,873	19	2,922
Soonawala/Cu	317	237	4	558
Szontagh (plain and Cu)	11,386	1,976	315	13,677
Tecna	290	0	0	290
U-coil (plain and progesterone)	606	39	18	663
Weiss	31	5	1	37
Ypsilon	824	44	153	1,021
Subtotal	25,787	6,152	3,408	35,347

TABLE 2.2 Continued

IUDs of Current Research Interest	Interval	Post Abortion	Post Partum	Total
Lippes Loops A, B, C	2,069	605	117	2,791
Lippes Loop D (LLD)	4,031	797	1,666	6,494
Loop Modifications:				
Tapered, Photoreduced	2,106	102	194	2,402
Copper Clad	703	205	15	923
Medicated	92	3	0	95
Prototype Postpartum	0	0	163	163
Chromic Sutured	0	0	1,286	1,286
Plain T	538	0	0	538
Nylon T	127	0	0	127
Pop Council Postpartum T	2	166	1,332	1,500
TCu-200	4,022	225	2,038	6,285
Copper T Modifications:				
TCu-220C, TCu-300, Finland T	1,062	276	296	1,634
TR-10, TR-11	719	23	5	747
Chromic Sutured	0	0	687	687
Copper-7 200	1,766	52	58	1,876
Copper-7 (small)	813	0	0	813
Copper-7 variations	808	47	350	1,205
Multiload (plain and Cu)	1,200	24	371	1,595
Progestasert	0	0	261	261
Subtotal	20,058	2,525	8,839	31,422
Total	45,845	8,677	12,247	66,769

The following summary of results is broken down into comparative studies, efforts to reduce menstrual bleeding (which continues to be the most immediate drawback to IUD use) and strategies to improve IUD performance by altering the time of insertion. Some of the results from these trials are preliminary and follow-up data continue to be collected.

Comparative trials

1. Cu-7 vs Lippes Loop D. Rates of expulsion, bleeding/pain removals and other medical reasons for removal were all significantly lower for the Cu-7 after 12 months of use in interval patients.
2. TCU vs Lippes Loop. The two devices had similar event rates at 12 months in interval patients.
3. Latex Leaf vs Lippes Loop D. At 12 months, pregnancy rates for the Latex Leaf were significantly higher than for the Lippes Loop, but continuation rates for the two devices were similar in interval patients.
4. Lippes Loop with and without Copper. The two devices had similar event rates at 6 months in interval and postabortion patients.
5. TCU 220 vs Lippes Loop D. The two devices had similar event rates at 12 months for both interval and postabortion patients.
6. TR-10 vs Cu-Soonawala. The two devices had similar event rates at 12 months in interval patients.
7. IUM vs IUM/Wishbone vs Lippes Loop. At six months, the IUM had a significantly higher pregnancy rate, but rates of continuation were similar for the three devices in postabortion patients. The IUM users had lower rates of removal for pain.
8. Tapered Lippes Loop D vs Lippes Loop D. The Tapered Loop had a significantly lower expulsion rate at 12 months in interval

patients, but the continuation rates for the two devices were similar.

9. Photoreduced Lippes Loop D vs Lippes Loop D. The two devices had similar event rates at 6 months in interval patients.
10. TR-11 vs TCU. The TR-11 had significantly higher pregnancy rates at 6 months in interval patients.
11. Multiload vs Multiload Cu-250. The two devices had similar event rates at 3 months in interval patients.

IUDs that reduce bleeding

12. U-coil with and without Progesterone. The addition of progesterone significantly reduced U-Coil associated bleeding.
13. Lippes Loop D with and without AMCA. The release of AMCA from the Loop appeared to reduce the amount of blood loss. The results of the study were equivocal as a result of problems associated with the in utero swelling of AMCA-loaded loops.
14. Lippes Loop with and without Trasylol. The Lippes Loop with Trasylol had a significantly higher rate of expulsion at 3 months in interval patients. The release of Trasylol was effective in reducing IUD-associated bleeding.

Timing of insertion

15. IUM vs Lippes Loop D vs TCU vs Postpartum T. For insertions performed 2-36 hours following a normal vaginal delivery, expulsion rates at 6 months were significantly higher for the Lippes Loop and the Postpartum T than for the other IUDs.
16. IPCS-52 mg vs TCU-200, Hand vs Inserter Insertions. The IPCS (a Progestasert IUD with a 3-year life) had a significantly higher expulsion rate at 6 months than the TCU when inserted immediately postpartum, regardless of the method of insertion.

17. Delta Loop vs Delta T. By three-months postinsertion the two devices had similar expulsion rates in postpartum patients.
18. Delta Loop vs Lippes Loop D. By six-months postinsertion the Delta Loop had a significantly lower expulsion rate than the Lippes Loop D in postpartum patients.
19. Delta T vs TCU-220 C. By three-months postinsertion the Delta T had a significantly lower expulsion rate in postpartum patients.
20. Delta Loop, Hand vs Inserter Insertions. By three-months postinsertion there was a significantly lower rate of expulsion in postpartum patients with hand insertions of the Delta Loop.
21. Delta T, Hand vs Inserter Insertions. By three-months postinsertion there was a significantly lower rate of expulsion with hand insertions in postpartum patients.
22. Lippes Loop D with and without Endometrial Aspiration. Endometrial aspiration before IUD insertion did not have an effect on event rates at 3 months postinsertion in interval patients.
23. Postcoital IUD Insertions. There was one suspected failure among the 191 IUDs inserted in women within 5 days of unprotected intercourse. Most women retained their IUDs for continued contraception.

The most promising development in this extensive series of investigations has been the development of devices for immediate postpartum insertion (Delta Loop and Delta T). These are standard, well-tried devices that have been modified by the addition of absorbable chromic suture material that projects from the surface of the IUD and appears to prevent expulsion during the weeks it takes for the uterus to return to its nonpregnant size.

Trials indicate that the IFRP-developed Delta Loop and Delta T can significantly reduce the high expulsion rates usually associated with immediate postpartum IUD insertion, opening up the possibility of offering women an effective contraceptive at a time when the individual commonly perceives the need for family planning and the professional skills are most readily available. The trials of the Delta IUDs currently being conducted by the IFRP will provide information on the best procedure for inserting IUDs postpartum and on the optimum time to insert IUDs postdelivery. Studies are being developed to test the Delta IUDs when inserted immediately following abortion.

The technology involved in modifying IUDs for postpartum use is simple and appropriate for low-cost, labor-intensive manufacture in developing countries. As more and more women spend a brief interval in a hospital--albeit under strained and overcrowded conditions--the further work on postpartum IUDs promises to provide a quantum leap in IUD acceptability and availability.

Steroidal Contraception

More than 50 million women around the world now use oral contraceptives and over one million use injectable contraceptives. The IFRP has initiated comparative studies, put a special effort into studying problems associated with third-world use (paying special attention to the needs of breast-feeding women), and is moving into the important area of monitoring long-term risks and benefits of use.

Although widely used, some important gaps remain in our knowledge concerning the long-term use of steroidal contraceptives, especially in the developing world. In the case of oral contraceptives, the IFRP RAMOS studies will help assess long-term risks and benefits of this and other methods in selected third world countries. In the case of injectable contraceptives, the IFRP has responded to the current debate over Depo-Provera by studying the

health status of users who have obtained the drug from independent sources for up to ten years.

The number of steroidal contraception cases on which reports have been received by the IFRP as of 1 October 1980 is given in Table 2.3 (p.27). On the next page results from IFRP supported comparative studies of oral contraceptives (OCs) are summarized.

TABLE 2.3

Number of Steroidal Contraception Cases

October 1, 1980

Comparative: Neogynon vs Lo-Ovral	433	805
Comparative: Norinyl vs Brevicon vs Nordette	452	246
Comparative: Norinyl vs Brevicon vs Loestrin	30	103
Comparative: Brevicon vs Loestrin	137	157
Comparative: Brevicon vs Lo-Ovral	231	326
Comparative: Nordette vs Loestrin	32	61
Crossover: Norinyl & Neogynon to Brevicon or Nordette	56	68
Crossover: Norinyl to Norinyl, Brevicon or Nordette	215	277
Crossover: Norinyl to Brevicon or Lo-Ovral	300	167
Straight: Depo-Provera	45	107
Lactation: Progestogen-only OCs	101	93

Comparative studies

1. Neogynon vs Lo-Ovral. No pregnancies occurred after 1,620 months of use. The six-month discontinuation rates were 33.4% and 38.5% for Lo-Ovral and Neogynon, respectively. Headache was the most common side effect experienced by both groups. Generally, users of Lo-Ovral reported low rates of side effects.
2. Comparative Studies of Norinyl, Norlestrin, Ovral, Brevicon and Lo-Ovral. Two complex and important studies have been conducted to assess the rates of side effects among women using combined oral contraceptives. In the first study, women were randomly assigned to Norinyl, Norlestrin or Ovral for 3 cycles and then either switched to one of the other two OCs or stayed on the same OC. For all three OCs, the rates of most side effects significantly declined with increasing duration of OC use. Cycle control appeared best for women using Ovral. There were some adverse effects caused by switching from one OC to another. Women who switched to Ovral experienced a decrease in the rate of breakthrough bleeding. Women who switched from Ovral were more likely than others to experience an increase in breakthrough bleeding. Discontinuation rates were similar for the three OCs.

In a second study, women who had used Norinyl or Ovral for at least three cycles were randomly assigned to either Brevicon or Lo-Ovral for six cycles. The most noticeable effect was a large increase in the rates of breakthrough bleeding, which remained above the rate before switchover even after six cycles. In the initial cycle after crossover there was also an increase in the rate of some other side effects. By the completion of the sixth cycle, the rates of side effects were generally lower than the rates before crossover. The results of the study indicate that although women on low dose OCs report lower rates of certain side effects, breakthrough bleeding occurs more frequently and might, in certain cultural settings,

have an adverse effect on OC continuation rates. The discontinuation rates were similar for Rrevicon and Lo-Ovral.

Oral contraceptives and lactation

1. Progestogen-only Oral Contraceptives for Lactating Women. Preliminary data from 101 admissions and 93 follow-up visits indicate that progestogen-only OCs given to lactating women immediately postpartum are not associated with any adverse effects. Among these 101 women, five discontinuations have occurred, ranging from six to fifteen weeks following admission to the study.
2. Additional clinical studies on the effect of combined oral contraceptives on the quantity and quality of human lactation are being designed and will begin in the current contract period.

Male Sterilization

Vasectomy is a simpler operation to perform than female sterilization, but, nevertheless, in need of documentation and possibly open to further improvement.

As of September 1980, data on 3,245 male sterilization procedures have been collected in IFRP studies. The distribution of procedures by occlusion technique is given in Table 2.4. Many of the studies collected surveillance data on methods; others evaluated electrocoagulation equipment. Twelve studies have been completed, one is active and four will begin in the next year.

TABLE 2.4

Male Sterilization Cases

October 1, 1980

Ligation	200
Excision and Ligation	2187
Electrocoagulation (Schmidt technique)	739
Silastic Ring	110
Other	9
Total	3245

The following summarizes results from male sterilization studies:

1. Vaseal Unit. One study of this equipment showed a 7.0% failure rate; failures were due to equipment malfunction. A second investigator had to abandon use of the Vaseal on six different occasions due to equipment problems. The IFRP concluded that the rather delicate Vaseal unit is not an appropriate technology for developing countries where repair facilities for electronic medical equipment are not widely available.
2. Silastic Ring. One study was conducted to evaluate this occlusive technique. Surgical difficulties were encountered in one fifth of the procedures, and surgical complications occurred for one fourth of the patients. Almost 13.0% of the patients had high postoperative semen test counts and thus were declared method failures. The silastic ring, which is similar to the tubal ring used for female sterilization, is no longer used for vas occlusion.
3. Prophylactic Administration of Antibiotics Prior to Vasectomy. Complication and infection rates were similar for those men who received antibiotics and for those who did not.

Barrier Contraception

In recent years attention has been drawn to the simplicity of barrier methods of contraception and their relative freedom from side effects. Research is required to determine the limits of their usefulness in a developing world setting.

Since August 1977, the IFRP has developed data collection forms, protocols and computer programs for studies of barrier contraceptive methods. Phase II studies of the Collatex sponge and Nec Sampooon foaming tablet have been completed. Data on 2,027 barrier contraceptive users have been collected by the IFRP (Table 2.5). The following is a summary of preliminary results from studies of the Collatex sponge and Nec Sampooon.

1. Collatex Sponge: Using pooled data from 8 centers, the IFRP found that the six-month life-table pregnancy rate was 3.8 per 100 women after 1,036.5 woman-months of use. Discomfort and other personal reasons accounted for the greatest proportion of discontinuations. The discontinuation rate was 36.7 per 100 women. In one study of 100 women in Yugoslavia, the 6-month pregnancy rate was 1.1 per 100 women. Discomfort during intercourse was a primary reason for subject discontinuation.

2. Neo Sampooon: Using pooled data from 9 centers, the IFRP found that the six-month life-table pregnancy rate was 6.3 per 100 women after 1,916.5 woman-months of use. The primary reason for discontinuation was pregnancy, which was followed by discomfort and other personal reasons. The most frequently reported reason for discontinuation was a burning sensation experienced by the women. The six-month discontinuation rate was 16.7 per 100 women.

TABLE 2.5
 Number of Barrier Contraception Cases
 October 1, 1980

	Admission	Follow-up
Diaphragm with Spermicide	464	1,026
Neo Sampoo	635	1,173
Collatex	462	729
Collatex vs Neo Sampoo	411	602
Collatex vs Diaphragm	55	26

Menstrual Regulation (MR) and Pregnancy Termination (PT)

The World Health Organization (WHO) estimates that 30 million induced abortions occur in the world annually. The IFRP has worked, and continues to work, on four distinct aspects of this formidable problem:

- a. To contribute to the epidemiological and clinical understanding of illegal abortion, in order to attempt to reduce numbers and deal with public health problems posed by large numbers of hospital admissions for incomplete abortions, which arise when the procedure is illegal.
- b. To improve on postabortal contraceptive counselling and service.
- c. To document the short- and long-term effects of alternative procedures for terminating pregnancy.
- d. To document the treatment and outcome of spontaneous miscarriage with retained products of conception.

The treatment of incomplete abortion following illegal interference, or spontaneous abortion and the induction of legal abortion can involve use of the hand-held gynecological syringe or a more complex apparatus and procedure.

Uterine evacuation within 10-14 days of the first missed period is called menstrual regulation.

As of September 1980, data on 31,907 MR procedures and 65,077 PT procedures have been collected in IFRP studies (Table 2.6). Many of the 226 studies collected baseline data and others evaluated equipment, such as vacuum sources, cannula, pregnancy tests and the gynecological syringe or the efficacy and safety of various procedures in comparative studies.

TABLE 2.6

Number of Menstrual Regulation/Pregnancy Termination Cases
October 1, 1980

	Menstrual Regulation	Pregnancy Termination
Vacuum Aspiration	30,324	30,239
Dilatation and Curettage	9	24,039
Prostaglandin	105	1,280
Intraamniotic Injection	0	2,311
Hysterectomy	0	124
Hysterotomy	0	1,122
Other	298	1,244
Combination	1,171	4,718
Total	31,907	65,077

Among the most important results of the work are the following:

1. Management of Incomplete Abortion. Two studies compared the use of vacuum aspiration versus sharp curettage performed on an outpatient versus inpatient basis. At one center, vacuum aspiration and sharp curettage had similar complication rates; at the second center, women treated by sharp curettage had higher complication rates. Data have been collected and information disseminated on the public health problems of illegally induced abortion. The IFRP Grant (AID/pha-G-1198) continued funding of similar studies as a service program.
2. Battelle Hand Pump. This pump can be used for the treatment of incomplete abortion or pregnancy termination. A five-center clinical trial conducted to evaluate the performance of the Battelle hand pump found there were no failed procedures and the low immediate and follow-up complication rates were comparable to those for the hand syringe and electric pump.
3. MR Procedures: Physicians vs Nurses. Data from two comparative studies show similar complication rates for MR procedures performed by physicians and nurses.
4. Capillary Tube Pregnancy Test. The Capillary Tube Pregnancy Test was compared with the Pregnosticon Dri Dot Test at three centers. The women were classified by the number of days from onset of the last menstrual period (LMP) to the day of the pregnancy test. Preliminary analyses show that the pregnancy tests were not as accurate in the less than 42 days LMP group, compared to the more than 42 days LMP group, in terms of the true positive and the overall accuracy rates. In the less than 42 days LMP group there was no difference in the overall accuracy rate for the Dri Dot Test and the Capillary Tube Test. Investigators noted that negative tests were difficult to read with the Capillary Tube Test.

5. Hormonal Pregnancy Tests. Evaluation of two injectable hormonal pregnancy tests (an estrogen-progesterone combination and progesterone alone) proved to be ineffective for the early diagnosis of pregnancy. The IFRP has taken steps to curtail the use of these exploitive and potentially dangerous drugs.

3. Proposed Research

The IFRP's research under the proposed contract will focus on the following:

- a) continuation of investigations that will be ongoing as of 1 August 1981, the scheduled date for completion of Contract AID/pha-C-1172;
- b) evaluation of the safety, efficacy, side effects, acceptability, cost and demographic impact of new and improved contraceptive methods, especially those that can be made available easily to women in rural areas;
- c) conduct of studies to evaluate issues related to contraceptive safety based on use of the IFRP's extensive data bank and conduct of appropriate epidemiological investigations;
- d) expanded phase IV (postmarketing) trials to further evaluate long-term contraceptive safety; and
- e) development of new and improved contraceptive methods suitable for use by developing nations.

a. Continuation of present research

Table 3.1 lists the type and number of studies, for each of the IFRP's major study areas, which are expected to be ongoing 31 July 1981, when Contract AID/pha-C-1172 terminates.

TABLE 3.1

Studies Expected to be Ongoing as of 1 August 1981

Study	Number of Studies
<u>Female Sterilization</u>	
Study to evaluate the ability of sterilization facilities to provide sterilization services to recently delivered women	1
Open laparoscopy with Laprocator:	
1. Topical vs no topical anesthesia	1
2. Insufflation with room air	2
Suprapubic endoscopy with Laprocator	6
Minilaparotomy:	
1. Rocket clip vs tubal ring	4
2. Bleier clip vs tubal ring	1
3. 3-year follow up of patients	2
Laparoscopy	
1. Bleier clip vs tubal ring	1
2. 5-year follow up of patients	3
Nonsurgical methods (Quinacrine hydrochloride)	
1. Follow up of patients sterilized with quinacrine pellets with or without sodium thiopenthal	4
2. Effects of quinacrine-loaded IUDs inserted pre hysterectomy	5
<u>Intrauterine Devices</u>	
Immediate postpartum insertions	
1. Trials of the Delta T and Delta Loop to compare the two IUDs with similar IUDs without chromic sutures, and to compare the timing of the insertion and insertion method	59
2. IPCS 52-mg vs TCu	2
Immediate postabortion insertions	
Comparative studies of the Delta T and Delta Loop	9
Interval insertions	
TCu-380 Ag vs Multiload Cu 375	6
TCu-380 Ag vs Cu-7	2
TCu-200 vs Nylon Wound T	2
TCu-200 with and without strings	4
Lippes Loop D with and without AMCA	3
I-Cu	1
Levonorgestrel-T vs Nova T	3
Effects of Levonorgestrel-releasing T on the endometrium	1
Concentrations of levonorgestrel in target tissues of users of the Levonorgestrel-releasing T	1

TABLE 3.1 Continued

Study	Number of Studies
<u>Steroidal Contraception:</u>	
Comparative studies of high and low estrogen dose OCs	7
Crossover studies of high and low dose OCs	3
Progestogen-only OCs used by lactating women	4
Studies of the health effects of long-term Depo-Provera use	3
Preliminary investigations of monthly injectables	2
Evaluation of effects of different OCs on lactation and their health effects on infants	1
<u>Male Sterilization</u>	
The long-term effects of vasectomy on the health of men	1
Percutaneous vas occlusion	3
<u>Barrier Contraception:</u>	
Comparative studies of the Collatex sponge	7
Comparative studies of Neo Sampocon	10
Diaphragm with spermicide	1
Vaginal chemoprophylaxis and sexually transmitted diseases	2
<u>Fertility Awareness:</u>	
Ovulation and symtothermal methods	3
<u>Pregnancy Termination</u>	
Evaluation of double-valve hand syringe	4
Midtrimester abortion with laminaria, urea and prostaglandin F _{2α}	1
Midtrimester abortion with 10% saline	1
Cervical osmotic dilators	6
<u>Epidemiologic and Other Investigations</u>	
Evaluation of the effects of female circumcision on maternal health, childbirth and contraceptive practice	2
Study of the relationships between contraceptive practice and the incidence of congenital abnormalities	1
Studies to evaluate the relationships between patterns of breast-feeding and the return of ovulation	3
Studies to evaluate the relationships between contraceptive use and mortality for different causes among women of reproductive age	2

TABLE 3.1 Continued

Study	Number of Studies
Studies of the effectiveness and safety of using traditional practitioners to provide contraceptive services	1
Study to evaluate changes in the planned method of contraception following childbirth and actual methods used 6 months after birth	1

eex129

b. New research directions

In addition to the continuation of the specific research studies described in the previous section, the IFRP proposes to:

1. evaluate the safety, efficacy and acceptability of new and improved contraceptive methods as they become available for clinical phase III trials, including fertility awareness methods;
2. develop new and improved contraceptive methods and continue with the development and promotion of methods currently under investigation by the IFRP;
3. expand its role in the postmarketing evaluation of contraceptive methods to evaluate issues related to contraceptive safety, efficacy, acceptability, side effects, cost and demographic impact;
4. evaluate, on a limited basis, factors that may limit either the availability of safe and effective contraceptive methods or the acceptability of these methods by either the potential users or the providers of contraceptive services; and
5. continue to widely disseminate information related to all aspects of contraception through the support of a medical journal, newsletters, media contacts, monographs and numerous clinical papers related to contraceptive evaluation, conferences and meetings.

Short descriptions of some specific studies to be undertaken by the IFRP are included for each of the IFRP's major study areas. However, the scope of work will not be limited to the specific studies described in the following sections since one of the most important aspects of the IFRP's work is to be responsive to new needs. Research conducted by other organizations and

individuals will almost certainly continue to bring to the forefront previously unrecognized risks and benefits associated with the use of some contraceptive methods. The IFRP, through its close association with other population research organizations, with schools of medicine in the United States and around the world and with individual investigators, keeps abreast of developments and responds as needs and opportunities arise. The IFRP will undertake, whenever feasible, evaluations of these hazards through the analysis of existing data at the IFRP and/or through appropriately designed studies. The IFRP will also continue to disseminate objective information in appropriate ways.

The IFRP will continue to monitor possible developments in fertility regulation, such as immunologic methods and LH-RH analogs, until they are sufficiently developed for the IFRP to undertake clinical evaluations.

Female Sterilization

Development of a nonsurgical method of sterilization will receive priority. To date, the use of quinacrine appears to be promising, but as work proceeds, research on alternative chemical sterilants will be kept under review and expanded if warranted. Efforts will focus on a simplification of the multiple quinacrine pellet insertion procedure and/or continued development of an effective quinacrine-bearing IUD. Studies that evaluate different quinacrine dosages, dissolution rates and delivery systems will be conducted. The endpoint of this research is to develop a safe and effective nonsurgical method of sterilization that can be delivered by paramedical personnel in a nonhospital setting. Preliminary data from IFRP-sponsored trials indicate that this goal may be achievable.

Simplifications of existing technology, as well as new and improved methods of tubal occlusion, will be evaluated in short- and long-term clinical trials. The focus of these

studies will be the suitability and acceptability of the simplified/new/improved methods for use in developing countries.

It has been suggested frequently that the acceptability of female sterilization may be greatly enhanced if a reversible method were available that could easily be performed and later reversed. One reversible procedure that shows considerable potential under development by the IFRP is the fimbrial hood, which will soon be available for evaluation in humans. On the basis of animal trials, the application of the fimbrial hood appears to be a relatively easy and safe procedure to perform and reverse.

To increase the availability of female sterilization, the IFRP will evaluate the use of specially trained auxiliaries (such as operating theater nurses) for performing postpartum sterilization procedures.

Epidemiologic investigations to evaluate the long-term effects of different tubal occlusion procedures will continue to be important. Specifically, the IFRP will evaluate changes in menstrual cycle parameters, the incidence of gynecologic surgery and poststerilization failure rates, including the risk of ectopic pregnancies. The investigations will rely on the IFRP's extensive data bank (over 50,000 cases to date), the continued collection of long-term follow-up data, and on case-control and cohort studies specifically designed to provide answers to the long-term effects of sterilization.

Intrauterine Devices

Following completion of the trials of the Delta T and Delta Loop IUDs, the IFRP will make the dissemination of the technology for the manufacture of these IUDs a priority, in order to assure the widest availability in postpartum family planning programs.

The IFRP will continue to evaluate in comparative trials new IUD modifications including medicated IUDs that slowly release antifibrinolytic agents, steroids and other drugs and Ts wound with nylon rather than copper.

Epidemiologic investigations will be conducted to evaluate issues that appear to limit the usefulness of IUDs, especially use by nulliparous women. Unresolved issues relating to IUD use include the risks of pelvic inflammatory disease (PID) among IUD users and the possibility of an increased risk of PID with increased duration of IUD use, the risk of infertility following discontinuation of IUD use and the risk of ectopic pregnancy among IUD users. These issues will be evaluated in part through the use of the IFRP's extensive data bank, which contains over 100,000 IUD cases, and by case-control and other epidemiologic studies designed to assess the risks of adverse events associated with the use of IUDs.

Steroidal Contraception

Continued evaluations of OC-related side effects will provide information on different OC formulations when used by groups of women who are ethnically and culturally dissimilar. These studies and studies that evaluate the metabolism of various OC preparations in different ethnic and cultural groups will provide leaders of national family planning programs and practicing physicians with the information necessary to minimize OC-related side effects and maximize OC continuation rates.

Working with PARFR and other organizations, the IFRP will evaluate the safety and efficacy of injectable contraceptive delivery systems including the microencapsulated norethisterone. At present, there is a large demand for a once-a-month injectable. Such a system may overcome some of the objections to the 90-day injectable contraceptive. The IFRP will conduct the necessary clinical trials to completely evaluate once-a-month systems that will utilize available delivery systems and drugs, with

the long-term goal of providing an option that could be added to social marketing programs and ensuring a high quality product for pharmacy distribution in developing countries. The use of existing compounds, eg, medroxyprogesterone acetate and norethisterone, will obviate the need for expensive animal teratology and toxicology studies, and will minimize the development time. Epidemiologic investigations of the long-term use of Depo-Provera will continue and expand depending on the findings from ongoing IFRP studies.

The ongoing trials of progestogen only OCs used by lactating women immediately postpartum will be expanded to include additional locations and more detailed investigations of the effects of the progestogen only OCs on the volume and composition of the mothers' milk and their effects on the infants. The effects of combined OCs and injectable contraceptives will also be evaluated in terms of the health effects on infants of lactating women.

The IFRP will conduct, as appropriate, clinical and epidemiologic investigations into the risks and benefits of steroidal contraception, including case-control studies to study carefully specified issues.

Male Sterilization

The IFRP will pursue the evaluation of simplified methods of vas occlusion that will limit short- and long-term side effects and complications, be efficacious and serve to increase the acceptability of the procedure. Percutaneous vas occlusion techniques currently being developed should be ready for clinical phase III evaluation by the IFRP in 1981. These techniques could greatly enhance the acceptability of male sterilization and permit more extensive use of paramedical personnel. The IFRP will also evaluate the safety and effectiveness of male sterilization procedures when performed by paramedical personnel.

Depending on the results from an ongoing US-based, IFRP-funded epidemiologic study of the long-term effects of vasectomy on health, additional investigations may be initiated in developing countries where results may be anticipated to be different from those obtained in the US.

Barrier Contraception

Renewed interest in barrier contraceptives has resulted in the development of new barrier contraceptive products that should become available for evaluation in clinical phase III trials in the near future. New products include foaming vaginal suppositories, contraceptive sponges, disposable diaphragms and condoms, and cervical caps. The IFRP will undertake clinical trials of products that may be appropriate for use in the developing world.

Controlled clinical trials and epidemiologic investigations will be conducted to assess the effectiveness of the use of barrier contraceptives against sexually transmitted diseases that are endemic in many countries.

Increased attention will be given to the evaluation of fertility awareness methods of contraception. Initially, the IFRP proposes to conduct controlled clinical trials to evaluate the effectiveness of some of these methods. To date, studies on the effectiveness of these methods have lacked methodological adequacy.

Pregnancy Termination

The IFRP will continue to explore ways to combat the public health problems presented by widespread abortion, striving to improve the treatment of incomplete abortion and ensure adequate postabortal contraceptive advice.

Alternatives to the surgical MR procedure will be explored. Current information indicates that some $PGF_{2\alpha}$ and PGE_2

analogs may be effective for inducing uterine bleeding within about two weeks of a missed menstrual period. If these analogs prove to be safe and effective when used in a hospital setting, expanded trials will be undertaken to evaluate them when used in more peripheral settings.

New and improved pregnancy tests will be evaluated in comparative trials.

The osmotic dilators being developed by the IFRP offer significant advantages over the available laminaria; they are less expensive and can rapidly dilate the cervix. If the IFRP's dilators live up to their initial promise for rapid and nontraumatic cervical dilation, clinical phase III trials will be undertaken to compare the osmotic dilators with other methods of cervical dilation and to evaluate them for routine cervical dilation prior to uterine evacuation. The dilators may also be evaluated in the treatment of intrauterine fetal death due to some pathological cause.

An ongoing concern relates to the long-term effects of different abortion procedures. The IFRP will critically evaluate, in appropriately designed studies, the long-term effects of different abortion procedures on the course of subsequent pregnancies and their outcomes.

Other Investigations

Factors other than contraceptive safety and efficacy help determine who uses contraceptives and for how long. They include the availability of contraceptives and their acceptability to both provider and user. Proposed IFRP studies will address the following:

1. Health and cultural practices that limit contraceptive use or suggest that a particular method will not be suitable in a given country. For example, the IFRP will evaluate the effects of female circumcision, widely practiced in parts

of Africa, on contraceptive use and the health of the mothers and children.

2. Interrelationships between breast-feeding practices and fertility regulation. Intervals of anovulation related to lactation continue to provide tens of millions with years of protection against pregnancy, but relatively little is known of the factors controlling the return of fertility. Clinicians and program managers urgently need more exact information to pass on to breast-feeding women about the adoption of modern methods of contraception. Time to first ovulation and menstruation requires further evaluation. Also, the impact of various contraceptive choices on lactation requires further exploration.
3. The attitudes and influence of providers of family planning on contraceptive use. Pharmacists represent one of the largest single bodies of family planning providers, but, in several ways, the least utilized. The IFRP, for example, will conduct a follow-up survey of Egyptian pharmacists to evaluate changes in their knowledge of and attitudes toward contraception, following the distribution of bulletins related to many different aspects of contraception.
4. Evaluation of the access to contraceptive services and the relationship between social and personnel support and acceptability of contraception.
5. Epidemiologic investigations to inquire into the possible beneficial and adverse health effects associated with different pregnancy intervals and previous contraceptive use. The IFRP is currently planning studies on the relationships of congenital malformations and events related to

pregnancy, including contraceptive practice. Other investigations of this type are planned.

Information Dissemination

The IFRP will continue to cosponsor the International Journal of Gynaecology and Obstetrics (IJGO) and will provide approximately 1,500-2,000 subscriptions to selected developing country physicians. Although Elsevier/North Holland Biomedical Press will assume the publication, distribution and promotion responsibilities for IJGO in 1981, the IFRP will continue to provide limited editorial support for manuscripts accepted from authors working in developing countries.

The publication of the quarterly newsletter Network, which started in 1979, will be continued. The mid-1981 circulation of this publication is estimated to be over 6,000. The IFRP will also continue publication of its monograph series, which began with the publication of the monograph that explained the rationale and methodology of the RAMOS studies.

The IFRP will continue to provide investigators with consultant reports (CRs) summarizing completed investigations. About 35 such reports will be prepared each year. These reports are designed to help and encourage investigators to publish the results of their IFRP-sponsored investigations. A list of CRs prepared since August 1977 can be found in Appendix D.

Approximately 60-70 scientific papers reporting the results of IFRP studies will be prepared by the research staff each year for publication in national and international journals. Research findings will also be disseminated at appropriate national and international meetings. A list of papers prepared by the IFRP since August 1977 is given in Appendix E.

The IFRP will sponsor one or two international conferences each year to provide physicians and other providers of contraceptive services in developing countries with updated information

related to contraceptive safety, efficacy, side effects and use, and on the provision of contraceptive services. The IFRP also will continue to disseminate its research findings at national and international meetings.

By virtue of the IFRP's considerable expertise in clinical and epidemiological investigations, the IFRP is frequently approached by the media for comment and advice on the scientific aspects of fertility regulation. The IFRP sees the 1980s as a time of continuing controversy in relation to existing and new methods of contraception and intends to continue to meet its obligations by responding rapidly and professionally to the inquiries of the interested and informed public with accurate and complete information. The IFRP's multilingual publications staff is comprised of professionals trained in communications.

Transfer of Technology

Each year the IFRP provides training in research methodology to persons associated with the IFRP's projects and programs. The IFRP is committed to expanding the research competence of its associated investigators, and will continue its program to provide them with specialized training in research procedures.

The research capabilities of selected IFRP programs and/or investigators will be enhanced by the provision of microcomputers that will be capable of performing many of the data processing and analysis functions currently performed at the IFRP on the Burroughs 6700 computer. Programs for these microcomputers will be written at the IFRP and will be immediately usable by investigators. Initially, the IFRP will place microcomputers at 2 or 3 carefully selected sites. Additional sites will be provided with microcomputers if the program is successful. On-site training by the IFRP's research staff will be provided to investigators on an as needed basis. Typically, on-site training will be provided by a senior IFRP researcher

over a period of several weeks. Priority countries for on-site training include Bangladesh, Brazil, Indonesia, Mexico, and Tunisia.

The medical staff will provide training to the IFRP's investigators in methods of fertility control, including, but not limited to, postpartum IUD insertion techniques, methods of tubal occlusion using new and/or improved techniques.

4. Proposed Work Plan

The research the IFRP elects to undertake is selected on the basis of:

- (a) its relevance to the objectives of AID;
- (b) the suitability of the research in terms of meeting individual and program needs of the developing countries;
- (c) the expectation that it will enhance the available knowledge on fertility control; and
- (d) the expectation that it will result in a new or improved contraceptive method suitable for use in developing countries.

New methods of fertility control will be given priority by the IFRP if they do not require sophisticated delivery systems or frequent administration, are not too complicated for the user to adopt and/or can be self-administered.

New initiatives for the IFRP may come from any of the following sources: AID, IFRP staff, IFRP investigators, other organizations and individuals. New initiatives are reviewed by IFRP staff and summarized once a year in the publication IFRP Directions. Comments and input from collaborators and others are invited. The Technical Advisory Committee (TAC) monitors research policy. The TAC is composed of experts actively engaged in reproductive and population research (see Appendix B), and attended by representatives of AID. Subcommittees of TAC and ad hoc advisory groups provide further technical review and assistance to the IFRP's research activities. The IFRP also makes use of consultants for additional technical expertise. A list of currently approved consultants is given in Appendix F. A Scientific Committee composed of the Executive Director, Deputy Director, Medical Director, Associate Directors for International Projects and Research and Senior Consultant establishes priorities for research. Separate Task Forces operate for each of the IFRP's major areas of research, namely, barrier contraception, pregnancy termination, sterilization, intrauterine

devices, steroidal contraception and operations research. The Task Forces serve as a forum for the in-house dissemination of activities related to each of the major study areas.

New research studies are submitted to AID for approval by the IFRP's technical monitor if the study has not been approved previously under a research strategy. Research strategies provide a short description of the studies, their justification, including the number of studies to be conducted and the number of subjects per study. Following approval of the research by AID, the Research Department staff develop the study protocols, forms and necessary procedures to assure the success of the study. The identification of appropriate study sites and implementation of projects are the joint responsibility of the International Projects and Research Departments. Subcontracts for the research are submitted by the Research Department to AID for approval, including approval by the AID mission, if there is one in the country where the research will be conducted.

Before a clinical trial is initiated, a study protocol is prepared that details the study procedures and data collection forms, specifies which subjects can be included in the study, the number of subjects, follow up and reporting requirements. All protocols and data collection forms are reviewed by the IFRP's research staff (including the medical staff and consultants whenever appropriate). Statisticians review the soundness of the study designs and the number of required subjects to assure that the basic principles of experimental design are followed. To facilitate the conduct of studies, selected forms and manuals are translated into the language of the country in which they will be used, including Arabic, French, Indonesian, Portuguese and Spanish.

Following AID regulations on research involving human subjects, all new research projects are reviewed by the IFRP's Protection of Human Subjects Committee (PHSC), which is responsible for safeguarding the rights and welfare of subjects who participate in IFRP-funded studies. The review by the PHSC includes assessment of

the relative risks and benefits of a subject's participation in a study, documentation of steps that will be taken by the investigator to safeguard the rights and welfare of the subject and informed consent documentation. The PHSC meets three or four times a year. At the end of each year, all ongoing projects are reviewed by the Committee and approvals renewed. The membership of the PHSC is given in Appendix C.

The IFRP keeps in close contact with its investigators. Input from investigators is actively sought in the initiation and design of new research leads. Throughout the course of a study, site visits are made to monitor the progress of a study and resolve any study-related problems. In addition to site visits, the IFRP regularly corresponds with investigators regarding data quality, research design and study implementation.

The International Projects Department maintains close liaison with the IFRP's investigators, develops new research centers, identifies the research needs of the developing countries and coordinates the IFRP's research efforts with those of other organizations.

5. The IFRP Network of Investigators and Research Methodology

In order to successfully conduct clinical trials, the IFRP maintains a close relationship with investigators around the world. These researchers form a network of investigators essential to the success of the IFRP's research activities. Specified below are the number of centers, by region, presently participating in IFRP research activities.

<u>Regions</u>	<u>Number of Institutions</u>
Latin America	26
Middle East and Africa	10
Far East	24
Europe and North America	<u>18</u>
Total	78

The network of investigators is a dynamic one, including a diversity of experience and range of research possibilities. Depending on the previous experience of the investigator(s) in conducting IFRP studies and the complexity of the study, IFRP staff may be present for the initiation of the study to deal with any problems that may arise as study procedures are followed. Throughout the course of the study, site visits are made to the investigators and, whenever possible, records collected during the research are checked against independent sources to ensure that data are accurately recorded. Site visits by physicians, regional coordinators and research staff are also used to resolve specific questions regarding the recording of data, data queries and errors.

The progress of all studies is constantly monitored at the IFRP. If an investigator is unable to follow the protocol, has an insufficient case load, or if the study is no longer relevant to the research needs of the IFRP or AID, the study may be terminated early. Studies may also be terminated if unacceptable adverse reactions occur or if the method under study is found to be ineffective or unsafe.

The IFRP investigators continue to have control over their data even after the data have been sent to the IFRP. Investigators are consulted before studies on their data are published.

The research conducted by the IFRP is based on:

- a. research conducted by the IFRP's network of investigators;
- b. data already available in the IFRP's computerized data bank;
- c. studies conducted by other research organizations under subcontract from the IFRP; and a
- d. combination of the above.

Many of the IFRP's studies involve collecting large quantities of clinical data. Data quality is monitored both in the field and in-house. The close working relationship between the investigators and the IFRP staff provides a continuous feedback to the investigators, which is one of the most important elements in the maintenance of high-quality data. In addition, checks are performed comparing forms returned to the IFRP with clinical records kept in collaborating institutions. Finally, data that the IFRP has helped collect are compared with other in-country sources of data and reviewed for internal consistency.

In-house, the IFRP has developed computer programs to check the forms for invalid responses, to reject forms if essential information is missing, to generate queries if responses to specific questions appear inappropriate or invalid and to edit the data in a way that facilitates the analyses. An outline of the procedures used for the processing of data from clinical trials is given in Appendix G.

One of the IFRP's most important investments is its development of over 200 computer loading, editing and analysis programs. In addition, the IFRP has an extensive library of packaged analysis programs (see Appendix H).

All reports and papers written by the IFRP staff are formally reviewed by selected staff and outside reviewers to assure that the

study results have been correctly and accurately presented and interpreted.

6. Researcher Competence and Facilities

The IFRP's specialist experience in the conduct of clinical trials to evaluate contraceptive safety and efficacy is unparalleled by that of any other organization. The IFRP has conducted over 380 clinical trials in 47 developing and developed countries. The IFRP's procedures and methodologies for conducting, monitoring and reporting on clinical trials are well established.

Under the direction of Malcolm Potts, MB, BChir, PhD, Executive Director of the IFRP, the IFRP has become a dynamic organization capable of responding to the needs of AID and those of the developing world. The management structure of the IFRP has been streamlined, making the organization extremely cost-effective. Dr. Potts is an international authority on contraceptive use and is the author of eight books and over 100 scholarly monographs and articles. Before coming to the IFRP in 1978, Dr. Potts served as a consultant to the International Planned Parenthood Federation (London) and prior to that served as the Medical Director of that organization.

Assisting Dr. Potts in the management of the IFRP are Peter Donaldson, PhD and David Edelman, PhD, who report to John Ganley, Deputy Director. Mr. Ganley came to the IFRP with experience in both the government and private business. In his most recent position he served as Group Vice President of Safetran Systems Corporation. He previously held positions as Deputy Director of ACTION, a federal agency fostering volunteer service, and as Auditor General of AID.

Dr. Donaldson, Associate Director for International Projects, came to the IFRP from the Population Council. He served as the Council's Representative in Korea where he administered a large technical and financial assistance program. Prior to going to Korea, Dr. Donaldson was stationed in Bangkok, Thailand, where he worked as the Population Council's advisor to the Thai Ministry of Public

Health. Dr. Donaldson has served as a frequent consultant for program development activities throughout Asia.

Dr. Edelman, Associate Director for Research, has been with the IFRP since 1972 and is knowledgeable about all aspects of the administration and scientific management of the IFRP. Dr. Edelman has extensive experience in the design, execution, analysis and management of field trials and contraceptive evaluation. He has authored or co-authored over 110 scientific papers and one book on contraceptive use.

Dr. Leonard Laufe, Medical Director of the IFRP, also holds a clinical appointment in the Department of Obstetrics and Gynecology, Duke University School of Medicine. Dr. Laufe is well known for his work in the design of obstetric forceps, but in recent years has concentrated on the development and evaluation of contraceptive technology, and has played a key role in the development of a transcervical chemical sterilization procedure and postpartum IUD. Dr. Laufe has travelled throughout the developing world to provide technical assistance and specialized medical training. He is knowledgeable of the medical needs of developing world countries and has successfully translated this knowledge into the development of improved contraceptive methods specifically designed to meet the needs of the developing world.

Dr. Elton Kessel is the founder of the IFRP and is an innovator in contraceptive development. Dr. Kessel lived and worked in India for several years and besides his knowledge and experience in contraceptive needs and development, he has particular interest in the use of traditional practitioners and auxiliary workers in the provision of health care and family planning services.

Dr. Roger Bernard, Director of Field Epidemiology, has particular skills in working with IFRP collaborators in the field, evaluating service data, and providing rapid in-country feedback to clinicians and policy makers.

The scientific and administrative management of the contract will be the prime responsibility of Dr. Edelman, Ms. Elena Tomaro, Research Administrator and Mr. Robert Hughes, Financial Services Manager.

The curriculum vitae of Drs. Potts, Donaldson, Edelman, Laufe, Bernard, Kessel and Mr. Ganley are given in Appendix I.

The IFRP is composed of four departments: Office of the Executive Director, Administration, International Projects and Research. An organizational chart of the IFRP is given in Appendix J.

The IFRP has an exceptionally well qualified staff with demonstrated research and administrative skills. An IFRP staff listing giving the name, title and academic degrees of all IFRP staff is found in Appendix K. The IFRP staff have demonstrated their ability to rapidly respond to the needs of AID, develop contraceptive methods that are appropriate for and acceptable to the needs of the developing world and design, implement and report on numerous types of studies that provide information relating to the safety, efficacy, acceptability, cost and demographic impact of contraceptive methods.

The IFRP is located in Research Triangle Park, North Carolina, an area specifically designated for research organizations. The IFRP has well-established working relationships with the University of North Carolina at Chapel Hill, Duke University, North Carolina State University and many of the organizations in the Research Triangle Park, which provide the IFRP with a broad range of scientific and technical skills. The IFRP is centrally located to the above three nationally known educational institutions. One of the assets of the IFRP's location is its ready access to Duke University and the University of North Carolina Schools of Medicine, the University of North Carolina School of Public Health, the animal research facilities at North Carolina State University and many private businesses such as Becton Dickenson, IBM and Burroughs Wellcome.

The IFRP staff, library and computer facilities are housed in a 21,000 square foot building. In May 1976, the IFRP completed the installation of a Burroughs 6700 computer which has 882 kilobytes of main memory and a capacity for over 520 million bytes of online disk storage that permit the rapid processing of large data sets. Facilities for 16 remote teleprocessing lines are available. The programming section of the IFRP employs six full-time programmers, all of whom have extensive experience with research systems development and programming.

In addition to having the ability to write its own analysis programs, the IFRP has a program library that includes SPSS, ECTA, Catlin/Lincat, PSTAT, BMD and others. The IFRP has completed many of its standard analysis programs. Its life-table program (LIFETAB) has been used by numerous researchers throughout the world. Computer programs for the loading and cleaning of data, and for performing standard analysis in the IFRP's major study areas have also been written.

Each year the IFRP staff prepare more than 65 scientific papers for presentation or publication. The IFRP's Publications and Graphics staff provide support services to authors, which are an important part of the technical assistance that the IFRP provides. These department staff provide editing services for the IFRP staff and collaborators.

The IFRP has a Text Processing Center built around a twin-computer text management system that allows rapid input, revision and output of documents to online, high-quality typewriters, high-speed printer and phototypesetter.

The IFRP library has direct access to the resources of the libraries of the University of North Carolina, Duke University and North Carolina State University. MEDLINE, POPINFORM and other bibliographic retrieval systems are used frequently. The library subscribes to over 50 professional journals and receives numerous

technical reports and bulletins on contraceptive development, evaluation and related topics.

7. Significance of Proposed Research to AID Objectives

AID sponsors, through grants and contracts, basic research in reproductive biology; the development of new and/or improved contraceptive methods, including the necessary preclinical and initial human trials; expanded human clinical trials to demonstrate the safety and efficacy of the methods; and studies to evaluate delivery systems for the distribution of contraceptive methods, contraceptive acceptability and use. Also, AID, either directly or through intermediary organizations (such as JHPIEGO, Pathfinder Fund, FPIA), provides contraceptive supplies and services to developing countries that request assistance.

Since most, if not all, developing countries do not yet have either the technical or the economic resources to independently evaluate the entire range of available contraceptive methods, AID must assure national health programs and individual users of contraceptives that they are being provided with the safest and most effective contraceptive methods and that those methods are culturally acceptable and can be provided to those most in need of them. This objective is achievable only if AID has access to pertinent data and can institute appropriate studies on which decisions regarding contraceptive safety, efficacy and acceptability can be based.

Nearly all research relating to the development of new and/or improved contraceptive methods including the evaluation of the short- and long-term effects of existing and widely used contraceptive methods has been conducted almost exclusively in developed countries. There is a paucity of data relating to contraceptive acceptability, use, side effects and effectiveness in developing countries. For example, the benefits and risks of oral contraception have been extensively evaluated in large-scale studies in England and the United States. As far as it is known today, the findings of these investigations are pertinent to other developed countries. There is, however, limited evidence to indicate that the findings are not totally pertinent to many of the

developing countries where the relative risks of pregnancy are quite different, and where nutritional insufficiencies and certain infectious and other diseases alter the probabilities of oral contraceptive risks and benefits. Both AID and developing country health authorities need to know how safe and effective contraceptive methods can be provided to developing countries, especially to the poor, undernourished women in rural areas. To provide safe and effective contraceptive methods, AID must have access to the necessary information regarding contraceptive safety and efficacy in the developing world. The IFRP is in a unique position to provide this information.

Since its inception in 1971, the IFRP has provided AID, the investigators with whom it works, and national and international health organizations with data upon which they can base decisions relating to the provision of contraceptive methods and services. During the past nine years the IFRP has demonstrated its ability to conduct clinical trials of contraceptive methods in a wide variety of clinical and cultural settings, particularly in the developing world. The IFRP has established a worldwide network of distinguished, experienced and committed biomedical investigators fully capable of conducting a variety of studies. The IFRP has trained investigators within its network of investigators in both clinical and research areas in order to improve their ability to provide solutions to the problems of how best to develop and improve contraceptive technology. The IFRP has also made extensive efforts to transfer to developing world institutions technology developed at the IFRP for the design, conduct, analysis and reporting of clinical trials and other studies to evaluate contraceptive-related issues pertinent to the particular country.

Studies of existing, improved or new contraceptive methods in developing countries are essential for the following reasons:

- a. The value of the methods under use conditions in countries where they will eventually be employed must be determined in advance of widespread use of these methods.

- b. Since different contraceptive methods are associated with problems specific to particular developing countries, further developmental work and/or modification of the methods may be required in order for the methods to become widely used.
- c. In-country resources and capabilities must be strengthened and expanded.
- d. In-country work, testing and evaluation is necessary to increase the speed with which the methods can become accepted and used within national family planning programs.
- e. The development of improved contraceptive delivery systems and the wider availability of contraceptive services, especially to those in need of them, is essential if the goal of health for all by the year 2000 is to be achieved and if hundreds of millions of couples adapting to the changing and increasingly harsh socioeconomic conditions are to reach their expressed fertility goals.

The IFRP, during its short existence, has evaluated many contraceptive methods in the developing world. This work is leading to the increasingly widespread use of several methods including voluntary sterilization, intrauterine devices and oral contraceptives.

Through the work of the IFRP, AID has been able to provide developing countries with new and/or improved contraceptive methods whose safety and effectiveness have been evaluated and established in the developing world by local researchers. The result has been the provision of safer and more effective contraceptive methods to more people. In addition, guidelines and policies have been established for program managers relating to every aspect of fertility regulation. These actions, in turn, are contributing to improved health and a better quality of life for some of the world's poorest citizens.

Continued use of the demonstrated capabilities of the IFRP will enable AID to follow up on the widest range of new leads in

fertility regulation. It will also provide the Agency with a cost-effective means of ensuring a continued flow of information to developing countries that can be used to make important programmatic decisions regarding the provision of health and family planning services. The continued work of the IFRP will play an integral part in the implementation of these decisions.

8. Relationship of Proposed Research to Existing Knowledge

Most of the contraceptive research and development conducted in the United States, or through United States based organizations, is for the development and evaluation of products (devices, drugs, etc) to be used in the United States. Many of these products are not suitable for use in developing countries, especially in rural areas that lack both trained personnel and adequate medical facilities. Also, the risks and benefits of contraceptive usage and pregnancy are very different for developed and developing countries. Given these differences, it is important for AID to be able to turn to an organization, such as the IFRP, to answer questions related to the safety, efficacy, cost and demographic impact of contraceptive products.

Pharmaceutical corporations in the United States evaluate new products to the extent required by the FDA. Issues relating to the safety of contraceptive products do not come from industry-sponsored research. In the past, answers to many of the questions related to contraceptive safety have come from nonprofit organizations such as the World Health Organization, the Population Council and the IFRP.

The major breakthroughs in contraceptive research that are occurring in the 1980s, for example, the use of LH-RH analogs for arresting spermatogenesis or controlling ovulation or antipregnancy vaccines, may not be widely available until the close of this decade or later, even if on the basis of current research they appear to be promising methods. In the critical intervening years, it is essential that the existing contraceptive methods and their modifications be made as widely available as possible. To do this will require ongoing documentation of safety and efficacy and continual adaptation to the needs of different communities. The IFRP has the obligation to design the appropriate protocols, conduct the necessary trials and evaluations and develop meaningful long-term studies to resolve current issues of contraceptive debate and

independently evaluate contraceptive efficacy, safety, side effects, costs, acceptability and demographic impact.

Since its inception, the IFRP has added significantly to the body of knowledge relating to contraceptive safety and efficacy. During this period more than 435 papers, monographs and books have been prepared and published with the support of the IFRP, and IFRP staff have made more than 200 presentations at national and international meetings. The IFRP has modified IUDs for insertion immediately postpartum and is in the process of developing a nonsurgical method of female sterilization. It has compared different brands of oral contraceptives to assist in decisions relating to commodity purchase. The IFRP has also developed and evaluated the gynecological syringe, which is now a common surgical instrument in worldwide use.

The IFRP, through its support of research centers around the world, has made a major contribution toward strengthening biomedical research, thereby improving programs that provide family planning services. Other accomplishments of the IFRP that have proved to be significant improvements in the development of contraceptive products are detailed elsewhere in this proposal.

9. Relationship of Proposed Research to Work of Other Investigators and Institutions

Contraceptive development and evaluation is not the sole responsibility of manufacturers of pharmaceutical products. Many departments of obstetrics and gynecology, individual researchers, corporations, and privately and publicly funded organizations support contraceptive development and evaluation. In the United States, both the National Institutes of Health (NIH) and AID provide funds for support of all aspects of contraceptive evaluation, including preclinical evaluations and clinical phase I, II, III and IV (postmarketing) trials.

Contracts and grants from AID fund a wide variety of activities related to the provision of contraceptive services, the development of new and improved contraceptive methods and the evaluation of contraceptive safety and acceptability.

In order to avoid duplication of effort the IFRP maintains an up-to-date knowledge and awareness of any new developments and ongoing research through its relationships with departments of obstetrics and gynecology throughout the world, major pharmaceutical firms, other AID-funded organizations, corporations and institutions, and other branches of government concerned with contraceptive development and safety. The IFRP will implement for NIH two contracts relating to contraceptive development in the USA.

The IFRP also maintains close liaison with all of the major population organizations that sponsor services and/or research in areas related to IFRP's interests. A brief description of the IFRP's relationship to some of the major population organizations follows.

WHO (World Health Organization): The Special Program of Research, Development and Research Training in Human Reproduction of the WHO evaluates many aspects of contraceptive development, safety and acceptability. The IFRP works closely with the WHO staff and leadership to avoid duplication of effort.

Representatives of the WHO are frequently invited to participate in IFRP meetings, comment on studies proposed by the IFRP that may be related to WHO activities and share the findings of IFRP-sponsored investigations. The IFRP contributes to the annual review of ongoing contraceptive research that the WHO conducts and international liaison meetings that are attended by all significant public organizations involved in biomedical contraceptive research.

PIACT (Program for the Introduction and Adaptation of Contraceptive Technology): PIACT is primarily involved with the production and packing of existing contraceptives to meet local conditions. The IFRP and PIACT have collaborated on several projects, including an effort to develop a more effective way for the cold sterilization of IUDs and the production and evaluation of technical bulletins for Egyptian pharmacists who are major providers of contraceptives in that country. Delta-Loop and Delta-T IUDs have been provided to the IFRP for research by PIACT through their affiliated organization in Mexico. Without this support, the IFRP's extensive evaluation and development of these IUDs for use in postpartum family planning programs would have been delayed by at least one year.

PARFR (Program for Applied Research on Fertility Regulation): The focus of the PARFR program, which is entirely funded by AID, is the provision of support through subcontracts for basic animal research and phase I and II clinical studies on innovative contraceptive methods. PARFR does not provide support for expanded clinical trials or epidemiologic investigations. The IFRP's Research Department staff work closely with PARFR. Regular meetings are scheduled with the PARFR staff to review and discuss each others' program so as to maintain close cooperation between the two organizations. PARFR does not have an extensive network of clinical investigators to conduct phase II, III and IV (postmarketing) clinical trials, a research and/or field staff to initiate and monitor these trials, or a

research staff to analyze the results of these trials. The IFRP, therefore, assumes the responsibility for conducting investigations to evaluate contraceptive methods and/or products that should be tested in expanded clinical trials based on favorable results from the PARFR-funded projects.

Population Council: The International Committee for Contraception Research (ICCR) of the Population Council funds the development of new contraceptive technologies. The IFRP works closely with the Population Council, thus minimizing any duplication of effort between the two organizations, and ensuring an efficient use of organizational resources. In the last few years the IFRP and the Population Council have collaborated on several projects. The IFRP is conducting studies of the TCU-380 Ag IUD developed by the Population Council and is using the TCU-220C in its studies of Delta-T IUDs. Future collaboration includes work on the levonorgestrel releasing IUD and studies of Norplant, a subdermal implant.

Population Information Program, The Johns Hopkins University: This program is funded to disseminate information on all aspects of family planning to physicians, policy makers, and family planning administrators. The IFRP staff often collaborate on the preparation and review of the Population Reports.

Similar relationships exist with other groups including IDRC, The Rockefeller Foundation and Nordic.

10. Contribution of Proposed Research to Institution Building

It is widely recognized that the IFRP's sponsorship of clinical contraceptive field trials in developing world countries has:

- a. greatly enhanced the development of the research capabilities of the cooperating institutions and countries;
- b. increased in-country awareness of contraceptive-related research needs;
- c. stimulated in-country sponsorship of other research pertinent to reproductive health and family planning; and
- d. speeded up the time required for countrywide acceptance of new or improved contraceptive methods.

The scientific and administrative staff of the IFRP are available to any institution or country with whom it works to provide technical assistance and consultation. The IFRP is actively working toward transferring its knowledge of the management, conduct and reporting of field trials to strengthen institutional capabilities. These transfers are accomplished by in-country training provided by the IFRP staff and by specialized training at the IFRP. The IFRP also makes available skills from one country or region to another as the opportunity arises.

Within the next few years the IFRP will expand considerably the research capabilities of some developing country institutions and national fertility research programs by providing them with specially designed microcomputers. Utilizing the extensive programming knowledge and skills available at the IFRP, many of the IFRP's loading, data editing and cleaning and analysis programs will be modified and adapted for use by these microcomputers. The use of the microcomputers will make the transfer of programs less expensive and considerably speed up the process of technology transfer to institutions in developing countries, thereby enabling them to conduct their own independent research.

Under Contract AID/csd-C-2979 the IFRP initiated the work to establish autonomous national fertility research programs. The funding of these programs is now provided through a grant from AID (AID/pha-G-1198). It is anticipated that funding for these programs will continue. Some of these programs also receive support for specific research work funded under the IFRP's contract to AID. The IFRP will continue to make available to these national fertility research programs the professional expertise of the IFRP and will continue to transfer to them all appropriate technical skills.

The credibility and recognition of the institutions with whom the IFRP works is further enhanced through publications relating to IFRP-funded research. The IFRP makes concerted efforts to encourage and aid its investigators in publishing and disseminating the findings of IFRP-funded research in local, national and international journals and meetings.

11. Expected Results from Proposed Research

It is generally agreed that it is not within the existing knowledge and available technology to produce the ideal contraceptive, one that is culturally acceptable to all men and women, that is 100% effective and without serious adverse effects. It is therefore mandatory that existing contraceptive methods and their modifications be made safer, more acceptable, more effective, less costly and easier to use. It is important that scientific evidence be made available to those responsible for the provision of contraceptive services. This evidence could then be used to provide the most effective, safe and acceptable contraceptive methods so as to minimize the risks of unwanted pregnancy and the possibility of irreversible and life-threatening contraceptive-related events. The IFRP, through its worldwide network of clinical investigators, is in a special position and is uniquely qualified to provide AID (a major supplier of commodities and contraceptive services) and individual investigators, programs and countries with the necessary data and technical assistance on which to base decisions regarding the provision, use, safety, effectiveness and acceptability of different contraceptive modalities.

The work of the IFRP will significantly shorten the time required to develop and market new and improved contraceptive methods, without jeopardizing the well-being of the user. The IFRP has provided AID, national governments, medical institutions, researchers, policy makers, contraceptive service providers and contraceptive users with relevant information on contraceptive innovations and improvements with minimal delay and expense.

The IFRP has been effective in promoting local interest on contraceptive evaluation and safety. Today, regional fertility research programs, funded by the IFRP, complement the work of the IFRP and the IFRP is committed to further upgrading the technical skills of these regional programs. It is expected that fertility research programs will continue to have a significant impact on decisions regarding the provision, use and development of contraceptives.

Through its various publications, the IFRP will continue to be a source and provider of up-to-date information, especially with regard to its research and development work, but also to a widening circle of decision makers and concerned individuals. Local and regional IFRP-funded conferences will effectively disseminate up-to-date information relating to contraceptive technology. It is expected that these conferences will promote and increase the use of effective methods of contraception. The IFRP will continue to provide help to investigators to aid them in publishing the results of their studies, and will encourage them to present results at local, national and international meetings.

The IFRP is an internationally known and recognized organization. The considerable experience and talent of the IFRP staff will be invaluable in the continuation of its work. The IFRP will continue to provide AID with information pertinent to its objectives for the development and provision of safe, effective and acceptable methods of contraception, especially to the developing world. The overall consequences of IFRP's work will be to bring improved health care to women and children and offer a better social and economic environment for tens of millions of families who, in implementing their free and private decision to limit their fertility, will finally reduce the many interlocking politico-economic problems associated with too rapid and uncontrolled population growth.

12. Proposed Five Year Budget and Budget Line Item Justification

	1981-82	1982-83	1983-84	1984-85	1985-86	TOTAL
	\$	\$	\$	\$	\$	\$
Salaries and Wages	828,556	903,126	984,407	1,073,004	1,169,574	4,958,667
Fringe Benefits	173,997	195,075	216,570	241,426	269,002	1,096,070
Consultants	30,269	31,177	32,112	33,075	34,067	160,700
Travel-domestic	39,785	44,161	49,018	54,410	60,395	247,769
Travel-foreign	145,638	160,202	176,222	193,844	213,228	889,134
Equipment	19,396	20,000	21,000	22,000	23,000	105,396
Material and Supplies	35,140	36,897	38,742	40,679	42,713	194,171
Subcontracts	529,363	545,244	561,602	578,450	595,803	2,810,462
Service Centers						
Computer	330,731	347,268	364,631	382,863	402,006	1,827,499
Data Entry	28,793	30,233	31,745	33,332	34,999	159,102
Graphics	33,815	35,506	37,281	39,145	41,102	186,849
Text Processing	136,217	143,028	150,179	157,688	165,572	752,684
Home Department						
Research	150,382	164,074	178,623	196,205	213,864	903,148
Programming	97,418	106,156	115,710	126,124	137,475	582,883
International Projects	34,737	37,736	41,350	43,565	47,485	204,873
Other Direct Costs						
Overseas Office Expense	27,000	40,500	42,000	43,500	45,000	198,000
Freight	12,344	13,332	13,999	14,699	15,434	69,808
Conference Expense	134,945	138,993	143,163	147,458	151,882	716,441
Information Dissemination	65,939	68,936	69,824	70,769	72,772	348,240
Other Purchased Services	7,142	7,356	7,577	7,804	8,038	37,917
Contract Labor	32,293	33,262	34,260	35,288	36,347	171,450
Total Direct Costs	2,893,900	3,102,262	3,310,015	3,535,328	3,779,758	16,621,263
General and Administration	662,845	722,501	787,526	858,403	935,659	3,966,934
Fixed Fee	72,348	77,557	82,750	88,383	94,494	415,532
TOTAL	3,629,093	3,902,320	4,180,291	4,482,114	4,809,911	21,003,729

77

BUDGET LINE ITEM JUSTIFICATION

<u>Salaries and Wages</u>	1981-82	1982-83	1983-84	1984-85	1985-86
\$	828,556	903,126	984,407	1,073,004	1,169,574

Estimated level of effort is approximately 40 full time equivalents

Over the five-year contract period, the IFRP will maintain the same level of effort as is presently funded by AID/pha-C-1172. The amount budgeted takes into account the recruitment of personnel for several positions that have been approved by AID, but are presently vacant. All positions appear on the organization chart in Appendix I, which also includes those currently vacant.

During contract year 1979-1980, AID/pha-C-1172 funded 53.7% of all direct labor charges. Although the level of effort expended on behalf of AID contract work will remain constant over the five-year period, the percentage of the total IFRP work the contract represents will decrease as the IFRP obtains additional non-AID contracts and grants.

The increase in salaries of 9% per year reflects projected salary increases.

<u>Fringe Benefits</u>	1981-82	1982-83	1983-84	1984-85	1985-86
\$	173,997	195,075	216,570	241,426	269,002
Fringe Benefit Rate	21%	21.6%	22%	22.5%	23%

The increase in the fringe benefit rate over the five years represents projected increases in the cost of the benefits and not any changes in the fringe benefit package.

<u>Consultants</u>	1981-82	1982-83	1983-84	1984-85	1985-86
\$	30,269	31,177	32,112	33,075	34,067

The IFRP is working toward making better use of the expertise available from the members of its Technical Advisory Committee (TAC) whose consultancies (13,896 for contract year 1982) are also included in this line item. The IFRP will rely on consultants to provide expertise for its staff on specific projects; to review projects and specific documents, and to share specialist knowledge.

<u>Travel-domestic</u>	1981-82	1982-83	1983-84	1984-85	1985-86
	\$ 39,785	44,161	49,018	54,410	60,395

Domestic travel includes travel of the IFRP staff to monitor ongoing projects and initiate new ones, travel of the professional staff to other research organizations to discuss collaboration or consult with experts, sponsored travel of consultants or collaborators and travel to present papers at scientific and population research meetings.

Staff travel is projected to remain at its present level during the contract period. However, the increase in funding level reflects anticipated increases in the cost of air travel.

<u>Travel-foreign</u>	1981-82	1982-83	1983-84	1984-85	1985-86
	\$ 145,638	160,202	176,222	193,844	213,288

With the initiation of pioneer projects, there is a greater need to monitor them more closely. The IFRP will also provide technical assistance to an increased number of projects, which may require that the professional staff remain at a research center for three or more weeks in order to assist with the analyses of data and provide technical inputs.

The IFRP will also sponsor travel of staff to give presentations at major international congresses, as well as sponsor its investigators to international meetings and to the IFRP for technical training.

The projected budget over the contract period reflects the projected increase in the cost of air travel and per diems.

<u>Equipment</u>	1981-82	1982-83	1983-84	1984-85	1985-86
	\$ 19,396	20,000	21,000	22,000	23,000

The IFRP does not foresee a major emphasis being placed on equipment purchases. However, drawing on the experience of contract years 1979 and 1980, the budgeted figure is an accurate reflection of the projected need for equipment to be used at the IFRP and to be loaned to contributors for the conduct of research projects.

<u>Materials and Supplies</u>	1981-82	1982-83	1983-84	1984-85	1985-86
	\$ 35,140	36,897	38,742	40,679	42,713

This line item includes purchases of study supplies such as pregnancy tests, IUDs, oral contraceptives and barrier contraceptives for clinical trials and other research projects as well as materials to be used in projects at the IFRP.

<u>Subcontracts</u>	1981-82	1982-83	1983-84	1984-85	1985-86
	\$ 529,363	545,244	561,602	578,450	595,803

The IFRP will continue to fund a significant proportion of its research through cost reimbursement subcontracts. These research projects will necessitate a greater commitment of time and resources on the part of investigators and the IFRP.

In the first year budget for research subcontracts, approximately \$110,927 are projected to be expended for forms reimbursement subcontracts. The IFRP is developing clinical trials that involve more complex protocols. The studies of Progestogen-Only Oral Contraceptives in Lactating Women and IUDs with and

without tails are examples of this new type of clinical trial. Laboratory tests that are required as part of the protocol for these studies significantly increase the price of the data collection. In addition, the IFRP will have an increasing number of ongoing Barrier, Fertility Awareness and Systemics studies.

The following list specifies both subcontracts that are expected to be ongoing in contract year 1981-82 and the funds earmarked to be spent during that year. Subcontract expenditures are projected to remain at an approximately constant level during the subsequent four years of this contract proposal.

<u>Project</u>	<u>1981-1982</u>
Health Effects of Vasectomy	\$ 32,102
Evaluation of Levonorgestrel-Releasing IUD	39,328
Local Effects of a Levonorgestrel-Releasing IUD on the Endometrium and Genital Organs	4,630
RAMOS studies Bali and Egypt	94,387
Longitudinal Breast-Feeding	55,619
Levonorgestrel Concentrations in Target Tissues of Users of a Levonorgestrel-Releasing IUD	3,870
Clinical Evaluation of Female Circumcision	30,000
Relationship of Congenital Abnormalities to Contraception	25,000
Negative Health Outcomes and Contraception	60,000
Once-a-Month Injectable	<u>20,000</u>
	364,925
New Projects	<u>53,500</u>
	Subtotal 418,436
Forms Reimbursement Subcontracts	<u>110,927</u>
	TOTAL \$529,363

<u>Service Centers</u>	1981-82	1982-83	1983-84	1984-85	1985-86
Computer	\$ 330,731	347,268	364,631	382,863	402,006
Data Entry	\$ 28,793	30,233	31,745	33,332	34,999
Graphics	\$ 33,815	35,506	37,281	39,145	41,102
Text					
Processing	\$ 136,217	143,028	150,179	157,688	156,572

The projected budget for the four service centers is based on expenditures incurred during contract year 1980. Increases projected over the five-year period reflect increases in salaries for personnel in the service centers and increases in maintenance costs and replacement parts. The projected increase in computer usage is likely to require the addition of another shift in the computer center. This increase is included in the five-year estimates.

<u>Home Department</u>	1981-82	1982-83	1983-84	1984-85	1985-86
Research	\$ 150,382	164,074	178,623	196,205	213,864
Programming	\$ 97,418	106,156	115,710	126,124	137,475
International					
Projects	\$ 34,737	37,736	41,350	43,565	47,485

The home department rate is based on the amount of salary dollars not specifically charged to contracts/grants by direct department personnel and the salaries of support personnel within each direct department.

The combined indirect rate for the three departments at the IFRP is 34.1% of salaries and wages. It is projected that this rate will remain at its present level over the five-year contract period.

Other Direct

<u>Costs</u>	1981-82	1982-83	1983-84	1984-85	1985-86
Overseas Office					
Expense	\$ 27,000	40,500	42,000	43,500	45,500
Freight	\$ 12,344	13,332	13,999	14,699	15,434

Conference						
Expense	\$	134,945	138,993	143,163	147,458	151,882
Information						
Dissemination	\$	65,939	68,936	69,824	70,769	72,772
Other Purchased						
Services	\$	7,142	7,356	7,577	7,804	8,038
Contract Labor	\$	32,293	33,262	34,260	35,288	36,347

Overseas Office Expense - includes rental of facilities and general office expenditures for the Geneva and Bogota offices. Included in this budget is the addition of a third regional office in Africa during contract year 1982-83.

Freight - is calculated at present rates and an increase of 8% per year is projected. This projection covers expected increases in the rates of air and surface shipping. Freight includes shipment of commodities, forms, study supplies, etc.

Conference Expense - The IFRP will continue to sponsor international conferences on family planning and fertility control. Up to three major conferences are planned each year that will be sponsored by the IFRP either alone or with the collaboration of other research and population agencies. This budget line item includes all expenses incurred in the conduct of these conferences, such as staff and sponsored participants travel and per diem, rental of facilities, translation services, if necessary, and development, printing and distribution of proceedings. The increase over the five-year period reflects anticipated increases in travel costs and cost of living.

Information Dissemination - This line item covers the purchase of subscriptions of the IJGO for overseas distribution at \$22.50 per subscription for FY 1981-82 as specified in the agreement with Elsevier/North Holland. It also covers the distribution of IFRP documents, reports and papers as well as the purchase of reprints of IFRP scientific papers published in journals.

Other Purchased Services and Contract Labor - For some projects, the IFRP contracts for services or labor outside of the organization. The Purchased Services line item includes projected expenditures for tests requiring facilities

not available at the IFRP. It also provides funds for fixed priced labor subcontracts. For some specific projects it is more cost effective for the IFRP to use contracted labor than to hire additional staff. Projects that have been funded under contract services include Phase I of the Identification of a Cold Sterilization Method of Copper IUDs and various computer loading and analysis systems/tables.

<u>General and</u>					
<u>Administrative</u>	1981-82	1982-83	1983-84	1984-85	1985-86
	\$ 662,845	722,501	787,526	858,403	935,659

The General and Administrative rate is projected at 80% of Salaries and Wages for the contract period.

<u>Fixed Fee</u>	1981-82	1982-83	1983-84	1984-85	1985-86
	\$ 72,348	77,557	82,750	88,383	94,494

The fixed fee for this contract is 2.5% of direct costs. This fee is considerably lower than that obtained by the IFRP for other government contracts.

eex129.1

13. Budget Analysis

As shown in the proposed five-year budget (Section 12), IFRP is requesting approval at a level of \$3,629,093 for FY 1981, with little increase over the subsequent four years of the contract proposal.

The average annual funding of the contract over the last three years, 1978-1980, was 3.2 million. Thus, the proposed budget for FY 1981 of 3.6 million reflects little change from the level of effort under the current contract, i.e., the proposed work plan (Section 4) will be conducted by the IFRP using the present level of staffing and with its present facilities.

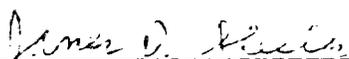
The funding requested by IFRP reflects projected price levels and the expenditure of time and resources required to develop and evaluate increasingly sophisticated new methods of contraception and in particular to conduct Phase IV (post-marketing) trials. We believe this reflects a reasonable projection of activity.

Having the primary responsibility for carrying out Phase III clinical trials and Phase IV studies vested in a single organization such as IFRP provides significant economies. Considering the great expense of carrying out contraceptive clinical trials, this mechanism has been shown to be cost-effective in serving AID's objectives in this area.

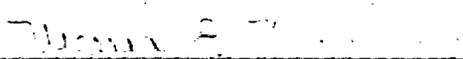
14. Proposing Office General Evaluation

The IFRP since its inception has been of continuous assistance to AID by testing and evaluating the performance, safety, and acceptability of different contraceptive modalities currently used in AID-sponsored family planning programs.

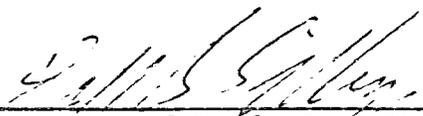
This includes a multitude of female sterilization instrumentation and methodologies, low-dose oral contraceptives, copper IUDs and Neo Sampoo foaming vaginal contraceptive tablets. An additional array of potentially useful methods are currently being tested. Moreover, the organization has entered the area of "Phase IV" studies to collect information on the long-term health effects of various fertility control methods and this information will become of increasingly greater importance to AID. The proposing office therefore considers this to be one of its most important projects. Its continuation is strongly urged.



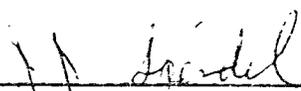
Signature of Monitor, J.D. Shelton



Signature of Monitor, M.E. Mamlok



Signature of Duff G. Gillespie
Chief, Research Division



Signature of J.J. Speidel
Acting Director, Office of Population