9320537-③
PD-AAG-271-F1

PROJECT STATEMENT

9320537004901

Date: March 21, 1974

A. PROJECT SUMMARY

1. Statistical

Project Title: International Fertility Research Program (IFRP)

New or Extension: Extension

Contractor and Address: Primary Contractor - Carolina Population Center
University of North Carolin
Chapel Hill, N. C.

Contract AID/csd-2979

Principal Investigator: Dr. Elton Kessel

Duration:

RAC authorized duration:	5 years (6/71 - 6/76)
RAC authorized funding:	3 years (6/71 - 6/74)
Additional funding requested:	3 years (6/74 - 6/77)
Extention or duration requested:	1 year (6/76 - 6/77)

Total Estimated Cost: $11,950,549

Amount Requested for RAC Approval: $ 7,044,549

Funding by Fiscal Years:

FY 71	$3,106,000	FY 74	$2,258,387
FY 72	$1,800,000	FY 75	$2,299,864
FY 73	0	FY 76	$2,485,298

Project Managers: PHA/POP/R. J. J. Speidel/M. I Perry/R. Carpenter

2. Narrative

The International Fertility Research Program has been established to conduct comparative field trials on new means of fertility control in the less developed countries. In the first 2½ years of operation, collaborating investigators have joined this program, studies have been developed and initiated relating to six major fertility control modalities. Considerable scientific data relating to the performance of several means of fertility control is now available from the IFRP to guide family planning program administrators.

BEST AVAILABLE DOCUMENT

B. Expanded Narrative Statement

1. Project Description, Background and Progress Report

a. Description and Background

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

The International Fertility Research Program (IFRP) was organized on 1 July 1971. The contract period was for a total of 5 years, to 30 June 1976, with initial funding for 3 years, to 30 June 1974. The request proposal is to continue support of the program for an additional three years, effective 1 July 1974 when the present funding authority expires. Approval of the request would provide authority to continue the program until 30 June 1977, one year beyond the present contract.

During its initial two and one-half years of existence, the IFRP has developed an extensive network of cooperating physicians primarily located in developing countries. There are now over 100 physicians reporting in six major study areas the fertility control methods they are using. IFRP study designs, including forms, protocols, and instructions are utilized in the studies. The headquarters in Chapel Hill manages the Program by continuous dialogue with the contributing physicians, by organized training programs, by site visits, and by selected contributor conferences

Continuation of this program is sought to provide an effective international mechanism for field testing fertility control methods, techniques, and devices so as to provide data relating to safety, effectiveness, and acceptability of these methods. The institutionalization of family planning in a large number of countries has heightened interest on the part of government officials, administrators, and clinicians in the means of achieving fertility control. Hence scientifically designed and carefully monitored studies at the clinics and hospitals under use conditions offer the best opportunity for impartial evaluation of the methods.

Clinical trials in the following six study areas are the major emphasis of the program: 1) Pregnancy termination, 2) Menstrual regulation, 3) Female sterilization, 4) Male sterilization, 5) IUD's and 6) Systemic contraceptives (oral contraceptives).

In addition, the IFRP supports research needed to bring promising methods of fertility control to the point where clinical studies are appropriate. The major efforts in this regard are studies of prostaglandins and the development of a new laparoscopicly applied tubal clip for female sterilization--both carried out in the Department of Obstetrics and Gynecology at the University of North Carolina.

An additional important activity is the training of collaborating investigators in the new experimental techniques of fertility control so that clinical trials can be initiated in the overseas setting. Formal clinical training in newer fertility control methods is only a small part of this total effort which includes establishing a records dialogue on standard data collection instruments and introducing comparative study protocols in an international network of study Contributors. Aspects of training are now beginning to include interpretation of computer programmed standard tables, which should impose a form of quality control in scientific reports.

b. Progress Report

The International Fertility Research Program was organized in 1971. The first six month period of its existence (July 1 - December 31, 1971) was spent in organizing the Medical Advisory Committee under the Chairmanship of Dr. Alan Guttmacher, recruitment of nucleas staff and a limited network of study Contributors, development of a data collection instrument for the Pregnancy Termination Study and pre-testing this instrument in several Centers, particularly in Asia. This early field activity served to both test IFRP's organizational structure and to develop a records dialogue with first Contributors.

Most aspects of the original plan of organization were found feasible. These included the concept of an international network of study Contributors who would become increasingly skillful in completion of IFRP data collection instruments the limitation on data collection instruments to one page: computerized assistance to data analysis, especially through pre-programmed standard tables for each study area; the use of these data on methods used in the Comtributor's clinic and to become part of comparative study protocols.

In the second six months (January 1 - June 30, 1972) the Contributor network was expanded, the records dialogue intensified in the Pregnancy Termination Study and data collection instruments developed for pretest in other study areas--Menstrual Regulation, IUD's, Female Sterilization, Male Sterilization and Systemic Contraceptives. All data collection instruments were approved for use by the Human Subjects Committee of the

School of Public Health. The first comparative study protocol was developed to compare two cannulae in vacuum aspiration abortion.

In the third six month period (July 1 - December 31, 1972) the Pregnancy Termination Study data collection instrument was finalized and all other study area instruments developed and placed in the field for pre-test. A Director for Research and Training was appointed and the definitive organizational chart of IFRP conceptualized with administration and three scientific divisions: Research Design and Analysis, Field Studies, and Data Processing.

Data sets in both Pregnancy Termination and Female Sterilization reached a size suitable for analysis. The format of Consultant Reports developed from the standard tables of these study areas was determined and the initial report was prepared for Professor T. H. Lean of Singapore.

The fourth six-month period (January 1 - June 30, 1973) was one of continued improvement in protocol development, data collection procedures, and data processing services. It was mainly a period of initiation of comparative studies, monitoring these studies and reporting on baseline data collected in Pregnancy Termination, Menstrual Regulation and Female Sterilization Study areas.

Revision of the Female Sterilization Study data collection instrument was completed as well as the standard tables based on this instrument.

In the fifth six month period (July 1 - December 31, 1973) there was a marked increase in study outputs, primarily based on background data collected in the Pregnancy Termination and Menstrual Regulation Studies.

Comparative protocols were prepared for the Male Sterilization Study, Female Sterilization Study and Menstrual Regulation Study. These were sent to appropriate committees for review and approval.

The computer program for the IUD study, including life-table event rates with their standard errors was tested on data for a few experimental IUDs and on a historically prospective 5-year study of the M-device.

The first comparative protocol was completed in Skopje, Yugoslavia, being a comparison of metal vs. plastic cannulae for suction curettage in first trimester abortion.

A straight (non-comparative) study of the Spring-loaded Clip for Laparoscopy sterilization was initiated in London, Bombay, Bangkok and Singapore. Toward the end of this period a Contributors Conference of study participants was held in Chapel Hill with the principal investigator, Dr. Jaroslav F. Hulka, and instrument manufacturers.

The Comparative Systemic Contraceptive Study was initiated in Seattle to compare three standard oral contraceptives primarily directed to nature and incidence of side effects.

During the sixth six-month period (January 1 - June 30, 1974) it is anticipated that additional first and second trimester comparative pregnancy termination studies will be initiated. The IUD study and Female Sterilization Study comparative protocols should be initiated and possibly the Menstrual Regulation Study comparative protocol will start. Straight studies will be initiated for the Male Sterilization Study.

Revision of the six-month and one-year follow-up form for the Female Sterilization Study will be made and computer programming of data management system, editing program and standard tables for this study area completed.

Further programming of standard tables will proceed for the IUD Study, Male Sterilization Study and Systemic Contraceptive Study, but these will not be completed until the following fiscal year.

In summary, in the first three years of the Program, an organization has developed capable of initiating studies in six study areas: Pregnancy Termination, Menstrual Regulation, IUDs, Female Sterilization, Male Sterilization and Systemic Contraceptives. Review mechanisms have been established to screen new methods for study. This review includes review by the IFRP Medical Advisory Committee and the University of North Carolina's Committee on Human Experimentation. Standard data collection instruments have been developed and comparative study protocols are nearing completion. Computer assisted data management, editing and analysis is well advanced. Background studies are nearing completion and straight and comparative studies of new methods of fertility control have been initiated. Study results have been disseminated by papers in appropriate scientific journals, at scientific conferences and meetings, and by consultant reports prepared by IFRP personnel.

In fiscal 1972, $1.8 million was obligated for field trials of prostaglandins in developing countries. At that time the only significant amounts of dosage from prostaglandin available for human use were in the hands of the Upjohn Company in the U. S., and it was assumed that these trials would have to be carried out on investigational drugs using the approvals granted to the Upjohn Company by the Food and Drug Administration and following protocols approved for such studies by the FDA.

In fiscal 1973 several events suggested the wisdom of altering the previous plan:

1. It has become apparent that only second trimester pregnancy termination with prostaglandins was advanced enough as a means of fertility control that it was ready for collaborative clinical trials in developing countries. Therefore the scope of the planned trials could be narrowed.

2. Upjohn requested from the FDA approval for marketing of $PGF_{2\alpha}$ as a means of fertility control in the second trimester in the U. S.

3. Great Britain has approved the use of $PGF_{2\alpha}$ for second trimester termination of pregnancies in settings where clinical back-up services are available.

Accordingly, a request was made and approval granted by EAC to allow clinical trials with $PGF_{2\alpha}$ for second trimester termination of pregnancy according to protocols not formally approved by the FDA but:

a. using materials manufactured under conditions FDA prescribes;

b. following protocols which have full scale review for the ethics of human experimentation as required by the Department of Health, Education and Welfare, and obtaining fully informed consents from the experimental subjects as required by the HEW guidelines;

c. following a research protocol which is superior to those currently used by Upjohn with FDA approval because they are based on this previous experience.

Studies now initiated using this new protocol have freed Upjohn from the responsibility of monitoring a worldwide clinical trials program in tandem with the IFRP. Although field trials on the use of $PGF_{2\alpha}$ did not progress as anticipated because of the difficulty the Upjohn Company experienced in receiving FDA approval to market the drug, the necessary quantities have now been obtained and are being distributed to the ten centers which will conduct IFRP studies.

Prostaglandin supplied to the University under the Upjohn IND has permitted research to be conducted before the drug was generally available. The result of the changed plans for prostaglandin studies is a saving of $1.1 million which will be applied as a carry on to the renewal request.

During the short lifetime of the Program a number of significant findings have been indicated through clinical field testing and reporting by Contributors. Originally published in some IFRP Reports, the following summarizes the major findings or progress made in each study area.

Abortion

A number of studies have defined the short term morbidity rates (total and specific) for first and second trimester abortions with Dilatation and Curettage (D & C) Vacuum Aspiration (VA) and intra-amniotic saline. The principal findings of these studies include:

1. Morbidity generally increases with increasing gestational age for D & C, VA. and intra-amniotic saline.

2. Early abortion (at less than 7 weeks' gestation) with VA is associated with sigmificantly lower complication rates than abortion by either VA or D & C later in the first trimester.

3. Complication rates are generally higher for hysterotomy than intra-amniotic saline.

4. When combined with sterilization, hysterotomy is associated with higher complication rates than sterilization and abortion by VA, D & C, or intra-amniotic saline.

5. VA when compared to D & C has a lower morbidity rate for gestations of less than 9 weeks, an equivalent morbidity rate at 9-12 weeks' gestation, and a higher morbidity rate at gestations of 13 weeks or more.

6. Following abortion, effective contraceptive methods are usually accepted.

Comparative Abortion Studies

1. Metal versus Plastic Cannula Study

   Four studies were initiated of which one has been completed and analyzed. In this single study, no significant differences in effectiveness and complications were noted between the two cannulae when used for performing abortion by VA in pregnancies of 7-10 weeks' gestation.

2. Ragab's Cannula Study

   Two studies were initiated and one has been completed but not analyzed.

3. D & C versus VA

   One study was initiated, but will probably not be completed until the fall of 1974.

4. Mid-Trimester Abortion Study

Studies utilizing PGF_2a at the University of North Carolina indicate the following:

a. the incidence of pelvic infection, post-partum hemorrhage, and cervical lacerations have been less than that associated with hypertonic saline.

b. Intravenously, constant infusion of the drug between 25 and 200 mg/min appears relatively safe.

c. Extraamniotic administered PGF_2a produced high rates of abortion with few side effects in a short period of time.- This method was abandoned because 1) intrauterine pressure monitoring was necessary to determine each dose, and 2) doses had to be repeated every half hour.

d. When 50 mg PGF_2a was administered three hours prior to suction curettage, 55 percent of the subjects needed further dilatation compared to 5 percent in the control group.

e. Practicable single and multiple intraamniotic administration dosage schedules have been developed. The most satisfactory single dose is 40-50 mg, while the multiple dose schedule is 25 mg initially, repeated at 6, 24, and 30 hours. The latter produces a lower instance of vomiting (70%).

f. In contrast to the hypertonic saline method, there is no evidence of intravascular coagulation with the PGF_2a mehtod.

g. Significant increased efficacy was noted when the multiple dose schedule was augmented with laminaria tents.

h. A clinically practicable dose schedule for the intramuscular administration of 15 ME_{E2} has been defined. Effectiveness is comparable to the intraamniotic rates of PGF_2a with clinically acceptable rates of side effects.

These field studies have been initiated, but their progress was delayed due to lack of an adequate prostaglandin supply.

Incomplete Abortions

The principal findings of Studies on incomplete or inevitable (septic or aseptic) abortions include:

1. Septic abortions are associated with higher rates of death as well as serious and potentially serious complications than the non-septic incomplete abortions.

2. Women with septic abortions require longer hospitalization and surgical times than women with aseptic abortions.

3. Criminal abortions are associated with higher rates of complications than spontaneous or artificially induced abortions.

4. In one study, the proportion of women who were single, under 25 years of age, but with more formal education was higher in the criminally aborted group compared to the spontaneously aborted group.

Menstrual Regulation

Menstrual Regulation (MR) is defined as any method, initiated within 14 days of the missed menstrual period, used to disrupt the intra-uterine environment making it incompatible with the continuation of pregnancy. To date only vacuum aspiration has been studies for MR. The principal findings are:

1. MR is a safe, effective (0.25% failure rate), and technically simple procedure when performed under general anesthesia and under controlled conditions in carefully selected patients, (75% pregnant). Although there was nearly a 10 percent morbidity rate, at least 86 percent of the complications were attributed to the general anesthesia.

2. On an outpatient basis the failure rate of MR ranged from 1.7 to 4.4% in different studies. In these studies about 50% of the subjects were documented to be pregnant. The morbidity in all studies was 1.3 percent. Complications were significantly higher for the gravida than the non-gravida.

3. The morbidity and failure rates increased significantly after 40 days of amenorrhea.

4. In one study of 3 clinics located in different areas (urban, slum, rural) of the Howrah District, India, requests for MR increased significantly in all 3 clinics during the initial 8 months that the service was offered.

5. After MR women generally initiated more effective contraceptives compared to prior to the MR. A similar finding has been reported after abortion.

Female Sterilization

Major findings based on surveillance studies include:

1. Most of the sterilization cases were over 35 years of age and of parity 3 or more.

2. Interval sterilization cases are younger, of lower parity, and have more formal education than the post-abortion and post-partum cases.

3. Sterilization cases had not necessarily practices contraception previously.

4. Interval sterilization by the abdominal approach, regardless of the technique used to "ligate" the tubes, has a low morbidity rate (about 3%).

5. Sterilization, by the abdominal approach, combined with vaginal delivery, or with induced abortion by D & C or vacuum aspiration also has a low morbidity rate and thus is a medically safe and recommendable method.

6. The morbidity rates were similar for vaginal delivery-combined with sterilization on the same day or a few days later.

7. Insufficient data are presently available after sterilization to evaluate possible changes in menstrual patterns and failure rates of specific methods and techniques.

Support of research of female sterilization by the Hulka Clip at UNC-CH has produced significant developments during the last two years. Major developments in this project are:

1. Even though the failure rate has been higher than desirable (approximately 1.5%) investigation indicates that improper application of the clip is responsible for all failures to date.

2. Sterilization may be accomplished on an outpatient basis, under local anesthesia using short acting drugs (fentangl) with only comfortable chairs and possibly a couch as recovery area furnishings.

3. Studies in the use of nitrous oxide in Chapel Hill indicate the superiority of this gas over carbon dioxide because of reduced pain and vegal reflexes.

4. The present model of the clip has now even proven acceptable and at least one large production run is planned.

5. Nine prototype models of the clip applicator have been placed in the field for testing and evaluation. At the Hulka Clip Contributor Conference in December, participants concluded that the current design must be simplified to reduce damage in the field and make it more easily producible by industry. Steps are now being taken to accomplish this.

6. Research in the reversibility of this sterilization procedure is now being conducted on pigs.

Male Sterilization

A comparative protocol and forms have been finalized in anticipation of initiating Studies in the U.S.A. A single Study of resection of the vas and folding and ligating the cut ends indicated this technique to be medically safe and acceptable to the patient.

Contributor Network

The established international Contributor network involving 33 countries mechanism for field testing and reporting scientific data on fertility control methods, techniques and devices. Functioning at varying levels of activity, they continue to provide input to IFRP at an increasing volume.

As the staff of IFRP continues to seek more contributors who are capable of conducting studies and reporting accurate data, and eliminate those who cannot meet the Program's standards, the network will continue to change both in numerical and geographical scope.

Latin America is one of the geographic areas in which developmental energy will be placed during the coming year. An Area Coordinator was recruited in September, 1973, and as a result, a number of apparently excellent contributors have initiated their first studies there. The desire of clinicians in Latin America to participate in scientific research with IFRP is an assurance that this will be a promising area for conducting further field testing. As an indication of this, a paper on data from a new contributor will be presented in April at the APPP meeting.

Africa is another location in which marked interest in participating in IFRP studies has been found. Initial training of some contributors there has been completed, while training of others is planned. Of particular interest in the African countries are IUD studies.

Emphasis will be focused on both these geographic areas in the future since preparations to effectively work with the countries in these areas have been completed. A map showing the distribution of current collaborating centers is attached at the back of this project statement.

2. Significance to Aid Objectives

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 is also clear that the most successful programs have offered a variety of techniques, including post-conceptive means of fertility control. It is auspicious for the success of family planning programs that there are now a number of very promising new fertility control techniques which are ready or will soon be ready for clinical trials. This program has demonstrated its ability to carry out trials under actual use conditions in a wide variety of countries and cultures particularly in LDC

The IFRP permits high quality comparative clinical trials of new means of fertility control with maximum involvement of local contributors in LDC's whose institutions may assume increasing increments of responsibility for conduct of studies as experience is gained over time.

Most contraceptive development work is focused in countries with drug regulatory boards, patent protection and often in places which fit into the marketing strategy of pharmaceutical firms. For these reasons, the LDCs are relatively ignored as test sites.

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

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

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

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

4. LDC participation in the research and developmental work on a new drug or method can be expected to greatly enhance the speed with which it can become accepted and operational in a national family planning program. Any research effort which can speed up the acceptance timetable for a new means of fertility control is highly important. Everything possible should be done to avoid the situation which occurred with oral contraceptives which were introduced into most programs very late.

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

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 3 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 3rd step in this procedure. This is frequently neglected by drug companies--they have no interest in seeking the best drug, just in marketing their own. Furthermore, in the 2nd step, that of product development, there are many leads which deserve exploration which may not fit in with corporate policy of drug firms; for example, non-clinically based methods on which there is little chance of profit may not interest them; or, the clinical trials which this study will carry out may seem too expensive to warrant the investment. This is particularly true because of the intense scrutiny and additional testing required by the FDA for contraceptives compared to other drugs.

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

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

1. Abortion. At present there is almost no objective data concerning relative safety and morbidity of various techniques of pregnancy termination when carried out in the LDC's. For example, IFRP studies showed for the first time in an LDC that vacuum aspiration results in lower complication rates. Additional studies of various abortifacient drugs, including prostaglandins, and other variations of surgical techniques are needed.

2. Menstrual Regulation. Practically all of the presently available data on menstrual regulation (i.e., termination of pregnancy at or close to the time of the missed menses) has been established by the IFRP. The efficacy and safety of various techniques of Menstrual Regulation such as the Mini-suction syringe and the Prostaglandin Impact method need testing. The already demonstrated evidence that this is a very safe procedure will likely stimulate its use in the LDC setting.

3. 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. It's major drawback is thermal trauma to abdominal structures when the tubes are occluded by electrocautery. The spring loaded (Hulka) clip and the Yoon ring show great promise in surmounting this infrequent but serious side effect. These new methods need testing in the LDC clinical setting.

4. Male Sterilization. Several new techniques of male sterilization,

including sealing the ends of the vas with clips and fulgarization of the vas, need comparative trial with the routine surgical techniques now in use.

5. IUDs. There are now a great variety of IUDs in existence and under development, both inert and containing active agents such as hormones and metals. Most of these IUDs need clinical testing on a small population (less than 1000 subjects) to obtain a preliminary assessment of their worth. Promising designs can then be entered into comparative trials.

6. Systemic Contraceptives. AID assisted programs have reported great variations in the side effects and acceptability of various preparations provided to LDC family planning pro ams. There is a most urgent need for comparative studies to establish the rate of subjective side effects for different preparations in LDCs. Determination of other performance characteristics would be a secondary goal.

4. Relation to Other Research

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

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

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

b. Evaluation of the 50cc Menstrual Regulation syringe with vacuum lock.

c. Evaluation of the IUM and inserter in early limited clinical trials already underway and in a series of full scale international clinical trials.

d. Evaluation of prototype, hand held abortion equipment.

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 University of Minnesota: Several of the research programs supported by PARFR will include evaluation of data submitted on standard IFRP forms. In particular at this time, arrangements are underway to

collect data from Dr. Lippes research on copper-bearing Lippes Loop IUDs in New York and Jamaica. Additionally, research on hysteroscopic sterilizations will be evaluated in conjunction with PARFR.

The Southwest Foundation for Research and Education: Dr. Goldzieher's research on physical and subjective side effects of oral contraceptive will be supported by evaluation of data using IFRP forms submitted by the University of Ibadan and other sites to be finalized by Dr. Goldzieher.

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 increasing and during 1974 closer cooperation with the PIP will be arranged to enhance the dissemination of these findings.

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

5. Proposed Work Plan and Methodology

Through previous support from AID, the Program has developed standard data collection instruments in six study areas: Pregnancy Termination, Menstrual Regulation, Female Sterilization, Male Sterilization, IUDs and Systemic Contraceptives. Computer programs have been or are being developed for management of data in each study area and for editing data collected. In addition, standard tables are being 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 a Human Subject Committee of the University of North Carolina at Chapel Hill.

It is planned to utilize these standard forms to collect baseline data from new centers chosen as Contributors to the IFRP. This provides a learning period through a records discipline during which the meaning of

questions on the forms become understood. The data are useful for comparison of present fertility control methods with those introduced in straight (non-comparative) studies.

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

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

The following lists those major elements which are perceived now as the most significant program undertakings in the next contract period:

1. Initiate studies recommended by IFRP Medical Advisory Committee, approved by the UNC Human Investigation Committee and the AID Project Manager.

   a. Prostaglandin Studies

      An initial series of 10 comparative studies including a total of 2,950 patients, 1,800 of whom will have pregnancies terminated by the use of PGF_2a. These studies are programmed in Fiscal Year 1974.

      A second series of comparative studies to compare the efficacy, complications, and acceptability of intrauterine PGF_2a method and the suction method of Menstrual Regulation is programmed to begin early in calendar year 1974 and will be carried on into 1975.

      Additional comparative studies will be initiated in 1974 employing:

      (1) PGF_2a augmented with laminaria

      (2) Prostaglandin suppositories for late first and early second trimester abortion

(3) Prostaglandin suppositories for cervical dilitation prior to suction curettage

(4) The 15 methyl analogue of prostaglandin

b. Oral Contraceptive Studies

In response to a number of requests from Contributors, additional comparative oral contraceptive studies are being programmed to be initiated in calendar year 1974. These studies will emphasize the incidence and nature of side effects associated with particular oral contraceptives. IFRP forms and protocols will be offered for studies involving oral contraceptives of foreign manufacture as well as those of U.S. origin.

c. IUD Studies

Several new IUDs have been developed and are in early testing phases. One is the IUM. Subsequent tests will be programmed during 1974. Comparative studies involving the Dalkon Shield, the Lippes Loop with copper, and the CU-7 device are also projected for Fiscal Year 1974. Initial planning to modify the Spring Coil Device with a hydrophilic coating has indicated that this is practical. The hypothesis is that the coated Spring Coil Device would maintain the low pregnancy rate of the device but the incidence of expulsion and removals for pain and bleeding would be considerably lessened.

As the devices are produced, field testing will commence. Other features which are under consideration for testing include the following: Alza (Progesterone); Weiss (testing a fixed shape device vs. a conforming device); Spring Coil-Small (to be studied in conjunction with a "memory" core); Provera Releasing (to test problems of expulsions after full release or Provera); Fluid Filled Teena (to be studied from a biomedical viewpoint since release characteristics of silastic are known and to assess the effect of release of medicaments).

d. Female Sterilization Studies

IFRP data collection instruments are being used for evaluation of the laparoscopy clips developed by Dr. Jaroslav F. Hulka. Extended trials are underway at several sites and are being closely monitored by Dr. Hulka. As the tests continue and specific conditions are met, including the availability of the clip and applicator, it is planned that IFRP will make the instrument available to a number of Centers in the U.S. and abroad. During the period 1974-75 a total of 20,000 of the laparoscopic clips will be distributed.

A number of Female Sterilization Studies involving comparative procedures are planned during the 1974-76 period. The reporting of the Female Sterilization procedures following Pregnancy Termination procedures is expected to provide a large amount of data from a number of Contributors. Modification of abortion and sterilization legislation in several large countries would greatly widen the scope for study of Female Sterilization procedures.

e. Male Sterilization Studies

IFRP will continue to develop and refine study procedures. A limited number of studies are to be initiated in the next 2-3 year period. The Schmidt method with instruments developed by Battelle will be investigated.

f. Menstrual Regulation Studies

Menstrual Regulation Studies will continue to be initiated during the 1974-75 period. While further development of $PGF_{2}a$ as a menstrual regulating agent is expected, the use of the 50 cc syringe and aspiration will be further studies. One particular area of emphasis relates to the assessment of operator requirements. Comparative studies of physician and nurse operators will be programmed in some Centers. Other aspects of the Menstrual Regulation procedure, including the late sequelae are to be studied, as recommended at the Menstrual Regulation Conference in Hawaii in December, 1973. Comparative studies of rigid and flexible cannulae and prostoglandins versus vacuum aspiration are planned for 1974.

2. Family Planning Program Information System: Utilizing a data collection system developed by IFRP, prototype forms for a simple and effective Family Planning Program Information System have been devised and are ready for field pretesting. This system is being designed to provide the clinic administrator with a simple, flexible, and effective mehtodology for monitoring the function and performance of the clinic requiring a minimum of additional effort to collect the needed data. The system will provide the clinic administrator with rapid feedback on a periodic basis. By combining information from a number of clinics it will be possible for program directors at the national and international levels to compare performance profiles. The Program Information System is being structured to account for each client's contraceptive history. As a result, the system can function as a tool for the clinic administrator. Number of visits, acceptance rates, and measures of patient flow and turnover rates will be made available to the clinic administrator at frequent intervals. Aside from having these data on hand at the clinic, optional analysis of the data could provide the administrator with a variety of program performance indices. These indices would prove most useful in relating clinic information to the allocation of resources and design and implementation of program objectives.

6. Researcher Competence

In the first contract period, the necessary facilities and personnel have been developed to effect the development of the Program. IFRP can now continue the significant progress already made in the Program.

Scientific Personnel

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

Name	Title	% of Time
Kessel, E., M.D., M.P.H.	Director	100%
Bernard, R., M.D., M.S.P.H.	Deputy Director for Field Development	100%
Bhiwandiwalla, P., M.B.B.S.	Research Associate	100%
Brenner, W., M.D.	Director for Research & Training	85%
Chi, I., M.B., Dr.P.H.	Epidemiologist	100%
Edelman, D., Ph.D	Biostatistician	100%
Ferguson, J., Ph.D.	Deputy Head, Data Processing	100%
Goldsmith, A., M.D., M.P.H.	Area Coordinator for Latin America	100%
Gordon, J., M.S.	Research Assistant	100%
Harkins, P.	Head, Data Processing	100%
Hogue, C., Ph.D.	Research Associate	33%
Lucas, H.,	Program Administrator	100%
Omran, K., M.D., D.P.H.	Area Coordinator for Middle East	50%
Pachauri, S., M.D., D.P.H.	Area Coordinator for Asia	100%
Saha, A., M.D., D.P.H.	(Area Coordinator for Asia Replacement)	100%
Stathes, G., M.S.P.H.	Field Studies Coordinator	100%
Thomas, M., M.A.	Research Assistant	100%
Vakilzadeh, J., D.V.M., M.P.H.	Epidemiologist	100%
Wallman, J.	Research Assistant	100%

Prostaglandin Research and Training

Hendricks, C., M.D.	Principal Investigator	10%
Dingfelder, J., M.D.	Research Physician	70%
Ogburn, P., M.D.	Research Associate	100%
Kumarasamy, T., M.D.	Research Physician	50%
Staurovsky, L.	Mid-Wife/Nurse	100%
Runquist, J.	Social Worker	33%

Clip Sterilization

Name	Title	% of Time
Hulka, J., M.D.	Project Director	50%
Omran, K., M.D.	Research Physician	50%

The investigators, particularly Bernard and Kessel, are thoroughly experienced in the conduct of these trials, having organized the Pathfinder IUD Program.

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

Dr. Roger Bernard was previously project Director of Pathfinder International IUD Program.

Dr. William F. Brenner is Associate Professor of Obstetrics and Gynecology and director for Research and Training in the IFRP.

Dr. Charles Hendricks is Professor and Chairman of the Department of Obstetrics and Gynecology UNC Medical School. An expert on uterine contraction and prostaglandins, he directs the special studies on prostaglandins and serves as a consultant for prostaglandin clinical trials.

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

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

An ultimate objective of IFRP is to transfer this method development and field trial capability to LDCs. An important first step has been taken in this direction with the formation of the India Fertility Research Programme. This research organization, established under

Indian law, utilizes the research methodology developed jointly by IFRP and its international Contributors. Data collection and processing can now be completely accomplished within India for three study areas: Pregnancy Termination, Menstrual Regulation and Female Sterilization.

An important contribution to institutional development results from IFRP training programs. The IFRP training programs. The IFRP provides training in the areas of improved research techniques, data collection, and analysis of data to further develop the field testing and reporting skills of Contributors. The IFRP also provides clinical training in the newer methods of fertility control and in the methodology to conduct clinical trials. Primarily being done by the Department of Obstetrics and Gynecology at the University of North Carolina at Chapel Hill, training will be concentrated on the use of Prostaglandin, including newer applications as they become available for testing. Included will be laparoscopic sterilization with the Hulka Clip and other procedures.

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

8. Utilization Plans

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

The publication program of the IFRP will be utilized to ensure widespread dissemination of the results of these studies. The IFRP is already producing many research outputs, both from the University of North Carolina at Chapel Hill and from its Contributor network. These need to be systematized in logical series under a distinctive format. An IFRP Field Report series will be initiated to include consultant reports, study reports at conferences and reprints from journals. An IFRP monograph series is also anticipated to provide in-depth studies based on IFRP data. A classification of the series include:

a. Monographs -- Extensive and detailed presentation of comparative studies to include descriptive and background materials; multi-country presentations of sufficient depth and interest would be included.

b. Consultant Reports -- Relatively short descriptive and tabular presentation generally based on single data sets.

c. Reprints -- Appropriate groupings by subject matter of formal reprints.

d. Conference Reports.

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

Facilities and Equipment: The University of North Carolina at Chapel Hill has provided 9,694 square feet for office and supply storage space.

9. Budget Analysis

In the scheme of contraceptive development, clinical trials are usually the most expensive step. In his Bellagio Paper, Berelson estimates a cost of $2-3 million to complete development and thoroughly evaluate a single method. Dr. Djerassi, former director of Syntex Research, writing in Science estimates a cost of about $800,000 to complete clinical trials on a single method. Over the 3 years, 1969-1971, AID spent approximately $1.5 million to thoroughly evaluate less than a dozen IUDs in the International IUD Program. The present program uses the same backup group for data processing and analysis for each of the methods tested. This will be considerably more economical than using a separate analytic group for each method, and of course it is more economical to provide centralized data processing for the network of collaborating clinics at a single point. Therefore, there is no provision made for clinical studies in other AID-sponsored contraceptive development contracts; the IFRP provides this support. Considering the great expense of contraceptive clinical trials, this budget is not excessive. The additional special studies, when integrated into this program, will be completed at considerably less than it would ordinarily cost.

The IFRP approaches the end of its first contract period with an anticipated carryover of $1.146 million which is planned to be spread evenly across each of the projected yearly budgets of the requested three-year extension. This is primarily due to a change in the initial plan for conducting field testing of PGF_2a which was to be performed under a sub-contract with the Upjohn Company at an approximate cost of $1.8 million. Of significant assistance in this endeavor has been the receipt of a small amount of funds from the Scaife Family Charitable Trust. These grants have enabled the IFRP

to extend the support to the India Fertility Research Programme necessary to establish it as an independent functioning institution. This funding also allowed IFRP to initiate the establishment of a freestanding clinic offering family planning services. Both Scaife and recently General Services Trusts have additionally supported extremely important studies in India which could not be supported with AID funds because the Indian Government would not permit the expenditure of U.S. owned rupees as is required by AID.

A $550,660 decrease in the Contractor's proposed budget for the requested three-year extension to the project was realized in the elimination of the "Program Information" element of the project extension. This deletion, explained more fully on page 24, has resulted in the revised budget total reflected in the budget summary hereunder.

A summary of the budget follows:

Budget Worksheet - Summary
International Fertility Research Program
Actual and Projected Expense
July 1, 1971 - June 30, 1977

	Actual FY - 1971	Actual FY - 1972	Projected FY - 1973	Projected FY - 1974	Projected FY - 1975	Projected FY - 1976	Cumulative Total
Personnel Costs:							
Salaries	$ 298,738	$ 509,891	$ 787,000	$1,000,849	$1,025,231	$1,084,112	$4,705,821
Fringe Benefits 14.8 %	26,547	74,444	114,902	148,125	151,734	160,448	676,200
Total Personnel	$ 325,285	$ 584,335	$ 901,902	$1,148,974	$1,176,965	$1,244,560	$5,382,021
Overhead 48.13 %	$ 96,456	$ 169,080	$ 260,969	$ 481,703	$ 493,443	$ 521,782	$2,023,438
Consultants	7,325	21,925	35,000	38,000	32,000	32,000	166,250
Fellowships	26,672	31,496	32,000	35,000	35,000	35,000	195,168
Domestic Travel	14,226	18,768	40,000	51,000	52,000	57,500	233,494
Foreign Travel	26,707	29,479	70,000	100,000	96,000	100,000	422,186
Equipment & Supplies	56,674	83,835	114,000	130,500	120,500	130,500	636,009
Other Direct Costs	59,902	118,581	240,000	215,350	226,100	287,100	1,147,033
Sub Contracts and Data Purchase	2,950	114,000	120,000	140,000	150,000	160,000	686,950
Purchase of New Drugs and Devices		78,000	80,000	300,000	300,000	300,000	1,058,000
Expenditure totals	$ 616,197	$1,249,499	$1,893,871	$2,640,532	$2,682,008	$2,868,442	$11,950,549
AID Recommended Total Annual Budget	$1,077,478	$1,895,264	$1,933,258	$2,258,387	$2,299,864	$2,486,298	$11,950,549
Unexpended Carryovers	$ 461,281	$ 645,765	$ 39,387	$ 382,145 (2)	$ 382,144 (2)	$ 382,144 (2)	

(1) Includes Publication Costs
(2) Carryovers from FY 71 - 73 ($1,146,433)
distributed equally to FY 74 - 76

10. Internal and External Reviews

Internal AID review of the requested extension to this project has been conducted by the Research and Institutional Grants Council, the Office of Population Research Division and the Office of General Counsel.

At the request of RIGC, a thorough professional outside evaluation of the project will be conducted during the coming fiscal year.

Further POP/P review has determined that the Contractor-proposed "Program Information" element of the project extension will be omitted. Measured against its limited data processing value, that component was judged too technically and administratively cumbersome to be an asset to the project. The elimination of the Program Information element from the project proposal results in a savings of $550,660 in the budget for the three-year extension requested by the Contractor.

AID General Counsel review has found this project unobjectionable from the standpoint of conflict with recently added Section 11[illegible] of the amended Foreign Assistance Act of 1961 concerning abortion activities provided that an appropriate provision is included ~~in the~~ next amendment to the contract to assure compliance with the law.

Independent external reviews of this project extension are in process and will be provided when available.

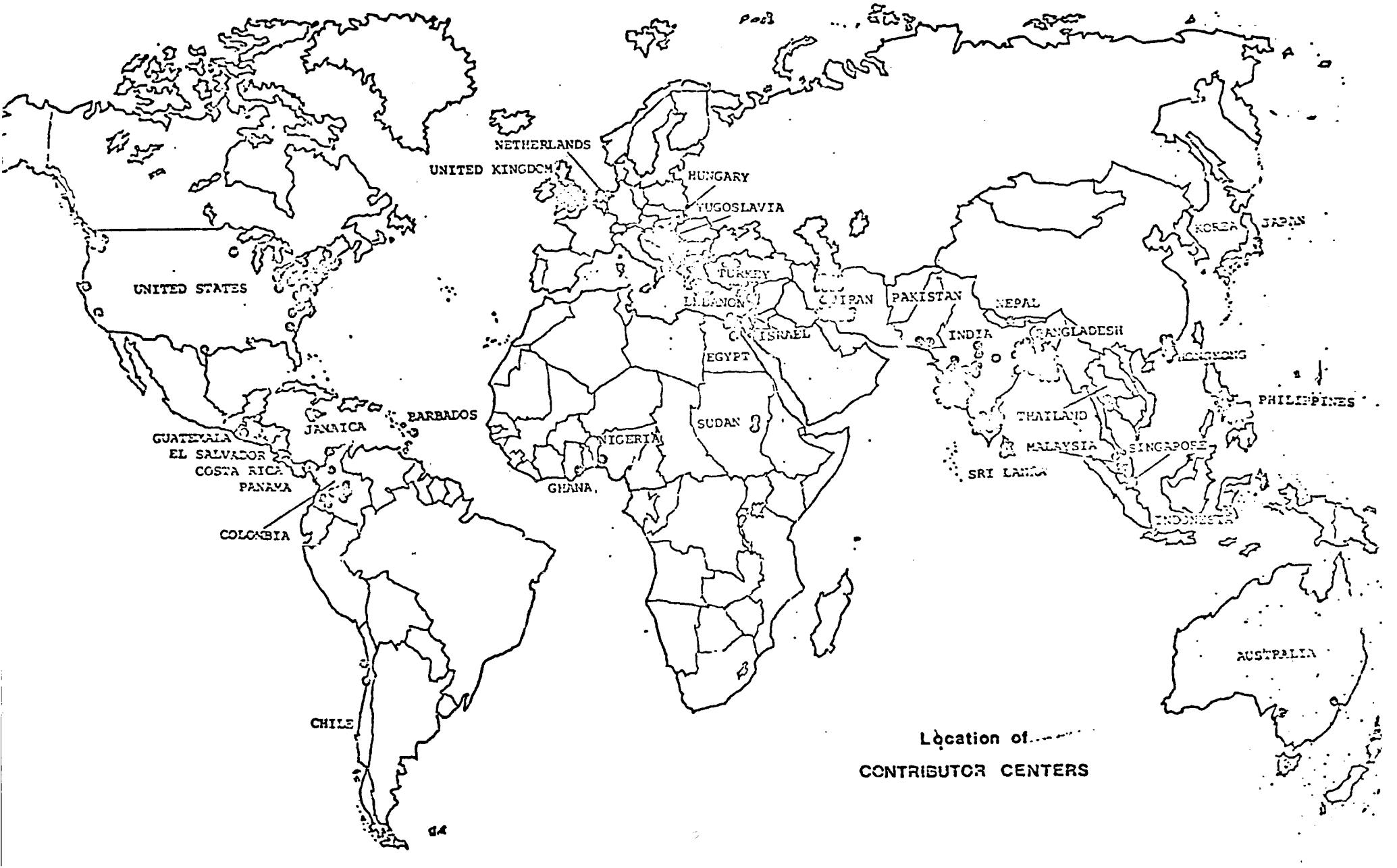
Signature of Monitor - J. J. Speidel

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

Signature of Monitor - Mary I. Perry

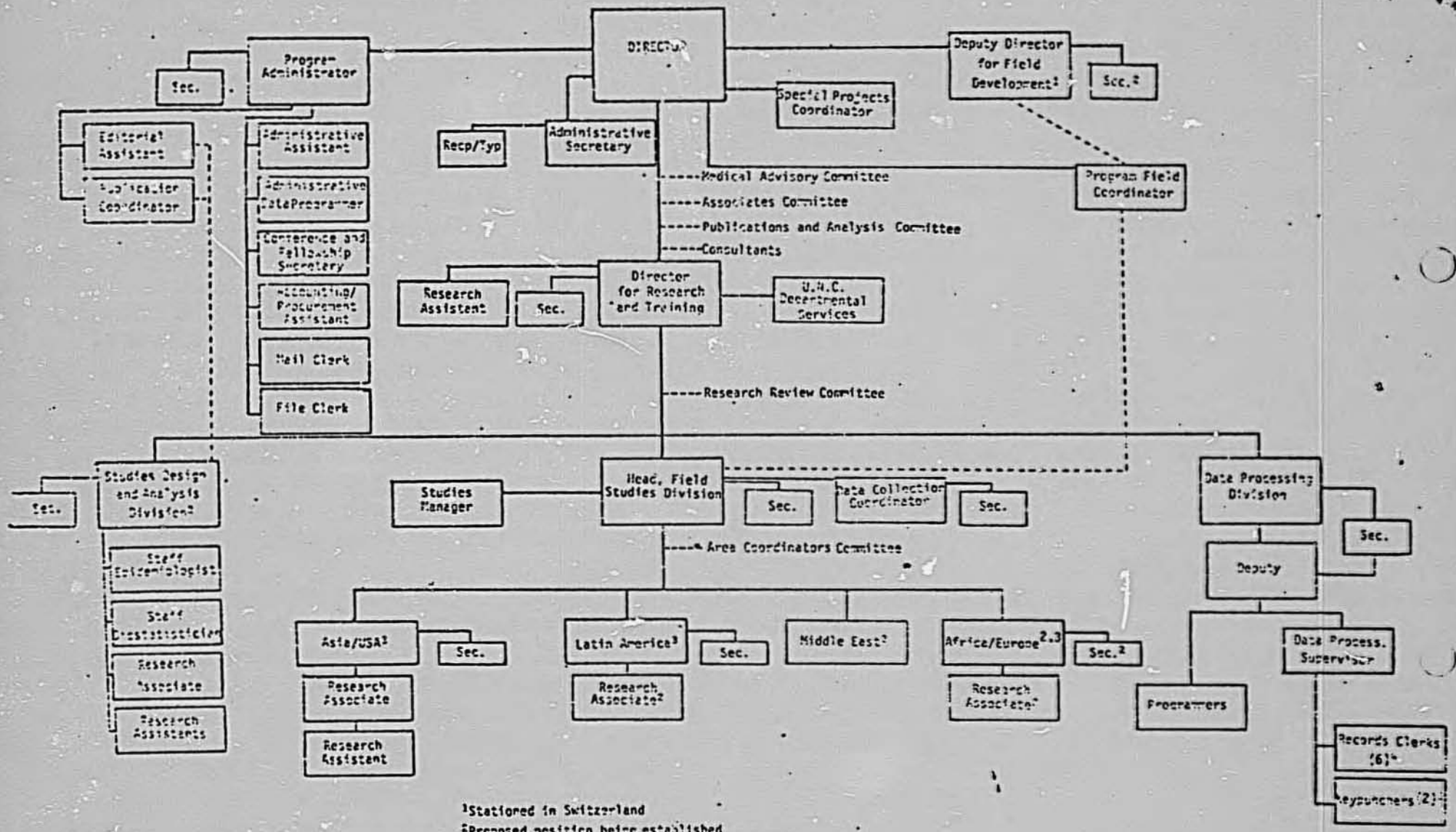
Signature of Monitor - Robert Carpenter

Signature of Jarold A. Kieffer
Assistant Administrator for PHA



Location of
CONTRIBUTOR CENTERS

INTERNATIONAL FERTILITY RESEARCH PROGRAM



[1]Stationed in Switzerland
[2]Proposed position being established
[3]Area Studies Coordinator, Stationed in U.S. or Area
[4]Five employed, the balance to be recruited as volume and workload increase

FIGURE 2

Proposed 7/74