

PROJECT STATEMENT

Date: January 31, 1978

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. Elton Kessel

Duration: RAC authorized duration: 7 years (6/71 - 7/78)
RAC authorized funding: 7 years (6/71 - 7/78)
Additional funding requested: 3 years (8/78 - 7/81)
Extension or duration requested: 3 years (8/78 - 7/81)

Total Estimated Cost: 26,190,876

Amount Requested for
RAC Approval: 10,500,000

Funding by Fiscal Years:

FY 71	3,106,000	TQ	0
FY 72	1,800,000	FY 77	3,590,266
FY 73	0	FY 78	3,250,000
FY 74	1,499,610	FY 79	3,500,000
FY 75	2,695,000	FY 80	3,750,000
FY 76	3,000,000		

Project Manager: DS/POP/J.J. Speidel/
DS/POP/R E.S. Maguire/J.D. Shelton

2. Narrative

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

a. Over the past six and a half years, IFRP has made the following major contributions to the field of fertility control technology. It has demonstrated:

- (1). the safety, efficacy and acceptability of female sterilization by minilap in developing countries, particularly in the outpatient setting,
- (2). the safety, efficacy and acceptability of female laparoscopic sterilization via the tubal ring in developing countries,
- (3). the safety, efficacy and acceptability of menstrual regulation in developing countries,
- (4). the relative lack of safety of female sterilization by colpotomy,
- (5). higher pregnancy rates with the Hulka clip technique of female sterilization,
- (6). the safety of local anesthesia for laparoscopic sterilization,
- (7). the acceptability of vasectomy in a Latin American setting,
- (8). the safety and efficacy of using a hand pump in the performance of menstrual regulation,
- (9). the competence of paramedical personnel to perform menstrual regulation,
- (10). the effectiveness of copper containing IUDs (Cu-T-200) for up to six years of use, and
- (11). the symptoms associated with three different oral contraceptives, and symptoms associated with "crossover" to another oral contraceptive.

b. IFRP and AID have agreed to undertake, or are discussing undertaking, the following research projects:

- (1). Conventional or "barrier" methods of contraception such as foaming vaginal tablets and suppositories, the vaginal collagen sponge and "C-Film" spermicidal agent.
- (2). Intrauterine quinocrine pellets for female sterilization.
- (3). Needlescope and laparocator techniques for female sterilization.
- (4). Bleier clip for female sterilization.
- (5). Techniques for reversal of male and female sterilization.
- (6). Use of "vas flushing" along with vasectomy to obtain azoospermia at the time of the operation.
- (7). Evaluation of low dose (30-35 mcg estrogen) oral contraceptives.

- (8). Immediately post-placental IUDs with biodegradable extensions to obtain acceptable rates of expulsion.
- (9). Medicated IUDs with antifibrinolytic agents as well as IUDs medicated with longer acting steroids.
- (10). Long-term follow-up study of abortion sequelae.
- (11). Thromboembolic surveillance study of Asian women.
- (12). Analysis of the world's largest data base on IUD's and on menstrual regulation.
- (13). Evaluation of the new "laparocator" for female sterilization.

During the last review of the IFRP contract on April 1, 1977, the Research Advisory committee (RAC) recommended that the project be extended for one year at the level of 3.7 million for continuation of current research activities. Future support and funding levels of IFRP were to be contingent on the outcome of a special RAC evaluation to be carried out during 1977.

The RAC subcommittee conducted its site visit of IFRP on September 6 and 7, 1977. While their overall evaluation of IFRP was favorable, a list of specific recommendations were made concerning the future scope and level of IFRP's activities (See Progress Report, Expanded Narrative Statement). These recommendations have been complied with in full and this compliance is clearly reflected in the Project Statement.

c. During the next contract period, the following changes can be noted:

- (1). IFRP's scope of work will be narrowed to focus on Phase III clinical testing of fertility control technologies and limited Phase I and Phase II research. Following the expiration of Contract AID/pha-C-1111, development and testing of new and improved IUDs will be conducted under the IFRP research contract. Other IFRP activities, outside "pure research", will be funded under an extension of the current grant.
- (2). The number of active Research Centers conducting sophisticated investigations will be reduced to 55.
- (3). A tightened organizational structure and revised study development and approval process will be in effect.
- (4). Proposed funding levels for FY 78, FY 79 and FY 80 represent more than a 50% reduction in the funding request submitted for RAC review in 1977.

B. Expanded Narrative Statement

1. Project Description, Background and Progress Report

a. Description and Background

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

During the six and one-half years of its existence, the IFRP has produced standardized study protocols, data collection instruments, instruction manuals and computer programs to rapidly analyze research data in eight major study areas: intrauterine contraception, systemic contraception (both oral and injectable), female sterilization, male sterilization, barrier contraceptives, menstrual regulation and pregnancy termination, epidemiological surveys and equipment integral to fertility control technology. The IFRP now has a significant capability for Phase I and II research on intrauterine devices. IFRP has established relationships with over 300 physicians in over 40 countries, primarily less developed countries (LDC's).

The headquarters of the IFRP is in Research Triangle Park, North Carolina, where management of the programs is effected through continuous dialogue with the contributing physicians, site visits, and periodic Contributor conferences. As IFRP research methodology has attracted the interest of national groups in LDCs, several national semiautonomous fertility research programs have begun to be established, using IFRP standard forms and computer systems as the basis for their organization.

The research efforts of IFRP add significantly to the body of scientific knowledge in the field of fertility control technology. Feedback from IFRP to its contributors in the form of computer generated standard tables and special analyses enable leading clinicians in LDCs to write research reports of excellent quality. The IFRP staff also prepare reports of pooled data from many parts of the world. Information about methods which have proven safer, more effective and more acceptable is disseminated widely through scientific conferences and publications including the International Journal of Gynaecology and Obstetrics which is the official organ of the IFRP and the International Federation of Gynaecology and Obstetrics (FIGO).

A Medical Advisory Committee determines broad research priorities among the many drugs, devices and procedures that are appearing in the field. A Protection of Human Subjects Committee approves each new method and study design and periodically reviews study results to assure that the

benefits derived outweigh the risks to volunteers participating in them.

Support of this program is sought in order to continue this uniquely effective international mechanism for field testing fertility control methods, techniques and devices, which provides data relating to the safety, effectiveness, and acceptability of these methods. The institutionalization of family planning in many countries has heightened interest on the part of government officials, administrators and clinicians in the means of achieving fertility control. Scientifically designed and carefully monitored studies under use conditions at the clinics and hospitals offer the best opportunity for impartial evaluation of the methods. The present and projected computer data base of IFRP is an important source of information in the eight general study areas cited above. IFRP also will support research needed to bring promising methods of fertility control to the point where clinical studies are appropriate. As needed, limited Phase I and Phase II research is done on a limited basis. This has been particularly true of IUDs. The IFRP international network of Contributors will continue to be the final common path for field trials, under use conditions in the LDCs, of new and improved fertility control technology developed at IFRP, under other AID projects and through other public and private agencies.

Continuation of the program will provide for training of collaborating investigators in the newer techniques of fertility control so that clinical trials can be initiated in the LDC setting. Interpretation of computer programmed standard tables imposes a form of quality control in scientific reports.

During the last few years of the Program, the level of expertise has been developed to such a degree among Contributors in several LDCs that semiautonomous research programs are being organized, utilizing IFRP research methodology, i.e. India, Bangladesh, Colombia and the Sudan. Further transfer of technology and responsibility to national fertility research programs will be funded through other avenues.

IFRP was organized on July 1, 1971. The initial contract period was for a total of five years, to June 30, 1976, with initial funding for three years, to June 1974. Subsequently, authorization was provided to extend the period of services and funding to July 30, 1978, a total of seven years. By the end of 1974, IFRP had developed into a large international field trial Center with its own administration. It was then decided by mutual agreement of the University of North Carolina, AID, and IFRP that the program could operate as an independent non-profit foundation. On February 14, 1975, the IFRP officially separated from the University and is now located in Research Triangle Park, North Carolina. The current proposal requests continued support of the Program for an additional three years, effective July 31, 1978 when the present funding authority expires.

b. Progress Report

An comprehensive evaluation of the program was made by the Research Division of the Office of Population and by a Subcommittee of the

Research Advisory Committee (RAC) in September 1977. Both evaluations recommended continuation of the project. The following were the RAC recommendations:

RAC SUBCOMMITTEE RECOMMENDATIONS

1) IFRP should set and then try to respect its ceilings on the number of participating centers, the amount of data to be generated, and the duration of data collection for each study.

2) IFRP should invest less effort and be more selective in maintaining accumulated data as a repository of data for future use.

3) IFRP should develop more complex study designs and use more sophisticated analytical techniques in processing existing data.

4) IFRP should terminate those studies where enough data have already been gathered.

5) Institution building efforts should be limited to those required for direct research objectives.

6) IFRP should continue to place its greatest emphasis on practical Stage-3 research although a limited amount of relevant Stage-1 and Stage-2 research should be continued.

7) IFRP should create overall study plans for each of the six major areas of work and should give priority to specific elements in progressive time periods.

8) IFRP should concentrate on studying the clinical and closely-related allied services needed for the implementation of the various contraceptive technologies.

9) IFRP should not attempt to cover the much broader administrative, community and social aspects of family planning program development and operation except on a pilot basis, and then only after review and approval by AID.

10) IFRP library and information services should aim at meeting the directly related needs of IFRP staff and collaborators and not at developing a world library resource in the field.

11) IFRP should reassess its staffing pattern and the makeup of its consultative groups to be sure that they meet the future needs of the program.

12) IFRP should similarly reassess its overall structure and its internal administrative mechanisms to be certain

that they are designed to produce the desired results with the least possible expenditure of time and effort.

13) IFRP funding should be reduced from that requested in its February 1977 proposal in keeping with the above contractions of the scope of work, more strictly limiting its activities to its primary goal of "pure research."

14) In the future, only the research components of the IFRP program to be undertaken with AID funding should be reviewed by RAC for its approval prior to their implementation.

Changes Instituted as a Result of RAC Subcommittee Recommendations

(1). Elements covered under the Project Statement. A limited number of activities are proposed in this document, all closely related to research and consistent with the RAC subcommittee recommendations. These include:

- (a). Stage-3 contraceptive research (the major component);
- (b). A limited amount of Stage-1 and Stage-2 research;
- (c). A limited amount of training and equipment relevant to the research;
- (d). Analysis of data already in the IFRP data bank; and
- (e). Limited distribution of research findings such as presentations at meetings and the International Journal of OB-GYN.

(2). Participating Centers.

During the past year, the organization has carefully scrutinized the institutions where these physicians are located and evaluated the capability of the medical staff. Fifty-five (55) of these facilities have been classified as research centers capable of excellent, highly sophisticated investigations. Five (5) are located in the United States, seven (7) in other developed countries and forty three (43) in LDCs. There are an additional twenty one (21) centers in LDCs capable of reliable research of limited sophistication.

(3). Overall Structure and Staffing Pattern

The IFRP has recently undergone an in-depth self evaluation. First, its objectives were reviewed and reaffirmed as: (1) field testing of new developments in fertility management technologies which (a) offer improved protection against unwanted pregnancy over technologies in general use in LDCs or (b) offer equal protection at lesser costs in resources or (c) offer equal protection with reduced discomfort or side effects to the user; (2) building a professional, capable, international cadre of clinical investigators in the fertility management field; and (3) assisting less developed countries in establishing their

own fertility research programs.

An organization was then designed to meet the needs of management by objective for the next five years. All work estimated to be required was reviewed and new position descriptions were written to assign responsibility and distribute workload. Qualifications for each position were then defined and staffing adjustments were implemented in September, 1977. In addition, the Medical Advisory and Protection of Human Subjects Committees are currently under review in line RAC subcommittee recommendations.

(4). Reevaluation of Ongoing Studies and Revised Procedure for New Study Development.

As the revised organization began to function, a comprehensive review of all activities was instituted. Protocols for each study area are being revised to move away from straight technological comparisons and toward more comprehensive research and more sophisticated analysis.

The next step, conducted concurrently with protocol revision, was a comprehensive review of all studies underway and in the planning stage. Data collection for studies on which adequate data existed were terminated. Research centers were scrutinized and reclassified. Centers with demonstrated capability for high quality sophisticated research were classified as Research Centers. The number of Research Centers will be maintained at about fifty. At the conclusion of the reorientation of work within the organization, the process of study development and approval was reexamined. The modus operandi of IFRP at present is: to review carefully, with a Medical Advisory Committee of experts outside the IFRP staff, each modification of existing and new human reproductive management techniques to assess its characteristics as well as its appropriateness for widespread use in reproductive management programs, particularly those concerned with delivery of service in rural areas of the developing world. From this review, technologies are chosen for field trials under use conditions.

Once a technology has been chosen, the Associate Director for Research convenes a staff Task Force composed of scientific personnel with relevant expertise to plan a study strategy. This strategy is reviewed with the Protection of Human Subject Committee. Following clearance by this Committee, the scientific staff designs the study. This includes production of a protocol, data collection instruments, instruction manuals, data processing screening programs, computer analysis programs, and all other tools necessary for the conduct of the field trials. As this work progresses, Research Centers are selected on the basis of their capabilities to meet the requirements of the study. An agreement for the conduct of the field trials is then arranged between the IFRP and the Centers.

Data are collected from the one or more Centers where the field trials are taking place, screened visually and by computer, and loaded into computer memory banks. From these banks, the data are analyzed and publications prepared by the Contributors for dissemi-

nation within their own country and by IFRP for professional journals, international conferences, and through other media in order that widespread knowledge of the effectiveness of the technology may be brought to the attention of all program managers.

Priorities within each of the eight study areas are determined by the Task Force responsible for the individual area. Overall priorities for studies are set by a committee composed of the Director, Medical Director, and the Associate Directors of IFRP. Priorities are reviewed on a monthly basis.

(5). More Complex Study Design.

Although basic, straightforward, randomized clinical trials have been the backbone of IFRP's research, IFRP recognizes the need for more complex study designs and is vigorously pursuing implementation of such techniques. Some examples prepared or already underway are:

- (a) Multivariate analysis of pooled IUD data to determine factors influencing efficacy and discontinuation;
- (b) Multivariate analysis of factors (including induced abortions) influencing spontaneous abortion, stillbirths and low birthweight infants in Singapore;
- (c) Correlation of objective measurements of blood loss with subjective representations using the Automatic Interaction Detection (AID) computer program;
- (d) Case-control study of Thromboembolic Disorders in Asian Women;
- (e) Development of improved life-table technique for evaluating IUD continuation;
- (f) Development of an "irregularity index" for assessing degree of menstrual irregularity.
- (g) Several "crossover" studies of oral contraceptives involving blind crossover from several brands of pills to each other.

IFRP will continue to strive for more sophistication in study design and analysis. In addition to individuals recently hired who have biostatistical backgrounds, IFRP is making increased use of expertise available at nearby universities.

(6) Institution Building.

Institution building will only be for the purpose of reaching direct research objectives. (See Section 7, "Contribution to Institution Building.")

(7). Reduced Funding Request.

Since this proposal is limited in scope to the more directly research related aspects of IFRP's activities, the funding is reduced from the February, 1977 proposal which called for 7,683,614 for FY 1979.

Additional information of the RAC subcommittee evaluation as well as

A.I.D.'s own evaluation is presented in section 10, "Internal and External Review."

Research Accomplishments

The work accomplished to date may be summarized as follows:

- (1). Straight and Comparative clinical study protocols and data collection instruments have been designed, pretested, refined and placed into wide field use in the major study areas, i.e. pregnancy termination, menstrual regulation, IUDs, male and female sterilization, and systemic contraceptives (orals and injectables).
- (2). Data processing and analysis have reached a high degree of sophistication, reliability and efficiency.
- (3). IFRP has established an international network of more than 300 Contributors in over 40 countries. These clinical investigators have been trained in IFRP research methodology and medical procedures, and are able to conduct standardized clinical trials.
- (4). Several national and regional fertility research programs are in the process of being organized to coordinate the research activities, including data collection management, in their geographic areas. Semi-autonomous programs are now functioning in India, Bangladesh, Colombia and the Sudan.
- (5). The computer capabilities have been employed to provide data on field use of new means of fertility control in the program context through a Family Planning Clinic Record system, a Maternity Record system, and record system for Community-Based Distribution of Contraceptives.
- (6). In collaboration with its Contributors, IFRP has played a major role in developing improved techniques of fertility regulation.
- (7). Research data on more than 300,000 cases in the study areas have been processed and loaded into the IFRP data bank.
- (8). In excess of seven hundred seventy five (775) scientific papers and consultant reports have been prepared by IFRP staff and Contributors to disseminate research findings. Presently, over one hundred (100) scientific papers are prepared each year.
- (9). Under IFRP auspices, and in cooperation with the International Federation of Gynaecology and Obstetrics (FIGO), the International Journal of Gynaecology and Obstetrics has been revitalized with a new expanded format, a markedly increased distribution and an improved quality of articles.

Significant work in the major study areas are detailed below:

Intrauterine Contraception

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

IFRP has prepared the following protocols with the associated data collection instrument, instruction manuals, computer programs, and other necessary procedures.

1. General Protocol for Comparative IUD Studies
2. Protocol for the Comparative Study of IUD Insertion Technique - Endometrial Aspiration Prior to IUD Insertion
3. General Protocol

As of the date of this Project Paper, the following studies have been completed with the results indicated.

1. Lippes D vs. Antigon F. After one year the pertinent event rates, continuation, and loss-to-follow-up were not significantly different.
2. IUM vs. Wishbone IUM. One year of use of both versions of the IUM resulted in low pregnancy rates, low expulsion rates, and low bleeding and/or pain removal rates in postabortion women.
3. Copper-T. The results of the long-term effectiveness study indicate that the Cu-T-200 is a safe and effective contraceptive for at least six years.
4. Copper-7. Evaluation of the long-term use (5 years) effectiveness of the Cu-7-200, indicated that the yearly rates of pregnancy, expulsion and removal for medical reasons did not increase with increasing duration of use.
5. Spring Coil with Hydron Coating vs. Spring Coil. The Spring Coil is associated with a low pregnancy rate but the accompanying removal rate for bleeding remained unacceptable with Hydron coating.
6. Lippes-C with Copper vs. Lippes C. There was no significant difference in any of the pertinent event rates.
7. IUM with Hydron vs. IUM-EVA vs. IUM. With the use of bleeding calendars, it was determined that the standard IUM was associated

with less bleeding than the Hydron coated device. The soft IUM-EVA was associated with high expulsion rates.

8. Ypsilon vs. Lippes D. A comparative trial of the Ypsilon and Lippes Loop D was terminated because of high expulsion rate of the Ypsilon.
9. Dalkon Shield for interval patients. The pregnancy and expulsion rates are low and the bleeding/pain rate is high in interval women.
10. Tecna Fluid Device for interval patients. Event rates are higher than those previously reported for the M-device, the Loop D and Dalkon Shield in this clinic. Bleeding associated with the use of this device was heavy and persistent.
11. Latex Leaf vs. Lippes D for interval patients. Preliminary results show a lower expulsion and bleeding/pain removal rate for the Latex Leaf, and no significant difference in the reports of leukorrhea.
12. TR-10 for interval patients. The pregnancy rate was high, but lower than that for two other inert T-shaped devices. This study confirmed the hypothesis that pregnancy rate is inversely associated with thickness of the IUD.
13. U-Coil and U-Coil with Progesterone, Quadracoil and Quadracoil with Copper, and U-Coil with AMCA and U-Coil with Copper. Analysis of the quantitative results indicates reduction of mean blood loss with insertion of progesterone U-Coils, while the mean blood loss increased with the Plain U-Coil. There was no difference between the Quadracoil and the Quadracoil with Copper. Reports of heavy menstrual bleeding were more prevalent at the one- and three-month follow-ups for the Copper U-Coil acceptors than for those using the AMCA-loaded U-Coil, demonstrating the capacity of tranexamic acid to reduce menstrual blood loss based on perceptual reports.
14. Copper-7 and Copper-7 with Zinc for interval patients. The addition of zinc reduces the rate of pregnancy and decreasing the size of the Cu-7 reduces the expulsion rate.
15. M 211 and M 213 for interval patients. The wider M 211 has a significantly lower pregnancy rate than the 213.
16. Latex Leaf with Copper and Zinc for postpartum patients. The Latex Leaf compares favorably with the Lippes Loop in this postpartum study.
17. IUM for postabortion patients. Pregnancy, expulsion and bleeding/pain removal rates derived from this study compared favorably to similar rates derived from a preliminary study of interval IUM insertions and to results from studies of postabortion insertions using other devices.

18. Lippes D and Lippes D with Silastic Extensions for postpartum patients. The expulsion rate at three months for the Lippes D with Silastic Extensions with insertions done within two hours of delivery was significantly less than in a comparable data set at the same center using the Lippes D.
19. Dalkon Shield for postpartum patients. The expulsion and pregnancy rates are higher for the Dalkon Shield than the Lippes Loop D.
20. Monterrey IUD for postpartum patients. Although the expulsion rate was low and pregnancy and bleeding rates were average, complication rates were high.
21. LEM for postpartum patients. The LEM does not have optimal retention properties when inserted immediately postpartum; however, the retention rate is well within the range of acceptability in comparison to the retention ability of other devices tested in such a program.

The following studies are now ongoing.

1. IUM vs. Wishbone IUM vs Lippes D.
2. Spring Coil for interval patients.
3. Weiss Device for interval patients.
4. Lippes Loops C and D for interval patients.
5. Szontagh for interval patients.
6. Plain T for interval patients.
7. U-Coil for interval patients.
8. IUM for interval patients.
9. Copper-T and Copper-T-220 for interval patients.
10. Lippes Loop C with copper for interval patients.
11. Finland-T for interval patients.
12. Copper Szontagh for interval patients.
13. Multiload for interval patients.
14. Tapered Loop vs. Lippes D.
15. Photoreduced Loop vs. Lippes D.
16. Latex Leaf vs. Lippes D.
17. Copper-T vs. Lippes D.

18. Lippes D with Copper vs. Lippes D.
19. Copper-T-220 vs. Lippes C.
20. U-Coil with Progesterone vs. U-Coil.
21. Lippes D with AMCA vs. Lippes D.
22. Soonawalla-Y vs. TR-10.
23. Copper-T-200 vs. TR-11.
24. Multiload vs. Multiload 250 with EACA vs. Multiload 375.
25. Postpartum T vs. IUM vs. Copper-T vs. Lippes D.
26. Lippes D with Silastic Extensions vs. Lippes D with Chromic Sutures.
27. Lippes D with Sutures vs. Lippes D with Molded Extension.
28. Tapered Lippes D and Photoreduced Lippes D.
29. Copper-T-200 for interval patients.
30. Copper-T-220 for interval patients.
31. Copper-7 and Multiload Copper for interval patients.
32. EACA and AMCA for interval patients.
33. Tapered Loop, Lippes D, and Postpartum T for postabortion patients.
34. Postpartum T, Copper-T, and IUM for postpartum patients.

The following studies are projected for the future.

1. Copper-T vs Multiload vs TR11 for interval patients.
2. Copper Loop D vs. Copper-T vs Multiload for interval patients.
3. Copper-T vs Lippes D for interval patients.
4. Multiload vs. Plain Multiload for interval patients.
5. Lippes D with AMCA vs. Lippes D Blank Loaded for interval patients.
6. Photoreduced Loop vs. Lippes D for postabortion patients.
7. Lippes D with Chromic Sutures vs. Lippes D for postpartum patients.

8. Lippes D with Chromic Sutures vs Copper-T with Chromic Sutures for postpartum patients.
9. Lippes D with Collagen Extensions vs Lippes D with Molded Extensions for postpartum patients.
10. Postpartum T vs Lippes D for postpartum patients.
11. Photoreduced Loop, Polypropylene T, and TR-11 for interval patients.
12. Copper Lippes D.
13. Copper-T-220.
14. Finland T.
15. Copper-7.
16. Multiload and Postpartum T for postabortion patients.
17. Lippes D with Collagen, Lippes D with Chromic Sutures, and Postpartum T for postpartum studies.
18. Experimental postpartum devices will be compared to standard devices to evaluate expulsion rates. Presently Lippes Loop D and Cu-T's have been modified with biodegradable sutures, collagen, and gelatin/polylactic acid projections and extensions. As more biodegradable and biocompatible materials are identified, they are used in modifications.
19. The method of insertion will also be studied. Inserters are being developed to insert the T and Loop in the open position. Their use will be compared to hand insertions for differences in infection and expulsion rates.
20. Devices modified to reduce bleeding will be studied. Two progesterone devices, Alza T and Progestacoil, represent two different sizes and shapes and will be studied for optimal use. Antifibrinolytic substances such as AMCA, Trasylol, and EACA will be tested using Loops and T's as carriers.
21. New devices to increase continuation for interval patients will be studied as they become available, both from the IFRP development work and from independent developers. The TR series and the Tapered Photoreduced Loop will be studied.
22. Studies will be started to evaluate methods of reducing infection. Two suggestions are the use of a medicated string and the use of neosporin gel on the inserter before insertion.

Systemic Contraception (orals and injectables)

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

IFRP has prepared the following protocols with the associated data collection instruments, instruction manuals, computer programs and other necessary procedures.

1. Comparative Oral Contraceptive Study.
2. Protocol for the Evaluation of Effects of Different Systemic Contraceptives on Lactation.
3. Revision of the Comparative Systemic Protocol.
4. General Comparative Protocol for Systemic Contraceptive Studies.
5. Ramadan Pill Protocol.
6. Lactation Pill Protocol.
7. Husband Pill Protocol.
8. Comparative study of two oral contraceptives including endocrine and nutritional assessments in Sri Lanka and Nigeria.

As of the date of this Project Paper, the following studies have been completed with the results indicated.

1. Norinyl 1/50, Norlestrin 1, and Ovrал Cross-over Study.
 - (a). The side-effects of Ovrал were generally of longer duration compared to Norinyl or Norlestrin.
 - (b). The incidence of various side effects in these studies was higher than generally reported in the literature. The incidence of breakthrough bleeding (excluding spotting), for instance, obtained in this study was 18 to 26% compared to about 11% reported in the literature.
 - (c). Changes in the amount of menstrual flow (either an increase or decrease compared to prior to pill use) were reported by most women during the study. Of Ovrал, Norinyl and Norlestrin users, 60, 80 and 90% had reported changes in the menstrual flow.

- (d). The incidence of breast discomfort was higher for Norinyl users (43.0%) than for Ovral (25.8%) or Norlestrin users (28.6%).
- (e). The incidence of breakthrough bleeding was lower in the first cycle for Ovral users but increased in the subsequent cycles. For Norinyl and Norlestrin users, the trend was reversed.
- (f). The incidence of nausea was higher for Ovral users than the other OCs.
- (g). A switch from Ovral to Norinyl or vice versa resulted in an increased incidence of nausea. The Norlestrin users, when switched to Ovral, reported a higher incidence of nausea; no significant changes were reported when the switch was made to Norinyl (from Norlestrin).
- (h). There was significant increase in the incidence of abdominal bloating when Norlestrin users switched to Ovral.
- (i). The Norlestrin users, when switched to Norinyl, reported a higher incidence of acne.
- (j). The incidence of breakthrough bleeding increased significantly when Ovral users switched to either Norinyl or Norlestrin. When Norinyl or Norlestrin users switched to Ovral, the incidence of breakthrough bleeding declined.
- (k). Ovral users, unlike Norinyl and Norlestrin users, showed no change in the probabilities of bleeding for the different days of the contraceptive cycle.
- (l). When grouped into three weight categories--underweight, normal weight, and overweight--women using oral contraceptives differed significantly in the incidence of reported side effects.
- (m). Norinyl and Norlestrin have similar patterns of breakthrough Ovral. For Norinyl and Nolestrin, withdrawal bleeding started sooner after ingestion of the last contraceptive pill and there was a higher probability of breakthrough bleeding than with Ovral.

2. Comparative Study of Norlestrin, Norinyl, and Ovral.

- (a). There is no significant increase in breakthrough bleeding among smoking oral contraceptive clients compared to nonsmoking clients.
- (b). A method for quantifying breakthrough bleeding in oral contraceptives was developed to compare bleeding patterns of women on different oral contraceptives.
- (c). A index was developed to combine two aspects of break-

- (c). An index was developed to combine two aspects of breakthrough bleeding: severity and duration.
- (d). Norinyl and Norlestrin have similar patterns of breakthrough bleeding and withdrawal bleeding (average duration of breakthrough bleeding 2 days; average onset of withdrawal bleeding 24 days). Ovral differs slightly (average duration of breakthrough bleeding 1.7 days; average onset of withdrawal bleeding 23 days).
- (e). 71.0% and 78.9% of the Norlestrin and Norinyl clients stated a decrease in the amount of menstrual flow (compared to their cycles prior to initiation of contraception), while 53.3% of the Ovral clients stated a decrease in the amount of menstrual flow.
- (f). The highest probability of breakthrough bleeding for all 3 groups was between days 15-21. The lowest risk of breakthrough bleeding for Norinyl and Norlestrin users was between days 1-7 while the lowest risk for Ovral users was between days 8-14. There was little change in the probability of breakthrough bleeding with Ovral (p. 0.179-0.249). The probability of breakthrough bleeding of the Norinyl/Norlestrin clients varied from 0.067 between days 1-7 to 0.471 between days 15-21.
- (g). The following significant differences were observed in the side effects of oral contraceptives by weight groups of the clients:
 - (1). Underweight women reported a higher incidence of dysmenorrhea than normal or obese women.
 - (2). Vomiting, nausea and breast discomfort were lower among obese women compared to the normal and underweight women.
 - (3). Normal women had fewer headaches than either underweight or overweight women.

3. Crossover Study: Ovral or Norinyl to Brevicon or Lo-Ovral

- (a). The rate of reported side effects was consistently higher when women were specifically queried about symptoms compared to when the mode of inquiry was a general query.
- (b). The percentage of women reporting symptoms was higher for the two contacts (13th and 23rd days of the cycle) than the one contact schedule (28th cycle days).
- (c). The four symptoms occurring most frequently among the oral contraceptive users were the same for both Ovral and Norinyl users before cross-over.

- (d). All symptoms decreased after cross-over to the low-estrogen pills with the exception of breakthrough bleeding which increased (these symptoms included nausea, headache, abdominal discomfort, acne, breast discomfort).
 - (e). Breakthrough bleeding was 4-5 times greater among the Ovral users who changed to Brevicon and Lo-Ovral and 2-3 times greater among the Norinyl clients who changed to Brevicon or the Lo-Ovral.
 - (f). The maximum change in decrease in diastolic blood pressure for any group after cross-over was 3.7 and in systolic 10.1. There were essentially no differences in the declines in blood pressure between the two low-estrogen pill groups.
 - (g). There were essentially no differences in the average day of onset of menses among women in the Brevicon and Lo-Ovral groups, nor was there any difference in the average duration of withdrawal bleeding among these two groups.
 - (h). About half the clients reported a decreased amount of menstrual flow in all 4 cross-over groups. However, the largest proportion of clients reporting delayed menses was among the Brevicon clients (both those who had previously been on Ovral and those previously on Norinyl.) In spite of this finding, only 0.5% of the Brevicon clients discontinued because of amenorrhea (delayed menses).
 - (i). Ten percent (10%) of the clients discontinued pills during the first 6 months after cross-over. Thirty five percent (35%) of the Brevicon clients and 54% of the Lo Ovral clients discontinued for reasons unrelated to pill symptoms (i.e., moving, parents had found out they were taking contraceptives, discontinued seeing sexual partner, etc.).
4. Comparative Clinical Oral Contraceptive Study in Sri Lanka (done in collaboration with the Southwest Foundation). The endocrine and nutritional data from this comparative study of Norinyl and Ovral is currently being analyzed by Drs. Joseph Goldzeiher and George Nicholds. The IFRP role in this study was mainly one of data processing. A brief analysis of reported symptomatology and reasons for discontinuation was done at the IFRP. These results are as follows:
- (a). Of the clients who discontinued contraception, 29.4% gave "husband's objection" as their reason.
 - (b). After 1 year of contraceptive use, 82.6% of the clients were continuing to use contraception.
 - (c). The pregnancy rate per 100 women was at one year 2.6 for the Norinyl clients and 1.6 for the Ovral clients. All these pregnancies were associated with irregular use of the pills (deleting more than 5 pills per cycle, waiting more than 5 days between cycles to get the next supply from the clinic).

(d). There were no significant changes in the average duration of menses and length of menstrual cycles after initiating contraception in either of the pill groups.

(e). Between cycles 1 and 6, 3-4% of the clients complained of some irregular bleeding. After the 6th cycle, $\leq 1\%$ complained of irregular bleeding.

The following studies are now ongoing.

1. Comparative study of Norinyl-Brevicon-Lo-Estrin.
2. Straight study of Depo Provera.
3. Comparative crossover study of Norinyl-Brevicon-Lo-Estrin.

The following studies are projected for the future.

1. Comparatives between 2 or more low-estrogen pills.
2. Comparatives between 1 or more low estrogen pills and a high estrogen pill.
3. Comparatives between 1 or more low estrogen pills and a progesten only pill.
4. Cross-over studies of high to low dose estrogen pills.
5. Cross-over studies of low-dose to low-dose estrogen pills.
6. Comparative studies of injectables currently available.
7. Lactation Pill Studies (to be done in developing country rural populations). Phase 1 will study the acceptability of a progesten-only pill and continuation; phase 2 will study the effect on infant weight gain and mother's continuation rates for progesten-only pill.
8. Husband Pill Studies (to be done in developing country rural populations). There are 2 objectives of these studies. First, to determine if pills are more acceptable and continuation rates higher if the husband is involved initially and second, to determine if the husband has an accurate knowledge of his wife's health status.
9. Ramadan Pill Studies (to be done in urban and rural developing country populations). These will test the acceptability and continuation of an oral contraceptive initiated during Ramadan to prevent menses during Ramadan (63 day cycle).
10. Resumption of Menstruation and Menstrual Patterns Following Discontinuation of Systemic Contraceptives. These studies are to be conducted in developing and developed countries to determine differences in return to regular menses and changes in menstrual pattern after discontinuation of systemics.

Female Sterilization

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

IFRP has prepared the following protocols with the associated data collection instruments, instruction manuals, computer programs, and other necessary procedures.

1. Comparative Female Sterilization Study.
2. Intergovernmental Coordinating Committee (IGCC) Anesthesia Studies.
3. Topical Anesthesia Female Sterilization Study.
4. A Preliminary Study of IUD Use and Fallopian Tube Inflammation in Women Undergoing Sterilization.
5. Female Sterilization Acceptability Study.

As of the date of this Project Paper, the following studies have been completed with the results indicated.

1. Laparoscopy: Electrocoagulation vs. Spring-loaded Clip (prototype). Data were analyzed from two comparative studies of interval sterilization via laparoscopy with electrocoagulation and division of the tubes, or the application of spring-loaded clips. The technique of tubal occlusion was randomly assigned to a total of 600 subjects. Technical difficulties were more frequent with the spring-loaded clip (7.3%) than with electrocoagulation (4.1%), primarily as a result of mechanical problems with the laparoscope. Rates of surgical and early postoperative complications were similar for the two techniques. The six-month pregnancy rates in one study were 0.8% for electrocoagulation and 0.0% for clip patients; in the other study there were no pregnancies within one year after sterilization.
2. Laparoscopy: Electrocoagulation vs. Tubal Ring (KLI). In two 300-case comparative studies of sterilization performed in women who had not recently been pregnant, laparoscopic electrocoagulation and tubal ring application were evaluated. The surgical complication rates of the two techniques were similar in both studies (2.7% and 1.3%, respectively, at one Center and 2.0% and

3.4%, respectively, at the other Center). In one study, a significantly higher proportion of tubal ring patients experienced moderate or severe pain during the procedure (41.2%) when compared with the electrocoagulation patients (20.7%), but in the other study these rates were similar for ring (10.2%) and cautery (6.6%). Pain during the recovery period before discharge was significantly more frequent among tubal ring patients in both studies, while pain during the recovery period between discharge and the 7- to 21-day follow-up visit was similar for both techniques. At one Center there were no pregnancies during the first year after sterilization; pregnancy rates from the other study have not yet been reported.

3. Laparoscopy: Spring-loaded Clip (prototype) vs. Tubal Ring (KLI). Data were analyzed from a comparative study of postabortion and postpartum sterilization via laparoscopy with the spring-loaded clip (prototype) and the tubal ring (KLI). The assigned procedure could not be performed for two of the ring cases and three of the clip cases, and equipment problems caused a change in technique in an other clip case. Surgical and technical difficulties, chiefly the result of equipment problems, were significantly higher for both postpartum and postabortion clip procedures (31.3% and 14.8%, compared with 6.7% and 2.7% for the ring). Complications and complaints reported immediately after surgery and at the 7- to 21-day follow-up visit were low for all four groups. For both postabortion and postpartum patients, 6- and 12-month data show that pregnancy rates were significantly higher for patients sterilized with the clip than for patients sterilized with tubal rings. Twelve-month rates for clip patients were 9.4 (postabortion) and 11.1 (postpartum); for ring patients rates were 1.4 (postabortion) and 0.7 (postpartum).
4. Anesthesia Study Protocol (IGCC). Adding atropine to either pethidine/droperidol or pethidine/diazepam usually increased the incidence of side effects. Droperidol, when used in addition to other anesthetics, would probably reduce pain. Patients who were administered lidocaine epidurally reported a much higher incidence of side effects, but a significantly lower rate of pain, during the procedure.
5. In a study of culdoscopy in an outpatient setting, the procedure could not be completed in seven (1.3%) patients. In 16.6% of the procedures, technical difficulties which did not require a change in the planned technique were encountered. Surgical complications were reported for 2.1% of the patients.
6. Infundibulectomy via laparotomy was performed on women sterilized within ten days of a vaginal term delivery or abortion. Difficulties at surgery which prevented infundibulectomy were encountered in three cases (1.1%). Infection and other incision problems were the primary complications occurring in nine patients. There were no pregnancies among the 169 patients followed up for six or more months.

7. The safety and efficacy of the repeated transcervical instillation of 1.5 quinacrine hydrochloride in a suspension of 5 ml of 2% xylocaine was evaluated. The potentially serious complications following the instillation were four cases of cortical excitation and one case of acute adnexitis. The second instillation was not performed for 16.0%, and the third instillation was not performed for an additional 16.7% of the patients for medical and/or personal reasons. Fifty-one pregnancies were reported, 41 (80.4%) before completion of the three instillations. The results of this study show that the instillation schedule used is unsatisfactory for widespread use.
8. Follow-up data from Asian institutions on sterilized women, including women sterilized by laparoscopic electrocoagulation, laparoscopic application of spring-loaded clips or tubal rings, laparotomy with Pomeroy tubal ligation and culdoscopy with Pomeroy ligation, indicated that: The incidence of menstrual irregularities within 6 months of sterilization and the incidence of gynecologic abnormalities and the need for pelvic surgery within 12 months of sterilization were infrequent for all procedures. There were no significant differences for the different sterilization procedures.
9. Based on an analysis of interval laparoscopy procedures (electrocoagulation, spring-loaded clip and tubal ring occlusive techniques) and minilaparotomy procedures (ligation and tubal ring occlusive techniques):
 - (a). The rate of failed procedures in which both tubes were not occluded or in which laparotomy was required were significantly higher for laparoscopy (0.5%) than for minilaparotomy (0.1%).
 - (b). The rates of complications occurring during surgery were similar for laparoscopy (2.1%) and minilaparotomy (1.7%), but the type of complications varied with both the approach and the tubal occlusion technique. Among laparoscopy patients, the rate was highest for Rocket clip procedures (3.7%), significantly higher than those for cautery (2.0%) and the Hulka clip (0.9%), but similar to those for tubal ring (2.8%). Among minilaparotomy patients, the surgical complication rate was significantly higher for tubal ring (3.2%) than for the Pomeroy (1.4%) procedures.
10. Pooled data on posterior colpotomy demonstrated a major complication rate of 5.6% including three cases (0.3%) each of bowel injury and pelvic hematoma and two cases (0.2%) of pelvic abscess. Culdotomy was abandoned and laparotomy performed in 16 (1.5%) procedures.
11. Follow-up data on women sterilized by laparoscopic electrocoagulation or application of spring-loaded clips or tubal rings showed that:

- (a). The 12-month life table pregnancy failure rate among interval women was significantly higher among women sterilized by spring-loaded clip application (2.2 per 100 women) than among women sterilized by electrocoagulation (0.4), or by tubal ring application (0.6). The 6-month pregnancy rates among postabortion patients were also significantly higher for clip (22.6) than for cautery (0.7) or ring (0.0); 12-month data were not available. Among clip cases, the 6-month rates were significantly higher for postabortion patients than for interval patients. Half of the cautery failures were ectopic pregnancies, compared with one of the clip and none of the ring failures.
- (b). Rates of gynecologic surgery during the long-term follow-up period were low for all sterilization technique and pregnancy status categories, and none of the surgical procedures was performed because of complications resulting from sterilization. There were no significant differences in the rates of women with one or more gynecologic abnormalities among interval or postabortion patients at the time periods analyzed. No deaths related to sterilization occurred.
- (c). No consistent changes in menstrual patterns were observed among interval patients who had not recently used systemic contraceptives or IUDs. The majority of women reported no significant changes in menstrual cycle parameters.
12. In an analysis of 2,035 laparoscopic sterilization procedures performed in an outpatient clinic under local anesthesia, only one patient required hospitalization and laparotomy. There were no bowel or bladder injuries. In ten cases (0.5%), the procedure could not be performed via laparoscopy and in two cases (0.1%) an alternative tubal occlusion technique was carried out laparoscopically. The pregnancy rates were 0.5% for electrocoagulation, 2.0% for the spring-loaded clip, and 0.9% for the tubal ring; ectopic gestations accounted for four of the seven pregnancies following cautery but none of those following clip or ring application.
13. Based on data analysis of minilap and laparoscopy procedures, it was determined that the rates of major complications, technical failures, and pregnancy were acceptably low for both minilaparotomy and laparoscopy. However, the rates of the most serious complications (surgical injuries to the bowel and major blood vessels, and procedures requiring laparotomy) were somewhat higher for laparoscopy.
14. Analysis of culdoscopic procedures using four techniques of tubal occlusion--Pomeroy, Tantalum clip, fimbriectomy and tubal ring.
- (a). Women sterilized by fimbriectomy reported a significantly higher rate of surgical difficulties (31.5%) and a significantly higher rate of complications at the 7- to 21-day follow-up (11.7%) than women in the other three groups. All groups

experienced low rates of surgical and postoperative complications prior to hospital discharge.

- (b). Inability to occlude the tubes as planned was reported for 6% of the cases, including 1.4% in which one or both tubes could not be occluded by any technique. The rates of technical failures for Pomeroy and fimbriectomy were significantly higher than the rates for the clip or the ring.
- (c). Among the four groups, the pregnancy rates were significantly higher for tantalum clip patients (3.6 at 6 months, 7.7 at 12 months).

15. Analysis of minilaparotomy cases (Pomeroy technique).

- (a). Surgical difficulties were reported in 7.3% of the procedures and, of these, difficulties related to visualizing or exteriorizing the tubes were reported most often.
- (b). In about 1% of the cases, surgical complications were discovered prior to discharge. The most common complication was a torn and/or bleeding tube, which was reported for 0.6% of the women.
- (c). In 22 cases (0.9%), a change in technique from Pomeroy to fimbriectomy was required to complete the sterilization. In four cases (0.2%), an extended laparotomy was required.
- (d). At the 7- to 21-day follow-up, 7.5% of the women reported complications. Fever treated with antibiotics (3%) and incision infection (2.5%) were the two most frequently reported complications.

The following studies are now ongoing.

1. Laparoscopy: Spring-Loaded Clip (Prototype vs. tubal ring (KLI)).
2. Minilaparotomy: Pomeroy vs. Tubal Ring (KLI).
3. Minilaparotomy: Tubal Ring (KLI) vs. Tubal Ring (Dyonics).
4. Laparoscopy: Electrocoagulation vs. Tubal Ring (KLI).
5. Laparoscopy: El-Kady Technique vs. Tubal Ring (KLI).
6. Laparoscopy: Tubal Ring (KLI) Immediate vs. Delayed Post-abortion.
7. Open vs. Closed Laparoscopy Tubal Ring (KLI).
8. Laparoscopy-Electrocoagulation vs. Minilap-Pomeroy vs. Culdoscopy-Pomeroy.
9. Minilap: Pomeroy vs. Tubal Ring (KLI).

10. Minilap vs. Culdoscopy: Tubal Ring (KLI).
11. Culdoscopy: Tubal Ring (KLI) vs. Tantalum Clip (Weck).

The following studies are planned for the future.

1. The collection and analysis of tubal specimens from failed sterilization procedures to determine causes of failures. Failure of sterilization is one of the critical variables in the evaluation of sterilization techniques. Therefore, IFRP is now instituting a new reporting procedure to assist in the evaluation of these failures; this will be done by attempting to obtain information on every woman who becomes pregnant following voluntary sterilization, regardless of whether or not the woman was sterilized as part of an IFRP study. Part of this evaluation will include a gross and microscopic evaluation of the Fallopian tubes (to be done at Johns Hopkins).
2. Determining the ease of performance, safety, and effectiveness of a nonsurgical method of female sterilization (Quinacrine pellets). Preliminary data on the pellet method of quinacrine hydrochloride insertion have shown no pregnancies and only minor complications occurring with this transcervical method. Wider field testing will be accomplished. Patients will be followed up at 6, 12, and 24 months.
3. Evaluation of ease of the performance, safety, and effectiveness of new approaches/techniques of female sterilization, especially open laparoscopy. Several studies will be needed in which two or more routes of sterilization are compared (laparoscopy vs. open laparoscopy and open laparoscopy vs. minilaparotomy). Of particular importance are studies of laparoscopy vs. minilaparotomy. Open laparoscopy is seen as another important area of study in that the procedure eliminates the blind puncture of the abdominal wall by both the pneumoperitoneum needle and sharp trocar; instead, the abdominal cavity is entered under vision through a small "minilap" incision.
4. Evaluation of long-term sequelae of female sterilization including poststerilization menstrual pattern changes, gynecologic surgery rates, and pregnancy rates. Most studies have involved one-year follow-up of patients. In future studies, rates of pregnancy (intrauterine and ectopic), subsequent gynecologic surgery and menstrual pattern disturbances of approaches/techniques under study will be documented in a two-year (or longer) follow-up. For ongoing or completed studies which have shown a good follow-up rate in the past, Contributors will be asked if they can now contact the patients 2-3 years later. In addition, special protocols will be developed to obtain control groups for female sterilization patients. The wives of vasectomized men and women using barrier methods of contraceptives will be compared with female sterilization patients on menstrual pattern changes and gynaecologic surgery rates.

5. Determining ease of performance, safety and effectiveness of new developments in female sterilization equipment, such as mechanical devices (Bleier, Rocket, and Wolf clips and Wolf and Chimcon rings), thermocoagulation and bipolar electrocoagulation and the lapractor. Included in the first group are, primarily, new spring-loaded clips and tubal rings being produced by several companies. As most of the clip and ring studies to date are with prototype spring-loaded clips and KLJ tubal rings, comparative studies of other manufacturers' clips and rings are of importance. New concepts of occlusion techniques include both mechanical and electrical techniques. The Bleier (Hug) clip is considerably different in design from the spring-loaded clip and thus merits testing, via all approaches and in all patient categories. Thermocoagulation (or electrocautery) and bipolar electrocoagulation equipment should also be tested in comparative studies. The lapractor, a combined tubal ring applicator/laparoscope, is designed to provide single incision tubal occlusion and electrosurgery at a significant reduction in cost of equipment. The lapractor would be easy to maintain, could use room air for insufflation and may be particularly useful in the open laparoscopy procedures.
6. Ease of performance, safety, and effectiveness of female sterilization in immediately postabortion patients compared with interval and postpartum patients. IFRP has very few postabortion studies. Of particular interest are comparative studies in postabortion patients of minilap Pomeroy vs. tubal ring and of minilap vs. laparoscopy, with tubal ring. Two or three straight studies of tubal ring application via minilap in postabortion patients at Centers unable to conduct comparative studies will also be of value.
7. The relationship of the site of tubal occlusion to the effectiveness of the sterilization technique. The efficacy of isthmic ampullary application of occlusive devices must be studied; results will have implications for modification of current techniques as well as reversal procedures.
8. The relationship of extra- vs. intraperitoneal tubal occlusion to pelvic/abdominal pain. There is the need for several additional studies comparing Pomeroy and tubal ring, applied in the pelvis, via minilaparotomy. Because mechanical devices can be applied via minilaparotomy without exteriorizing the tube, the tubal occlusion process should be less painful than ligation.
9. Evaluation of the effectiveness of topical administration of lidocaine in reducing or eliminating pain experienced during and immediately after female sterilization procedures. This protocol has recently been finalized and approximately five studies are needed to compare intrauterine vs. tubal spray application of lidocaine vs. no topical anesthetic.
10. The determination of which techniques of female sterilization have the greatest chance for successful reversal (a reversal that results in an intrauterine pregnancy). All Centers which are

called upon by their patients to perform such procedures will be asked to participate. The establishment of regional referral Centers for sterilization reversal will be encouraged, as it is a delicate procedure requiring skill and experience. Monitoring of reversal of permanent female sterilization procedures will be emphasized until reversible female sterilization procedures have been developed.

MALE STERILIZATION

Several new techniques of male sterilization, including sealing the ends of the vas with clips and fulgarization, and chemical injection of the vas, and application of Falope rings need comparative trial. Nonsurgical techniques are being developed and will need testing in the near future. IFRP has prepared the following protocols with the associated data collection instruments, instruction manuals, computer programs, and other necessary procedures for the conduct of studies.

1. Comparative Study of Male Sterilization (April 1977).
2. Comparison of Bovie and Vaseal Units for Electrocoagulation of the Vas Deferens (May 1977).
3. Silicone Ring for Vas Occlusion (August 1977).

As of the date of the Project Paper, the following studies have been completed with the results indicated.

1. A vasectomy study in Guatemala showed vasectomy to be an acceptable method of contraception. Complications were infrequent and most men resumed intercourse within two weeks.
2. A vasectomy study in El Salvador, showed vasectomy to be a safe, acceptable, effective method of permanent contraception. Couples seeking male sterilization were better educated than those choosing female sterilization, but they were less likely to have practiced contraception prior to sterilization.
3. Multiclinic trials of the Vaseal wire were initiated. From the beginning there were equipment problems which have caused delays. Some of the Vaseal Units have had to be returned to Battelle for readjustment and repair. Preliminary reports indicated a higher than acceptable failure rate when the Vaseal Unit is used in conjunction with the Schmidt technique of vas occlusion. One Contributor makes the following points:
 - (a). The buzz which occurs during electrocoagulation alarms the patients, making them tense. Perhaps a light indicator would be better.
 - (b). The needle electrode must be changed after 20 operations.
 - (c). Surgical time is short and the procedure is effective.

The following studies are now ongoing.

1. Comparison of Bovie Unit vs. Vaseal Units.
2. Silicone Ring for Vas Occlusion.

The following studies are projected for the future.

1. Determine the sperm antibody response resulting from the various techniques of vasectomy (ligation, clip, electrocoagulation, ring). The mechanics of the initiation of the antibody response seen in some men as a result of vasectomy are not yet understood. It has been suggested that leakage of sperm from the vas at the time of vasectomy, or leakage until the vas stump scars, results in the formation of antibodies. Use of the tubal ring for occluding the vas should eliminate leakage of the sperm and, in turn, antibody formation.
2. Document the effectiveness, complications, and technical ease of the use of various spermicidal and nonspermicidal solutions for flushing and eliminating residual sperm in the distal portion of the vas. In the past, saline, distilled water or weak solutions of euflavine, potassium permanganate, rivanol and ethaeridine, and nitrofurazone have been used. Vas flushing has the potential for resulting in azoospermia at the time of the operation, regardless of the technique of vas occlusion. If effective, it may eliminate the need for postoperative contraception and sperm testing.
3. The new thermocoagulation Vasector unit will be studied and compared to other methods of occlusion, such as ligation and excision, electrocoagulation, and tubal ring. Study of the tubal ring method of occlusion will be expanded.
4. Performance of vasectomy by paramedics will be evaluated. Use of paramedics for performing this procedure could greatly increase its availability.
5. Evaluate the use of nonspermicidal condoms for the collection of postvasectomy semen specimens.
6. Percutaneous electrocoagulation of the vas and infiltration of the vas with a sclerosing agent methods of male sterilization will be ready for testing in the near future.

Monitoring of attempts of reversal of male sterilization procedures will be conducted to follow development of reversible male sterilization procedures.

Barrier Contraception

Little attention has been paid to conventional barrier contraceptives and baseline data does not exist. As LDC programs move into the rural areas where 85% of their population live, these contraceptives become of increasing importance. Baseline data must be developed against which new developments, such as Neo Sampoons, can be tested. The contraceptives may also offer significant health advantages heretofore disregarded, such as protection from venereal disease. Work in this area is just beginning and must move ahead at an accelerating pace.

IFRP has developed the following protocols for "barrier contraception" (includes diaphragm, condom, foaming vaginal tablet and suppositories, and vaginal sponges, etc.) with the associated data collection instruments, instruction manuals, computer programs and other necessary procedures.

1. Protocol for General Female Barrier Contraceptive Studies.
2. Protocol for Pilot Studies of Collatex (vaginal sponge).
3. Protocol for the Evaluation of Neo Sampooon Loop Tablets for Prophylaxis Against Gonorrhoea in Females.

The following studies are projected for the future.

1. A straight study of barrier methods in common use will be initiated to gather baseline data on efficacy and acceptability in a variety of LDC settings.
2. A pilot study of the efficacy of Neo Sampooon as a prophylactic against gonorrhoea will be undertaken. If this study indicates that Neo Sampooon has significant prophylactic properties, the testing program will be expanded. A comparative study of Neo Sampooon Loop Tablets and other forms of vaginal contraception will be initiated if results from the straight studies indicate such action is appropriate.
3. A pilot study of the polymer sponge (Collatex) will be conducted to determine rates of failure and side effects. If failure rates and side effects are acceptable, comparative studies will be initiated with other barrier methods to document efficacy, safety and acceptability.

Menstrual Regulation and Pregnancy Termination

Practically all of the presently available data on surgical menstrual regulation (i.e., aspiration within 14 days of the time of the missed menses) has been established by the IFRP. The efficacy and safety of various techniques of surgical menstrual regulation such as the minisuction syringe is now reasonably well established. Menstrual regulation with prostaglandins remains promising and additional studies of the method are needed. Pregnancy tests for use at the time of the first missed menses need testing. Considerable information now exists with respect to risks of first trimester surgical pregnancy termination; however, a number of new techniques for use in the second trimester including urea, new prostaglandin analogs and dilatation and evacuation require additional evaluation. New mechanical and pharmacologic means of cervical dilatation which require testing are, or soon will be, available. Pharmacologic means of first trimester abortion appear to be promising and should be tested as they become available.

IFRP has prepared the following protocols with the associated data collection instruments, instruction manuals, computer programs and other necessary procedures.

Equipment Studies

1. Comparative Vacuum Sources.
2. Evaluation of the Battelle Hand Pump.
3. Metal vs. Plastic Cannulae.
4. Flexible vs. Nonflexible Plastic Cannulae.
5. Vented (jetstream) vs. Nonvented Cannulae.
6. Comparative Cannula Size.
7. Evaluation of Pregnancy Tests.
8. Evaluation of the Durability of Menstrual Regulation Kits.

Procedure Studies

1. General Protocol for Midtrimester Abortion.
2. General Protocol for Menstrual Regulation Studies.
3. Dilatation and Curettage vs. Vacuum Aspiration for Induced Abortion.
4. Dilatation and Curettage vs. Vacuum Aspiration for Incomplete, Inevitable or Threatened Abortion.
5. Saline vs. Prostaglandin vs. Urea for Midtrimester Abortion.
6. Paracervical Block with Saline or Prostaglandin for Midtrimester Abortion.

7. Prostaglandin Vaginal Suppositories for Midtrimester Abortion.
8. Medical vs. Surgical Methods of Menstrual Regulation.
9. Induction of Withdrawal Bleeding after the Administration of Estrogen/Progestogen Compounds.
10. Administration of Oxytocics Prior to Vacuum Aspiration in First Trimester Abortion.
11. Induction of Menstrual Bleeding by the Postcoital Insertion of an IUD.
12. Management of Incomplete Abortion by D C vs. Vacuum Aspiration on an Inpatient vs. Outpatient Basis.

Other Studies

1. Menstrual Regulation Performed by Physicians vs. Nurses.
2. Reader Reliability in Histopathology.

As of the date of this Project Paper, the following studies have been completed.

Equipment Studies

1. Comparative Vacuum Sources. After the operator had become familiar with the equipment there was no difference in the rates of complications and incomplete procedures between the 50 cc plastic hand syringe and the Battelle vacuum flask.
2. Evaluation of the Battelle Hand Pump. Preliminary analysis of these data indicates that the hand pump is comparable to other sources of vacuum.
3. Metal vs. Plastic Cannulae. With respect to all criteria of performance (rates of specific complications, blood loss, frequency of cannula reinsertion, amount of retained tissue) there are no significant differences between the two types of cannula for terminating pregnancies of 7-10 weeks' gestation or menstrual regulation procedures performed when there was up to 14 days of menstrual delay by vacuum aspiration.
4. Flexible vs. Nonflexible Plastic Cannula. There was no difference between the two types of plastic cannula.
5. Vented (jetstream) Cannulae vs. Nonvented Cannulae. Venting the cannula offered no significant advantage.
6. Evaluation of pregnancy tests. The Pregnosticon Dri-Dot pregnancy test is not a very reliable test for the diagnosis of pregnancy for amenorrheic women within 14 days of a missed menstrual period. Only 8.0% of positive results are false, but about 41.2% of negative results are false. As the number of days' delay in

onset of menstruation increases, the false-positive and the false-negative rates of the test decrease.

7. Evaluation of the durability of menstrual regulation kits produced by three different manufacturers shows that there are no differences in the durability of cannula made by the different manufacturers (average of about 24 procedures each). However, syringes produced by 52 procedures while syringes manufactured by Burnett and IPAS averaged 80-85 procedures. Although the disinfectant and soap used did not appear to affect the durability of the equipment, there were differences in the sterility of the equipment. Overall, 29% of bacteriological swabs taken from the cannula were positive, and this ranged from 25% with chlorhexidine to 36% with sodium hypochlorite disinfectant.

Procedure Studies

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

Intraamniotic hypertonic saline augmented with intravenous oxytocin is associated with shortened instillation-to-abortion times (median, 25.5 hours), compared to intraamniotic hypertonic saline without supplemental oxytocin (median, 33.3 hours). The instillation-to-abortion time does not depend on the rate of oxytocin administration (17-64 mIU/min), but does depend on the time of administration. Oxytocin initiated within eight hours after saline instillation decreases the instillation-to-abortion time. Instillation-to-abortion times for intraamniotic saline are not dependent on the patient's gestational age (16-24 weeks), age, race or parity. There are no apparent advantages to the removal of amniotic fluid (in various amounts--100 ml or 150 ml) prior to the instillation of 200 ml of 20% hypertonic saline.

Compared to the single intraamniotic 50 mg $\text{PGF}_{2\alpha}$ dose schedule, the 25 mg multiple dose schedule (additional 25 mg $\text{PGF}_{2\alpha}$ injected at 6, 24 and 30 hours if abortion has not yet occurred) results in shortened median instillation-to-abortion times (17.4 vs. 20.8 hours), and similar rates of complications and side effects except for vomiting for women at 16-20 weeks' gestation. Both the 50 mg and repeated 25 mg $\text{PGF}_{2\alpha}$ dose schedules have shorter instillation-to-abortion times than 200 ml of 20% hypertonic saline (median, 26.3 hours), higher rates of incomplete abortion and higher rates of gastrointestinal side effects.

2. General Protocol for Menstrual Regulation Studies. Regardless of the size of cannula (4, 5, or 6 mm), vacuum source (50 cc syringe, electric pump) or length of amenorrhea, rates of significant complications are low--less than 3% in most of the studies reported by the IFRP. In fact, the variation in complication

rates among Centers does not appear to be related to the equipment used but does appear to be related to the training and experience of the physicians performing the procedures. Higher rates of complications occur for pregnant compared to nonpregnant patients. The overall failure rate of MR (i.e., continuing pregnancy) is about 1.0%; an additional 1% have incomplete procedures. Any savings in complications by delaying the procedure for one week for women with negative pregnancy tests, to avoid procedures on nonpregnant women, is almost exactly balanced by the increase in complications for those women who do not have a menstrual period during the one week delay.

3. Dilatation and Curettage vs. Vacuum Aspiration for Induced Abortion. Overall complication rates are similar for women whose first trimester pregnancies are terminated by either vacuum aspiration (VA) or dilatation and curettage (D C). However, the complication rates were significantly higher when either procedure was used at 11-12 weeks LMP (5.7%) as opposed to 6-10 weeks LMP (3.8%). VA compared to D C when performed in gravidas at 13-15 weeks' gestation is associated with significantly higher rates of complications. Performing D C at 13-15 weeks' gestation appears to be safer than waiting until after 15 weeks' gestation and administering intraamniotic hypertonic saline.
4. Dilatation and Curettage vs. Vacuum Aspiration for Incomplete, Inevitable or Septic Abortion. Complication rates (especially blood loss) were higher for D C than for vacuum aspiration.
5. Paracervical Block with Saline or Prostaglandin for Midtrimester Abortion. The results of a study to evaluate the effects of serial, long-acting paracervical blocks on the abortifacient efficacy of intraamniotic $\text{PGF}_{2\alpha}$ (40-20 mg dose schedule) and intraamniotic 20% hypertonic saline indicated:
 - a. Among the $\text{PGF}_{2\alpha}$ treated patients who were administered paracervical blocks, there was a significant reduction in the rates of gastrointestinal side effects and incomplete abortion, and a reduction in the instillation-to-abortion interval compared to patients who were not administered paracervical blocks.
 - b. Rates of side effects, incomplete abortion and cumulative abortion were similar for patients aborted with hypertonic saline independent of whether they did or did not receive paracervical blocks.
6. Prostaglandin Vaginal Suppositories for Midtrimester Abortion. The safety and efficacy of the repeated administration of vaginal suppositories containing 1 mg 15(S)-15-methyl $\text{PGF}_{2\alpha}$ (tham) were evaluated. The median time to abortion was 17.5 hours and 89.6% of the patients aborted within 48 hours. Gastrointestinal side effects were a frequent response to the prostaglandin therapy. Complications were infrequent. The abortion was complete for 43.8% of the patients.

7. Medical vs. Surgical Methods of Menstrual Regulation. There are no advantages to the intrauterine administration of 5 mg PGF_{2α} for MR when compared to the vacuum aspiration procedure.
8. Induction of Withdrawal Bleeding After the Administration of Estrogen/Progestin Compounds. The intramuscular administration of an estrogen/progesterone preparation (50 mg progesterone and 3 mg estradiol benzoate in oil) was found to be ineffective in inducing bleeding in nonpregnant women. Two-thirds of nonpregnant patients began menstruation within one week of first requesting MR independent of whether or not they received intramuscular estrogen treatment. The administration of 100 mg progesterone I.M. to women whose menstrual periods were delayed by no more than 14 days is ineffective in inducing uterine bleeding. Women administered progesterone menstruated later on the average than women who were not administered progesterone.
9. Induction of Menstrual Bleeding by the Postcoital Insertion of an IUD. Preliminary analysis of only 64 cases shows that all patients menstruated at or about the expected time.

Other Studies

1. Menstrual Regulation by Physicians and Nurses. Preliminary analysis shows that rates of complications of the menstrual regulation procedure and the rate of incomplete procedures are similar for nurses and for physicians.
2. Reader Reliability of Histopathology Slides. There was about a 20% discrepancy rate between the pathologist at the study clinic and the U.S. pathologist. Analysis of the third reading is incomplete.

The following studies are now ongoing.

Equipment Studies

1. Evaluation of the Battelle Hand Pump.
2. Comparative Cannula Size.
3. Evaluation of Pregnancy Test (capillary pregnancy test).

Procedure Studies

1. Paracervical Block with PGF_{2α} for Midtrimester Abortion.
2. Prostaglandin with Urea for Midtrimester Abortion.
3. Induction of Menstrual Bleeding by the Postcoital Insertion of an IUD.

Other Studies

1. Menstrual Regulation Performed by Physicians vs. Nurses.

The following studies are projected for the future.

1. Midtrimester Surgical Methods of Termination.
2. An Evaluation of Different Methods of Cervical Dilation.
3. An Evaluation of the Various Pharmacological Methods of Termination of Midtrimester Abortion, Including their Different Routes and Dosages.
4. An Evaluation of Pharmacological Methods of First Trimester Termination (including very early first trimester, as such methods become available).
5. An Evaluation of any New Procedures or Equipment for Pregnancy Termination at any Gestation (including related equipment such as dilators or pregnancy tests).
6. An Evaluation of the Long Term Sequelae of Pregnancy Termination.
7. An Evaluation of the Safety of Pregnancy Termination Procedures (primarily at very early gestations) Performed by Nurses/Midwives.
8. An Evaluation of the Efficacy and Safety of Postcoital IUD Insertion to Induce Menstrual Bleeding.
9. An Evaluation of the Efficacy and Safety of Premedication with Oral Oxytoxics 24 Hours Before Vacuum Aspiration in First Trimester Abortion.
10. An Evaluation of the Safety and Practicality of Treating Incomplete Abortion on an Outpatient Basis with Either Dilation and Curettage or with Vacuum Aspiration.

Epidemiologic Surveys

Epidemiological studies of population in relation to contraceptives have not been done on any systematic basis. These studies can provide both data needed for contraceptive development and for national program distribution programs. Knowing the reactions of populations to continued usage, contraceptive shifting patterns and other data which epidemiological studies can produce may be significant when deciding the mix of contraceptives to be offered in a particular LDC setting, and when establishing the focus of programs to suggest changes under indicated conditions. Case control studies of infrequent events in contraceptive use can be conducted from the IFRP computer data bank.

IFRP has prepared the following protocols with the associated data collection instruments, instruction manuals, computer programs and other necessary procedures.

1. Epidemiologic Survey of Hospitalized Cases of Thromboembolic Disorders in a Singapore general hospital.
2. Epidemiologic Study of the Relationship Between Oral Contraceptives and Thromboembolic Disorders in Asian women.

As of the date of this Project Paper, the following studies have been completed with the results indicated.

1. Abortion in Four Asian Countries: Patient Characteristics, Morbidity, and Contraceptive Acceptance
 - (a). Most of the patients with no preexisting medical conditions (NPEMC) were married, multiparous, of urban residence, and ranged in median age from 29-32 years.
 - (b). Complication rates in patients with NPEMC were highest in patients less than 20 years of age, nulliparous, and more than 12 weeks' gestation.
 - (c). Patients with PEMC had different frequencies of specific patient characteristics, different management, and generally higher complication rates than patients with NPEMC.
2. Follow-Up Study of Oral Contraceptive Acceptors in Howrah District in India.
 - (a). Most women in this district were satisfied with oral contraceptives.
 - (b). While about one third of the women who used no contraceptive method after the project ended reported becoming pregnant or suspected that they were pregnant, less than 5% of those who reported using some form of contraception reported or suspected pregnancy.
3. Incomplete Abortions in Accra and Bangkok University Hospitals 1972-1973.

- (a). Independent of the Center, septic abortions are associated with higher rates of death, as well as with more serious and potentially serious complications than are the nonseptic abortions.
 - (b). Septic abortion is more costly than nonseptic abortion. The patients with septic abortion were hospitalized longer and consumed more surgical time.
4. A Study of Abortion in Countries Where Abortions are Legally Restricted.
- (a). Women treated for induced abortion tended to be of higher parity and more likely to have attained their desired family size than patients treated for spontaneous abortions.
 - (b). Morbidity rates were quite low for patients treated in Centers where vacuum aspiration was mainly used, particularly in contrast to the morbidity rates for patients treated in Centers where dilatation and curettage was used exclusively.
5. Female Sterilization Trends in Singapore.
- (a). The proportion of cases sterilized in the immediate postpartum period has declined dramatically during the four-year study period. Postabortion and interval cases have shown a corresponding increase.
 - (b). The percent of women being sterilized who are illiterate has declined during this four-year period, while the percent who are gainfully employed has increased.
 - (c). Mean parity, mean child loss, and mean number of living children have all decreased.
6. Postmarketing Surveillance of Intrauterine Devices. A scheme for continuous surveillance of marketed IUDs is presented in this methodological paper. The scheme includes IUD surveillance and investigational studies.
7. A Comparison of Menstrual Regulation and Abortion Acceptors in a Singapore Hospital.
- (a). Menstrual regulation acceptors in comparison with abortion acceptors on the average were younger, had more years of education, had one less live birth (controlling for the age difference), and were more likely to be using the procedure to space their children than to terminate fertility.
 - (b). Menstrual regulation acceptors were also more likely to have used contraception before the procedure and were more likely to have had previous experience with induced abortion.
8. Low Birth Weight After Induced Abortion in Singapore.

- (a). There was no significant difference in birth weight of the next pregnancy when the previous pregnancy was terminated by induced abortion.
 - (b). An analysis of the effect of type of abortion procedure on birth weight in subsequent pregnancies revealed that women who were aborted by D&C delivered lighter weight babies than women who were aborted by vacuum aspiration.
 - (c). Abortion by D&C appears to increase the risk of subsequent sequelae, including spontaneous abortion and stillbirth, and complications requiring surgical procedures.
9. An Epidemiological Analysis of Intrauterine Contraceptive Devices--A Preliminary Report. One-year gross cumulative life-table pregnancy, expulsion, and bleeding/pain removal rates were calculated for seven types of IUDs; and these rates were compared for women with different biological and socio-demographic characteristics and different situational factors affecting their IUD insertions.

The following studies are now ongoing.

- 1. A Case-Control Study of Pregnancies Following Female Sterilization.
- 2. A Computer-Matched, Case-Control Study of IUD Medical Removals.
- 3. An Epidemiologic Survey of Hospitalized Cases of Thromboembolic Disorders in a Singapore General Hospital.

The following studies are projected for the future.

- 1. A Computer-Related, Case-Control Study on Accidental Pregnancies in IUD Wearers.
- 2. Study on Effects of Steroidal Contraceptives in Asian Women. The IFRP will be cooperating with the Council of the South and Southeast Asia and Oceania Region of the IPPF on this study.
- 3. An Epidemiological Study of the Discontinued Oral Contraceptive Users in Howrah District In India.
- 4. Case-Control Studies on Rare Events Related to Fertility Regulation Methods.

Phase I and II Research

Phase I and II research should be done by groups other than the IFRP. However, the lines between Phase I and II and III are difficult to draw. Additionally, clinical testing of IUDs often indicates that a small change (which could be classified as Phase II or even in some cases Phase I) will produce a more effective device. It is more cost effective and more expedient to do such work at the IFRP. The total amount of this work is small in comparison to the remainder of the program, but it is essential. IFRP will not attempt to deal with other than mechanical devices and simple surgical instruments.

Phase I and II Research has been conducted on intrauterine devices focusing on development of an IUD with substantially reduced side effects.

1. Most of the devices developed in the IFRP IUD workshop as original prototypes were approved for human testing. Two variations of the Lippes Loop-D, one reduced in size in the lateral plane only and one tapered in thickness from the fundal end to the cervical end, were placed in trial.
2. Work was begun on a biodegradable carrier for the sustained release of Trasylol but was dropped when Trasylol was disapproved. It appears that none of the biodegradable materials under study--polylactic acid, polyglycolic acid, or polycapryl lactone--are appropriate vehicles for delivery of Trasylol or AMCA; however, one of our consultants has completed preliminary experiments that indicate Trasylol can be delivered from biodegradable collagen affixed to an IUD.
3. Estimates of dysfunctional menstrual blood loss and discomfort that is traceable to various types of IUDs were made based on information obtained from admission and follow-up forms, using the Automatic Interaction Detection (AID) computer program. The AID model estimated average blood loss with adequate accuracy for women using copper Loops, plain Loops, U-Coil IUDs (with and without progesterone), AMCA Loops and the Copper-T.
4. Joint work with Dr. Zipper has revealed that certain combinations of zinc and copper on IUDs cause the pregnancy rate to approach zero until the zinc is gone, indicating that voltage gradients in the uterus may be involved in the contraceptive action. Exploration of this finding is being pursued.
5. Sustained release of progesterone into the human uterus from a U-Coil IUD was found to reduce menstrual blood loss to values slightly below preinsertion levels. The Progestacoil has been developed to maintain the low pregnancy rate of the U-Coil and correct the insertion difficulties and poor shape memory of the U-Coil. The Progestacoil can be made in a variety of sizes and diameters.

6. A number of postpartum IUDs were developed, including devices for attaching an IUD to the uterine fundus. Field trials of the latter devices are awaiting further testing of self-anchoring IUDs that do not penetrate tissue. Self-anchoring, nondegradable projections for the Loop-D that extend in the anterior-posterior direction were developed. Also, biodegradable extensions were developed that extend the upper limb of the IUD in either the lateral or anterior-posterior directions. These self-anchoring extensions may be applied to the Loop-D, Copper-T, or Copper-7 IUDs. Chromic-gut suture, collagen, and a composite of polylactic acid and gelatin are the biodegradable materials that have been used thus far.
7. Postpartum inserters for several types of IUDs have been designed.
8. Techniques for the sustained release of many types of drugs into the cervical canal were developed. The carrier is a fusiform bead of ethylene-vinyl acetate that slides over the monofilament tail of an IUD. It is positioned on the tail so it resides within the cervix.
9. Specimens that provide a sustained release of copper salts were fabricated as an alternative to the release of copper by the corrosion of copper wire.
10. The Battelle Memorial Institute Uterine Caliper and Sound was evaluated in humans and a new sound for measuring inner-os-to-fundus distance was developed and tested.

The following work is in progress as this project paper is being written:

1. Development is now underway using:
 - (a). Silastic as a carrier for AMCA and EACA, with and without a diffusion barrier coating;
 - (b). a hydrogel reservoir with a polyurethane diffusion barrier for releasing AMCA; and
 - (c). a system to release Trasylol from a Loop-D.
2. Indices are being developed that measure IUD performance and acceptor satisfaction with higher sensitivity and a shorter response time than life table event rate analysis can provide.

These indices and others to follow will be used to determine whether dimensional variations of the Loop-D have a significant advantage over the plain Loop-D or other IUD options. By the end of 1978, a decision whether to continue evaluation of the dimensionally altered Loop-D will be made.

3. Work is proceeding on the development of a nontoxic biodegradable material with an adjustable degradation rate and the proper elastic modulus that can be molded or solution cast and will release

drugs having high molecular weights. In this connection, an improved material for making postpartum IUD extensions is expected to be ready for field testing by August 1978. Although best-effort contracts to provide systems for releasing AMCA and Trasylol are in place, the development of a back-up system in-house is also progressing. Clinical results from these systems are expected by the end of calendar 1978.

4. By July 1978 it will be possible to deliver from a "T", or similar IUD, many types of drugs over a wide range of release rates.
5. The Progestacoil and an improved version of the progesterone U-Coil will be ready for field testing by March 15, 1978.
6. Concurrent with clinical trial results on the current generation of postpartum IUDs, tooling for making molded anterior-posterior collagen anchors will be developed, and a supply of postpartum IUD inserters will be obtained by September 1978.

The following activity has been planned for the future:

1. Establish an IUD workshop outside U.S. borders.
2. Develop refined analytical models and methods for the prescription of IUDs.
3. Develop improved IUDs and inserters for immediate postpartum insertion.
4. Locate and screen biodegradable materials that are suitable both for drug release and for postpartum IUD anchoring.
5. Evaluate IUD-related ectopic pregnancy rates and PID rates.
6. Extend technical assistance to collaborators in LDCs performing IUD research.
7. Develop and evaluate medicated (i.e., steroid, antifibrinolytic, anti-inflammatory, and metallic) IUDs to reduce side effects and improve contraceptive efficacy.
8. Establish a community postpartum IUD program in an island environment such as Bali or Sri Lanka.

Equipment Integral to Fertility Management Technology

Most major surgical equipment manufacturers are working on new types of equipment which has application in the fertility management field. Much of this equipment is inappropriate for incorporation in LDC programs but some has definite benefits. The JFRP is an ideal organization for evaluation in LDC settings of new equipment. Test of the lapracator, which is considerably less expensive than a laparoscope, is now in progress with preliminary results expected in March, four months after it became available.

The following new equipment related to the fertility control technology indicated will be evaluated.

1. Female Sterilization.
 - (a). Lapracator.
 - (b). Minilap Retractor.
 - (c). Tubal Hooks.
 - (d). Uterine Elevators.
 - (e). New Occlusive Devices.
 - (f). Electrical Units.
 - (g). Air Insufflation for Laparoscopy.
 - (h). Open Laparoscopy Trocar.
 - (i). Chemical Instillation Instruments.
2. Male Sterilization.
 - (a). Occlusive Devices.
3. Intrauterine Contraception.
 - (a). Interval Inserters.
 - (b). Postpartum Inserters.
 - (c). Uterine Sounds and Calipers.
4. Pregnancy Termination and Menstrual Regulation.
 - (a). Vacuum Producing Devices.
 - (b). Cervical Dilators.
 - (c). Cervical Force Measurement Instrument to measure forces generated in cervical dilatation and IUD insertion.

(d). Large size Cannula for early midtrimester pregnancy termination (Battelle).

(e). Pregnancy Tests.

2. Significance to AID Objectives

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

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

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

Continued funding of the IFRP permits high quality clinical trials of new means of fertility control with maximum involvement of local Contributors in LDCs whose institutions may assume increasing increments of responsibility for conduct of studies as experience is gained. Clinicians have been trained to be skilled investigators, and in several countries semiautonomous fertility control, a significant step in the transfer of technology.

Most contraceptive development work is focused in the more advanced countries with drug regulatory boards, patient protection and often in places which fit into the marketing strategy of pharmaceutical firms. For these reasons, methods which are potentially the simplest, safest, least expensive and most appropriate for LDC settings are frequently not pursued, and LDCs are relatively ignored as test sites. IFRP works counter to this general condition by concentrating in LDCs where AID's interest is greatest.

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

- (a). Determining the value of new fertility control methods under use conditions in the countries where they must eventually be employed.
- (b). Determining if there are problems specific to the LDC setting which require developmental work. This work should go on concomitantly with that in the U.S. and Europe--rather than after the method is widely used or marketed.
- (c). AID is better able to satisfy the desires of major research elements in leading LDCs when work begins there with the most advanced new fertility control technologies.

- (d). LCD participation in the research and developmental work on a new drug or method can be expected to greatly enhance the speed with which it can become accepted and operational in a national family planning program. Any research effort which can speed up the acceptance timetable for a new means of fertility control is highly important.
- (e). If new fertility control technology results in a major shift in family planning strategy for delivery systems in LDCs, the sooner this new pattern emerges the better AID is able to make long term plans and meet the needs of these new program requirements.

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

3. Relation to Existing Knowledge

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

Contraceptive development depends upon three steps: (1) fundamental research in reproductive biology, (2) new product development including small scale, carefully controlled clinical trials for efficacy and safety, animal toxicology, drug formulation, establishment of manufacturing methods and standards, quality control, and dealing with drug regulatory agencies, (3) broad scale clinical trials to prove acceptability and evaluate safety and efficacy. The IFRP concentrates on the third step in this procedure. This is frequently neglected by drug companies whose interest is in marketing their own drugs and devices. Furthermore, in the second step, that of product development, there are many leads which deserve exploration which may not fit in with corporate policy of drug firms. For example, nonclinically based methods on which there is little chance of profit do not interest drug firms and the clinical trials necessary for study in LDC's may be too expensive to warrant their investment. This is particularly true because of the intense scrutiny and additional testing required by the FDA for contraceptives compared to other drugs.

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

A discussion of the status of the modalities of fertility control being studied is provided in the expanded narrative.

4. Relation to Other Research

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

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

- (a). Vas cauterly, the Schmidt Technique and portable cauterly unit
- (b). Evaluation of improved versions of the 50 cc menstrual regulation syringe with vacuum lock and accompanying cannulae.
- (c). Evaluation of a hand pump for vacuum aspiration.
- (d). Evaluation of the new mechanical cervical dilatation device.

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

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

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

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

PIACT (Program for the Introduction and Adaptation of Contraceptive Technology): This organization is primarily involved with adaptation of existing technology and in maximizing acceptance of new products in local areas. IFRP will continue to collaborate closely with PIACT.

The IFRP has the largest network in LDCs for international comparative clinical studies. Other organizations have established clinical trial net-

works for individual method studies, or concentrated on small Phase I and Phase II trials. Drug companies continue to sponsor multi-Center clinical trials, but they are not comparative trials which would allow the selection of the best among several similar drugs or techniques.

5. Proposed Work Plan and Methodology

During the period covered by previous contracts, IFRP has developed an international network of Contributors who are knowledgeable, closely linked and skilled in the IFRP research system. These clinical investigators have been trained in research methodology and medical procedures, and are able to conduct standardized clinical trials resulting in reliable, high quality data. Several national fertility research programs are in the process of being organized to coordinate the research activities, including the data collection management, in their countries. Through this established network of individuals and institutions, IFRP proposes to continue research in newer methods of fertility regulation and in closely related activities which contribute to the objectives of AID.

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

IFRP will continue to utilize these standard forms to collect baseline data from new Centers. This provides a learning period through a records dialogue during which the forms become understood. The data are useful for comparison of present fertility control methods with those introduced in straight (noncomparative) studies.

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

When results of straight studies are not definitive, the method will be field tested under a comparative protocol. These protocols provide random allocation of method to patient and, as far as possible, separation of operator doing the procedure, or providing the method, and the evaluator or person providing for the patient's follow-up care. In this way, bias is reduced and study results are more objective.

Major elements of the program in the next contract period are:

- (a). Continuing Phase III clinical testing of fertility control technologies.
- (b). Limited Phase I and II Research.

The bulk of the continuing program effort will continue to be clinical testing.

6. Research Competence

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

Listed below are the key professional and management personnel of IFRP and their titles. Their place in the Organization Chart of IFRP can be seen in the Figure at the back of this project statement.

DIRECTOR'S OFFICE

TITLE	NAME
Director	Elton Kessel, M.D., M.P.H.
Assistant to the Director	Charles Ausherman, M. Div., M.S.P.H., Ph.D.
Director for Field Epidemiology	Roger Bernard, M.D., M.S.P.M.
Medical Director	Leonard Laufe, M.D.
Assistant Medical Director	Pourchis Bhiwandiwalla, D.G.O., D.F.P., M.D., F.C.P.S.

RESEARCH DEPARTMENT

TITLE	NAME
Associate Director for Research	J.Y. Peng, M.D., D.P.H., M.S.P.M.
Epidemiologist	I-Cheng Chi, M.B., M.P.H., Dr. P.H.
Bioengineer	Robert Wheeler, Met. E.
Biostatistician	Vacant
Head, Research Design and Analysis Division	David Edelman, Ph.D.
Research Section Head	Judith Fortney, M.S., Ph.D.
Research Analyst	Alan Kay, M.S.P.H.
Research Analyst	Karen Stewart, M.S.P.H.
Research Analyst	Douglas J. Nichols, M.A.
Research Section Head	Ingrid Swenson, R.N., M.P.H., Dr. P.H.
Research Analyst	Istvan Batar, M.D.

Senior Research Analyst	Joy Wood, M.S.
Research Section Head	Stephen Mumford, M.P.H., Dr. P.H.
Research Associate	Margaret McCann, M.S.
Senior Research Analyst	Lynda Cole, M.A.
Research Analyst	Rhona Kantor, M.P.H.
Senior Research Analyst	Robert Taylor, M.P.H.
Head, Evaluation Systems Division	Peter Donaldson, M.A., Ph.D.
Evaluation Section Head	Michael Thomas, M.A., M.S.
Research Analyst	Cathy Cameron, M.S.P.H.
Research Analyst	Sharon Boue, M.S.P.H.
Evaluation Section Head	Barbara Janowitz, Ph.D.

FIELD OPERATIONS DEPARTMENT

TITLE	NAME
Associate Director for Field Operations	George Stathes, M.S.P.H.
Head, Pan American Division	Alfredo Goldsmith, M.D., M.P.H.
Area Coordinator, Latin American Division	Christine Colven
Assistant Area Coordinator, Latin American Division	Betsy Taylor
Head, African, Middle Eastern, and European Division	Jean Lecomte, M.D., M.P.H.
Medical Area Coordinator	Khairia Omran, M.D., M.P.H., Dr. P.H.
Medical Area Coordinator M.P.H.	Javad Vakilzadeh, D.V.M., C.P.H.,
Head, Asian Division	Anjali Saha, M.B., D.P.H., M.D., M.P.H.
Assistant Area Coordinator	Nashia Ahmad, M.D.
Assistant Area Coordinator	Thomas Hardy

TECHNICAL SERVICES DEPARTMENT

TITLE	NAME
Associate Director for Technical Services	Vacant
Head, Information Services Division	Harvey Lucas
Head, Data Processing Division	David Terwey, M.S.
Computer Center Manager	Christopher Whitener

ADMINISTRATION DEPARTMENT

TITLE	NAME
Associate Director for Administration	Gaines B. Turner
Head, Administrative Services Division	Margaret Morrow
Head, Financial Services Division	Walter Parris
Head, Personnel Services Division	Elizabeth Schultz
Contracts Administrator	Curtiss Swezy, M.P.H., Dr. P.H.

The qualifications and duties of the personnel from the above list who are key personnel for a contract with IFRP are:

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

Dr. Leonard Laufe is a Diplomat of the (American) College of Obstetricians and Gynecologists with extensive clinical experience in the U.S. and in LDC's. Dr. Laufe was Chief, Division of Obstetrics and Gynecology at Western Pennsylvania Hospital, Pittsburgh. He was also Clinical Director of the AID-supported Advanced Technology Fertility Management Program at that hospital, providing practical training in the latest fertility control methods to physicians from developing countries. Throughout his career he has been active in innovative medical equipment design and evaluation.

Dr. J.Y. Peng, Associate Director for Research, has had extensive experience in field work including field trial work in LDC's. He has monitored or conducted research work with The International Development Research Center of Canada, the University of Michigan, University of Washington and the Population Council. He will join IFRP in March 1978.

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

Mr. Gaines B. Turner, Associate Director for Administration. Mr. Turner has had extensive management experience in the U.S. Development (including the industrial establishment of the Navy), in private industry, in management consulting and in population program management and administration. For the eight years immediately preceding his employment at IFRP, he was the Director of Operations and Administration for The Pathfinder Fund, a major AID Grantee for population service programs.

7. Contribution to Institution Building

The availability of an international group of experts to provide assistance and consultation will greatly enhance the development of institutional capabilities in the cooperating LDCs. Another important contribution to institution building will result from the stimulation of early clinical research work in LDCs with new means of fertility control. It is hoped that by including investigators from a number of LDCs in these trials that their institutional strengths will be enhanced and the acceptability of this new modality increased so that if it proves valuable to LDC programs it will be incorporated in such programs, early on. Institution building will be limited to that necessary for conduct of research.

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

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

8. Utilization Plans

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

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

9. Budget Analysis

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

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

The present program uses the same backup group for data processing and analysis for each of the methods tested. This is considerably more economical than using a separate analytic group for each method, and, of course,

it is more economical to provide centralized data processing for the network of collaborating clinics at a single point. Therefore, there is no provision made for Phase III clinical studies in other AID-sponsored contraceptive development contracts; the IFRP provides this support. Considering the great expense of contraceptive clinical trials, the budget proposed is very modest. The additional special studies, when integrated into this program, will be completed at considerably less than they would ordinarily cost.

A summary budget is attached.

10. Internal and External Review

A formal AID evaluation of the program was carried out in the fall of 1977 by a three-person team. It was the general consensus of findings by that evaluation that:

- (a). Concerning the major function of IFRP, i.e., Phase III testing of fertility regulation methods, the organization has developed unique international capability. IFRP has effectively carried out this function.
- (b). IFRP has made objectively identifiable contributions to the population field which have been valuable from programmatic and policy viewpoints.
- (c). IFRP has in-house capabilities that are unusual in research organizations, allowing for efficient data processing, analysis, and dissemination of findings.
- (d). IFRP has established a network of Contributors that has enabled it to collect research data economically. This network has played, indirectly, a role in the diffusion of new fertility regulation methods and techniques.
- (e). IFRP's productivity and efficiency have seemed to increase over the years, as measured by the amount of research activities undertaken compared to staff and funds.
- (f). IFRP has had a history of poor internal communications. These have been recognized and are being addressed by IFRP management.
- (g). The setting of day-to-day work priorities has not been done in a systematic fashion. Here again, management has recognized this problem and attempts are being made to correct this flaw.
- (h). IFRP is a child of PHA/POP/R. To become a strong organization, it should broaden its funding base.
- (i). AID-IFRP communications have often been too narrow and limited in scope. Both organizations have taken steps to correct this and positive results have already occurred.

The same three-person team made the following statement:

In general, we came back from North Carolina with a more positive view of IFRP than when we left Washington. IFRP is an impressive organization with a strong record of accomplishments. We feel that there are ways in which the organizational activities can be improved and will attempt to insure that these improvements take place.

The Subcommittee of the Research Advisory Committee which evaluated the IFRP in September 1977 made the following general statement:

11. Conclusions

The Subcommittee concludes that the IFRP is a very ambitious and hard working group. The immediate purpose of its contract has been accomplished, and the institution is continuing to amass, process and distribute data and information on a very large scale. Moreover, the outreach capability of IFRP into developing countries is extensive and still growing. Its staff maintains continuous communication with contributing Centers and agencies in other parts of the world, offering collateral assistance in improving techniques of fertility control as well as in information gathering and reporting.

IFRP's potentials are significant, although the Subcommittee is not convinced that the organization is exploiting its previous work as fully as it might. For the future, IFRP should keep in the avant-garde of awareness of likely innovations in techniques of fertility control and should promptly institute field tests on their safety, effectiveness and acceptability. It should not proceed into the general domain of program research on family planning and maternal and child health without the prior review and approval of AID. The Subcommittee believes that the point of diminishing returns is quickly reached in amassing huge amounts of data (such as the monitoring of maternity cases all over the world), as interesting as they might be, for general health promotion purposes.

IFRP has already taken action to respond to the criticisms of both evaluations. By the end of the first quarter of calendar 1978, operations will be in line with the recommendations of both evaluation groups.

12. General Evaluation and Recommendation

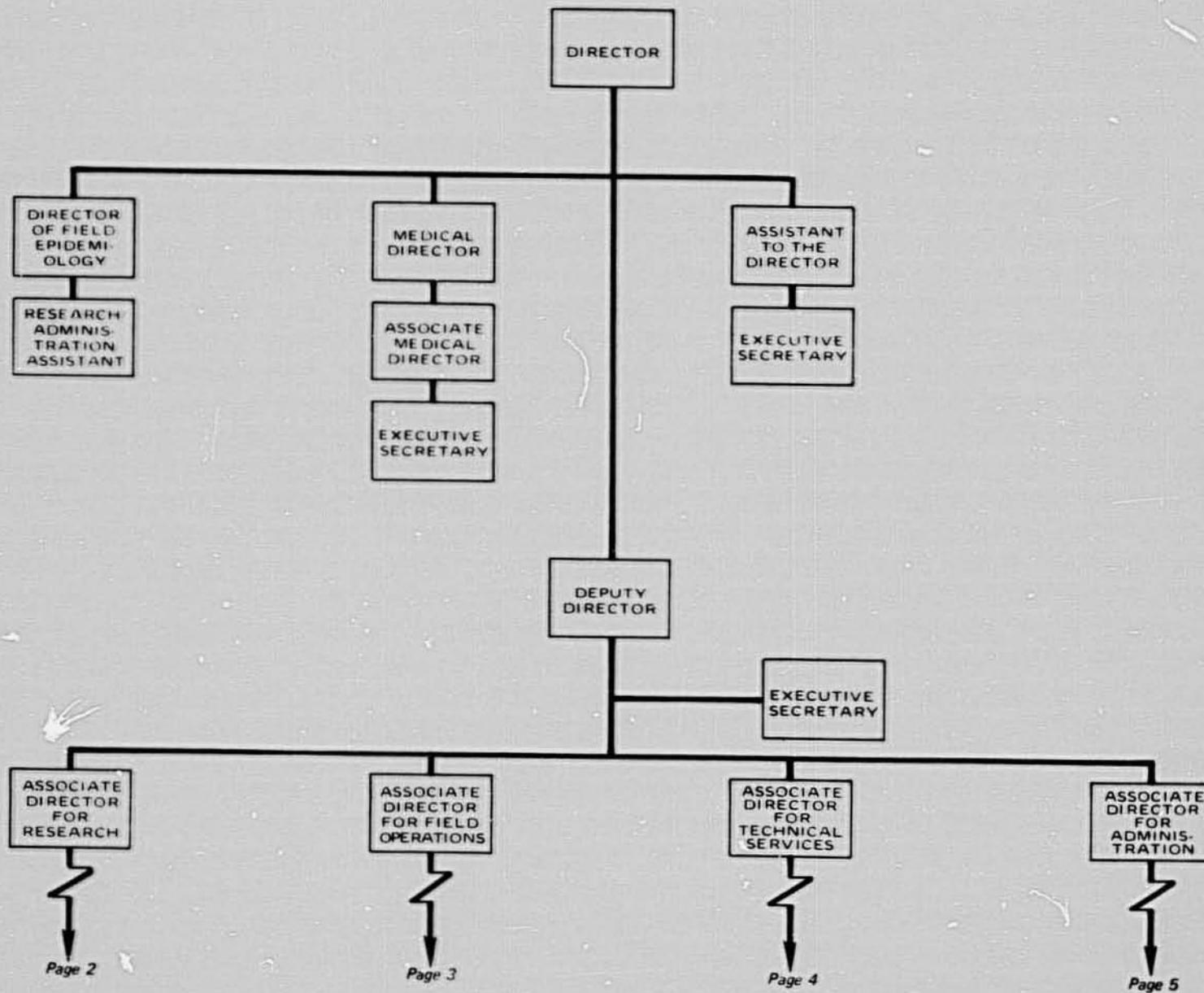
The proposing office considers this program to be one of its most successful. It is the largest single population research program supported by AID--a reflection of Agency priority and evaluation of performance of the program. Its continuation is strongly urged.

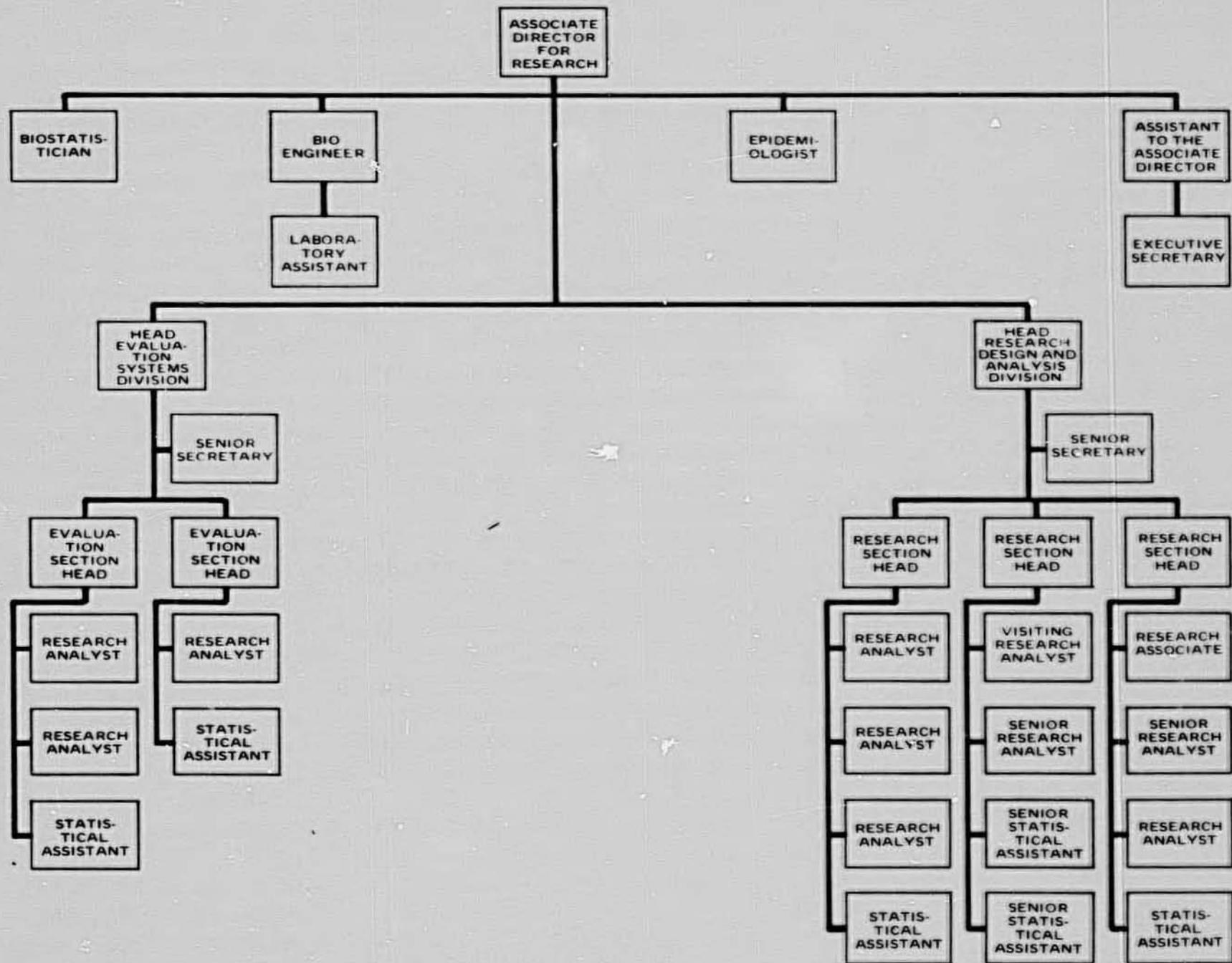
International Fertility Research Program
 Research Contract Budget
 August 1, 1978 to July 31, 1981

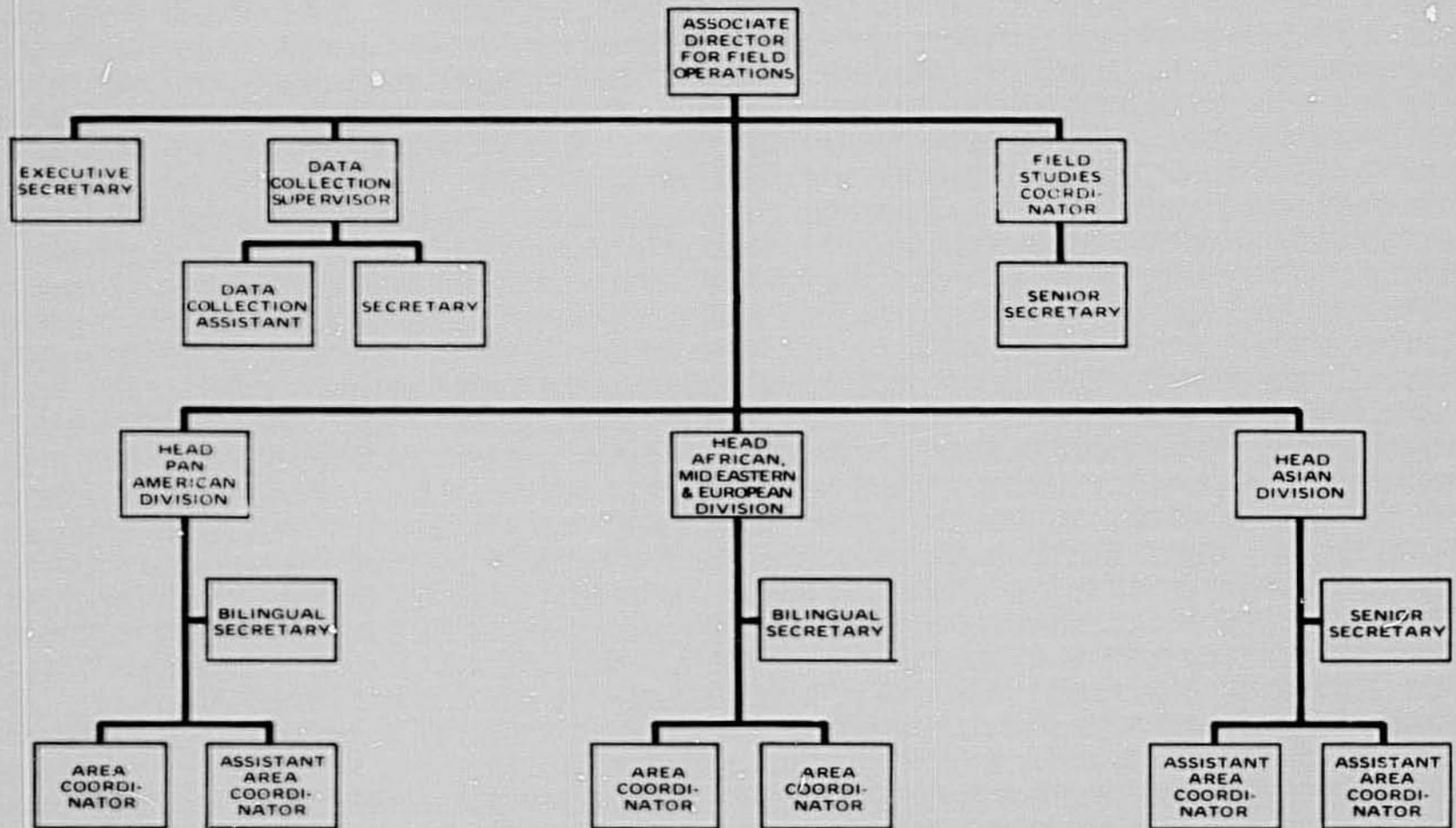
	<u>8-1-78 to</u> <u>7-31-79</u>	<u>8-1-79 to</u> <u>7-31-80</u>	<u>8-1-80 to</u> <u>7-31-81</u>	<u>Total</u>
Salaries				
Permanent	\$ 902,957	\$ 1,015,827	\$ 1,142,805	\$ 3,061,589
Overtime	20,000	20,000	22,000	62,000
Part-time	10,000	5,000	6,000	21,000
	<u>\$ 932,957</u>	<u>\$ 1,040,827</u>	<u>\$ 1,170,805</u>	<u>\$ 3,144,589</u>
Fringe benefits	<u>\$ 205,251</u>	<u>\$ 228,981</u>	<u>\$ 257,577</u>	<u>\$ 691,809</u>
Professional fees	<u>\$ 10,000</u>	<u>\$ 12,000</u>	<u>\$ 14,000</u>	<u>\$ 36,000</u>
Departmental administrative expenses				
Supplies-office	\$ 32,900	\$ 33,500	\$ 35,000	\$ 101,400
Dues	1,000	1,000	1,000	3,000
Subscriptions	2,000	2,000	2,000	6,000
Durable supplies				
- office	30,000	10,000	10,000	50,000
Equipment repairs	3,000	4,000	4,000	11,000
Equipment-office	10,500	12,000	12,000	34,500
Other direct				
expense	6,200	8,000	8,000	22,200
Printing & binding	24,000	25,000	26,500	75,500
Equipment rental	25,000	27,000	28,000	80,000
Telephone - long				
distance	32,000	34,000	36,000	102,000
Shipping	1,000	1,000	1,000	3,000
Depreciation	59,000	31,000	26,000	116,000
Geneva office	30,000	40,000	42,000	112,000
	<u>\$ 256,600</u>	<u>\$ 228,500</u>	<u>\$ 231,500</u>	<u>\$ 716,600</u>
Data purchases	<u>\$ 215,000</u>	<u>\$ 230,000</u>	<u>\$ 230,000</u>	<u>\$ 675,000</u>
Travel				
Domestic	\$ 40,150	\$ 43,000	\$ 45,000	\$ 128,150
Foreign	80,000	90,000	96,500	266,500
	<u>\$ 120,150</u>	<u>\$ 133,000</u>	<u>\$ 141,500</u>	<u>\$ 394,650</u>

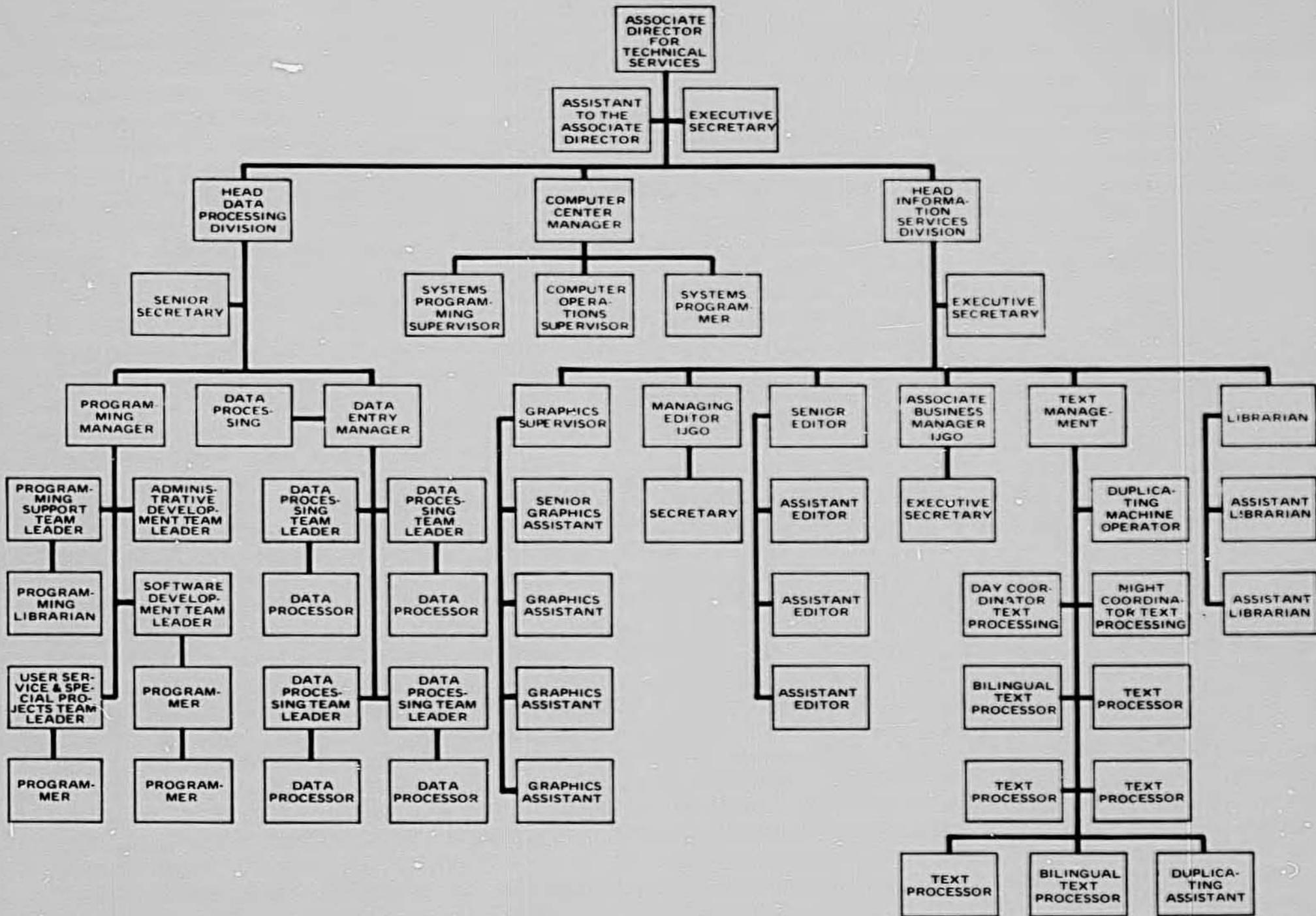
	<u>8-1-78 to</u> <u>7-31-79</u>	<u>8-1-79 to</u> <u>7-31-80</u>	<u>8-1-80 to</u> <u>7-31-81</u>	<u>Total</u>
Contributor related expenses				
Travel	\$ 5,300	\$ 6,000	\$ 9,000	\$ 20,300
Equipment -				
medical	9,000	16,000	20,000	45,000
Subcontracts	54,000	32,000	-0-	86,000
Medical supplies	7,500	10,000	14,000	31,500
Shipping	1,000	1,000	1,000	3,000
Printing & binding	8,000	10,000	10,000	28,000
Trainee travel	6,050	9,000	11,000	26,050
Conference & meeting	18,000	20,000	10,500	48,500
Drugs & devices	30,200	35,000	36,000	101,200
	<u>\$ 139,050</u>	<u>\$ 139,000</u>	<u>\$ 111,500</u>	<u>\$ 389,550</u>
Services				
Data processing	\$ 262,100	\$ 288,300	\$ 317,100	\$ 867,500
Occupancy	103,712	114,000	125,400	343,112
	<u>\$ 365,812</u>	<u>\$ 402,300</u>	<u>\$ 442,500</u>	<u>\$1,210,612</u>
Journal support	<u>\$ 75,000</u>	<u>\$ 50,000</u>	<u>\$ 25,000</u>	<u>\$ 150,000</u>
Subtotal	<u>\$ 2,319,820</u>	<u>\$ 2,464,608</u>	<u>\$ 2,624,382</u>	<u>\$7,408,810</u>
Overhead	855,180	960,392	1,050,618	2,866,190
Fixed fee	<u>75,000</u>	<u>75,000</u>	<u>75,000</u>	<u>225,000</u>
	<u>\$ 3,250,000</u>	<u>\$ 3,500,000</u>	<u>\$ 3,750,000</u>	<u>\$10,500,000</u>

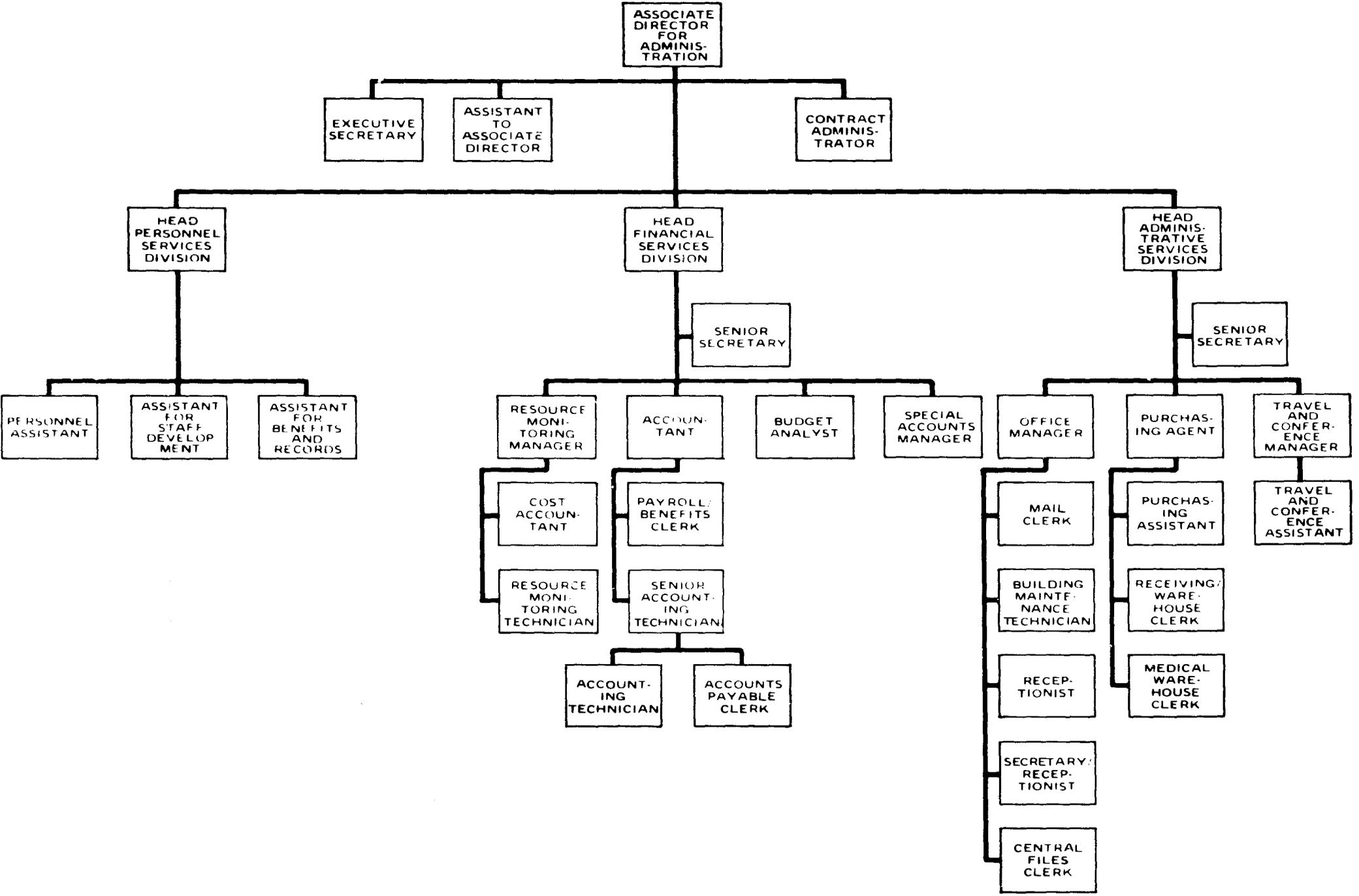
INTERNATIONAL FERTILITY RESEARCH PROGRAM
ORGANIZATION FOR MANAGEMENT
January 15, 1978











Joseph Speidel
Signature of Monitor - J. J. Speidel

Gary Merritt for D.C.
Signature of Duff G. Gillespie
Chief, Research Division

Jane D. Shelton
Signature of Monitor - J. D. Shelton

J. Speidel for RTR
Signature of R. T. Ravenholt
Director, Office of Population

Elizabeth S. Maguire
Signature of Monitor - E. S. Maguire

Sander M. Levin
Signature of Sander M. Levin
Assistant Administrator for
Development Support Bureau

International Fertility Research Program
 Research Contract Budget
 August 1, 1978 to July 31, 1981

	<u>8-1-78 to 7-31-79</u>	<u>8-1-79 to 7-31-80</u>	<u>8-1-80 to 7-31-81</u>	<u>Total</u>
Salaries				
Permanent	\$ 777,958	\$ 875,200	\$ 984,600	\$ 2,637,758
Overtime	20,000	20,000	22,000	62,000
Part-time	10,000	5,000	6,000	21,000
	<u>\$ 807,958</u>	<u>\$ 900,200</u>	<u>\$ 1,012,600</u>	<u>\$ 2,720,758</u>
Fringe benefits	<u>\$ 177,750</u>	<u>\$ 198,044</u>	<u>\$ 222,772</u>	<u>\$ 598,566</u>
Professional fees	<u>\$ 10,000</u>	<u>12,000</u>	<u>14,000</u>	<u>36,000</u>
Departmental administrative expenses				
Supplies-office	\$ 32,900	\$ 33,500	\$ 35,000	\$ 101,400
Dues	1,000	1,000	1,000	3,000
Subscriptions	2,000	2,000	2,000	6,000
Durable supplies office	30,000	10,000	10,000	50,000
Equipment repairs	3,000	4,000	4,000	11,000
Equipment-office	10,500	12,000	12,000	34,500
Other direct expense	6,200	8,000	8,000	22,200
Printing & binding	24,000	25,000	26,500	75,500
Equipment rental	25,000	27,000	28,000	80,000
Telephone-long distance	32,000	34,000	36,000	102,000
Shipping	1,000	1,000	1,000	3,000
Depreciation	59,000	31,000	26,000	116,000
Geneva office	25,000	35,000	40,000	100,000
	<u>\$ 251,600</u>	<u>\$ 223,500</u>	<u>\$ 229,500</u>	<u>\$ 704,600</u>
Data purchases	<u>\$ 305,000</u>	<u>\$ 315,000</u>	<u>\$ 330,000</u>	<u>\$ 950,000</u>
Travel				
Domestic	\$ 60,150	\$ 65,000	\$ 70,000	\$ 195,150
Foreign	125,000	135,000	140,000	400,000
	<u>\$ 185,150</u>	<u>\$ 200,000</u>	<u>\$ 210,000</u>	<u>\$ 595,150</u>

	<u>8-1-78 to</u> <u>7-31-79</u>	<u>8-1-79 to</u> <u>7-31-80</u>	<u>8-1-80 to</u> <u>7-31-81</u>	<u>Total</u>
Contributor related expenses				
Travel	\$ 5,300	\$ 6,000	\$ 9,000	\$ 20,300
Equipment-medical	21,500	25,000	30,000	76,500
Subcontracts	54,000	32,000	-0-	86,000
Medical supplies	7,500	10,000	14,000	31,500
Shipping	1,000	1,000	1,000	3,000
Printing & binding	8,000	10,000	10,000	28,000
Trainee travel	6,050	9,000	11,000	26,050
Conference & meeting	18,000	20,000	10,500	48,500
Drugs & devices	30,200	85,000	85,000	200,200
	<u>\$ 151,550</u>	<u>\$ 198,000</u>	<u>\$ 170,500</u>	<u>\$ 520,050</u>
Services				
Data processing	\$ 262,100	\$ 388,300	\$ 405,100	\$ 1,055,500
Occupancy	103,712	114,000	125,400	343,112
	<u>\$ 365,812</u>	<u>\$ 502,300</u>	<u>\$ 530,500</u>	<u>\$ 1,398,612</u>
Journal support	\$ 75,000	\$ 75,000	\$ 50,000	\$ 200,000
Subtotal	\$2,329,820	\$2,624,044	\$2,769,872	\$ 7,723,736
Overhead	795,180	700,956	761,128	2,257,264
Fixed fee	75,000	75,000	75,000	225,000
	<u>\$3,200,000</u>	<u>\$3,400,000</u>	<u>\$3,605,000</u>	<u>\$10,206,000</u>

9320537-①

PD-AAA-273-FI PROJECT STATEMENT

Date: January 15, 1981

A. PROJECT SUMMARY1. StatisticalProject Title: International Fertility Research Program (IFRP)New or Extension: ExtensionContractor and Address: Primary Contractor - International Fertility
Research Program, Inc.
Research Triangle Park,
North CarolinaPrincipal Investigator: Dr. Malcolm PottsDuration: 15 years, 5-year extension requestedTotal Estimated Cost: \$46,294,605Amount Requested for
RAC Approval: \$21,003,729Funding 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 thiopental 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 thiopental 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	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 Brevicon 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 Neo Sampoo 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 Neo Sampoo.

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
Female Sterilization	
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 thiopental	4
2. Effects of quinacrine-loaded IUDs inserted pre-hysterectomy	5
Intrauterine Devices	
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 Sampooon	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

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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_{2α} and PGE₂

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 suited 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	247,759
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

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.

General and

<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
	\$ 72,346	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.

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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.

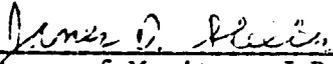
The funding requested by IFRP reflects projected price levels and the expenditure of time and resources required to develop and evaluate increasingly sophisticated new methods of contraception and in particular to conduct Phase I" (post-marketing) trials. We believe this reflects a reasonable projection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

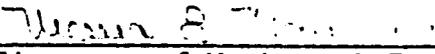
14. Proposing Office General Evaluation

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.



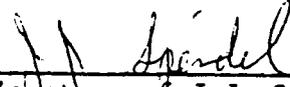
Signature of Monitor, J.D. Shelton



Signature of Monitor, M.E. Mamlouk



Signature of Duff G. Gillespie
Chief, Research Division



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