Tech File - Goal
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PROJECT STATEMENT

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A. PROJECT SUMMARY

1. Statistical

Project Title:	Development of Improved and New IUDs
New or Extension:	New
Contractor and Address:	International Fertility Research Programme NCNB Plaza, Suite 400 Chapel Hill, North Carolina 27514
Principal Investigator:	Leonard E. Laufe, M.D.
Duration:	3 years, 3 months
Total Estimated Cost:	$864,000

Funding by Fiscal Years:		
	FY 75 (current year)	$210,000
	FY 76	68,000
	Interim Quarter	269,000
	FY 77	317,000

Project Managers: PHA POP/R, Mary I. Perry/J. Joseph Speidel

2. Narrative:

The IUD is one of the most important contraceptives used in National Family Planning Programs. However, the success of these programs is seriously hindered by problems associated with side effects to present IUDs. A decade of experience with IUDs in developing countries now allows one to define research objectives more precisely. It has become clear that low use effectiveness is related more to removal for pain and bleeding than to expulsions which, in turn, are more important than pregnancy failures.

Therefore, this research program will focus on the two key factors of pain and bleeding, especially in the first three months of IUD use when discontinuation rates are highest. Clinical, engineering and pharmaceutical talents will be closely coordinated to carry out a program strategy whereby stepwise rational alterations of single critical parameters, in otherwise effective IUD designs, are made followed by rapid clinical evaluation. Designs showing significant improvement in pain and bleeding performance will be entered into larger international clinical trials. It is expected, through such a program of rapid incremental design modifications and rapid clinical feed back, to achieve development of an effective IUD, with early pain and bleeding side effects reduced to low enough levels that the IUD will find wide patient acceptance and improved use effectiveness in the developing world. The program will assist developing countries to gain the manufacturing capabilities for production of improved IUDs through consultation and limited support of services. Clinicians and engineers in developing countries will become involved in development and testing of new IUDs early in the program.

B. Expanded Narrative Statement

1. Project Description and Background

The Research approach to developing improved IUDs in this proposal is based both on experience with IUD research programs and on experience with the use of IUDs in developing countries.

Programmatic experience in family planning programs suggests that removals for pain and bleeding, especially in the first three months of use of an IUD, are the most important limitation of IUD effectiveness. Expulsions are perhaps the second most important event limiting use effectiveness, while other events such as pregnancy failure with the IUD in situ are of lesser demographic importance. Therefore, new objectives for IUD research have emerged, relating principally to pain, bleeding and early expulsion--all close to the time of insertion.

Previous IUD research programs have been based on a number of approaches or research philosophies:

(1) Perhaps the largest number of workers have pursued IUD research based on clinical evaluation of IUDs whose physical characteristics are based on an intuitive assessment of what might be the most effective. This school of thought making design changes based on trial and error could be labeled an empirical approach to IUD development.

(2) Another approach to IUD design is based on the premise that a favorable device with respect to pain, bleeding, and expulsion (often a small device) can be made effective in preventing pregnancy by the addition of pharmacologically active agents. The most successful devices exemplifying this research approach, that of developing bio-active IUDs, are the copper devices (Cu-T, Cu-7) and progesterone devices.

(3) Yet another IUD research philosophy, that pursued by the AID sponsored program at the Battelle Memorial Institute, has sought to correlate performance characteristics with physical and biochemical characteristics of individual devices. This bioengineering approach to IUD development has been able to isolate a number of device characteristics associated with improved performance, but the degree and specificity of such correlations has not been such that improved IUDs could easily be devised.

The current program recognizes that the most important IUD design advances have resulted from rapid empirical testing in the clinic of incremental modifications of IUD designs. Therefore, a multidisciplinary team including clinicians, bioengineers and pharmacologists will pursue this approach to IUD development in the proposed research program.

A number of devices have outstanding performance characteristics relating to a single factor, e.g., the lack of pain associated with the Battelle

developed IUM or the virtual elimination of expulsions by the M-Device. Attempts will be made to retain these outstanding characteristics but to modify these devices so as to eliminate their current drawbacks. Thus, modification of the best current IUD designs with the objective of decreasing events which limit IUD effectiveness early after insertion, especially pain and bleeding, will be carried out. A number of structural modifications and surface coatings to change physical properties such as edge sharpness will be studied. Additionally, surface coatings with various medications such as anti-bleeding drugs will be tested.

Central to this program will be the rapid interchange between clinical performance and stepwise design changes. With performance characteristics focused on the first few months, rather than the first year, of use it is now practical to base a research program on rapid clinical evaluation of multiple design changes.

2. Significance to AID Objectives

The availability of easily applied contraceptive techniques with minimal side effects and maximum effectiveness in prevention of pregnancy is essential to the ultimate success of large scale family planning programs in developing countries. Presently available contraceptives still fall short of this goal.

The IUD could be one of the most effective contraceptive measures in such programs. Ease of insertion by paramedics, high effectiveness, and reversibility are attractive features. Ideally, an IUD should function like a reversible sterilization, giving many years of protection after a single insertion and thereby simplifying the task of delivery of services and supplies, and the need for maintenance of continuous motivation. Also, it is most competitive in program costs when compared to oral contraception, condoms, and other reusable measures.

Unfortunately, success of IUDs in National Family Programs has been seriously hindered by the side effects associated with present devices. Through a decade of experience with IUDs in developing countries, it has become clear that low use effectiveness is related more to removals for pain and bleeding in the early months of use than to expulsions which, in turn, are more important than pregnancy failures.

Therefore, although improvements in safety, effectiveness and retention rates are desirable, it would seem to be of primary importance to develop an IUD free from the unpleasant side effects of pain and or bleeding that so often result in the user's request that the device be removed. This is particularly true in those developing countries where prolonged or intermenstrual bleeding is at great variance with the ethnic and religious values of the patient. Development of an "eventless" or "uneventful" IUD, particularly one that is bloodless and comfortable is a first priority of IUD research. If this were achieved, it would lessen the importance of the need for clinical inter-

vention for insertion and aftercare, the other great drawback to IUD use in the developing countries. Reducing IUD related events, particularly patient symptoms, would increase patient acceptability in developing countries. Development of a significantly reduced event associated IUD has potentially the greatest impact of all antifertility measures in the developing world, since it would not be related to highly skilled medical intervention, could be distributed and inserted via trained paramedics, and would not require continued patient motivation.

3. Relation to Existing Knowledge

The first true intrauterine device was a silk worm gut ring described by Richter in 1909. A most significant advance occurred in the late 1920s with the advent of the Grafenberg silver ring. In 1934, Ota working in Japan introduced his intrauterine spoked ring. As with many innovative medical advances, considerable controversy ensued over the next few decades. By the 1940s there appeared an overwhelming consensus that drawbacks, such as pelvic infections, far outweighed any benefits of IUDs.

Not until the late 1950s and 60s did technological progress and new data overcome medical conservatism. New and enthusiastic reports from Oppenheimer of Israel on the Grafenberg ring and Ishihama of Japan on the Ota ring on large clinical trials rekindled interest in the IUD.

Pioneers in the U. S. were Drs. Marguilies of New York with his coiled linear device and Lippes with his now well-known loop. The Margulies coil added a small amount of barium sulfate to make it visible by x-ray and the loop had a tail for the user to confirm its presence and for the physician to remove it. Manufactured entirely from an inert plastic, polyethylene rather than metal, the Lippes loop appeared to offer both cost and safety advantages over the earlier metal devices.

A wave of enthusiasm consumed the medical profession and family planning advocates, and a decade of empiric invention and design ensued. Bows, loops, rings, and coils with multiple modifications and variations in materials were tried. An intensive cooperative study was undertaken by the Population Council under Dr. Christopher Tietze and finally in 1970, after evaluating approximately 27,000 insertions and almost 470,000 women months of use, a conclusion was reached that remains valid after a decade of IUD research:

> "No single type of IUD has consistently lower rates than the others for all types of events (pregnancies, expulsions and removals), nor does any one IUD have consistently higher rates than the others."

The 1970s ushered in an attempt to modify IUDs with sophisticated pharmaceutical additions and bioengineering advances. Copper bearing devices appear to cause less bleeding than inert IUDs and are better suited for nulliparous

women because of their smaller size and ease of insertion. Unfortunately, they must be replaced when the copper is exhausted, usually after two years. Progesterone bearing devices, still in the experimental stage, can and do alter the endometrium to affect bleeding and implantation. Unfortunately, none have a life expectancy over one year and, hence, require replacement or recharging. To date, bioactive devices appear to offer only slight improvement in performance characteristics over the best of the inert devices.

Early bioengineering efforts were directed to produce an expulsion free device. The early ones, the M-Device and the Majzlin Spring, both made of stainless spring steel, had a high retention rate but presented other problems such as uterine performation, difficulty in removal, and pain and bleeding beyond tolerable limits.

A concentrated effort to capitalize on bioengineering expertise began in 1970 with an AID sponsored program for improved IUDs through the Battelle Memorial Institute. This program emphasized a bioengineering analysis of current IUDs with the accumulation of a vast volume of knowledge. From this data base, engineering attempts to develop new IUD designs were implemented. One of the most valuable studies performed was a multiple regression analysis. This analysis was made on open and closed IUDs together and as separate types. The results of the analysis indicated that surface area was the most important characteristic in controlling pregnancy and expulsion rates and that bowing and compression were the most important characteristic in controlling pain/bleeding removal rates. Other data and dividends accumulated during these years included early studies of candidate materials, controlled release rates of pharmaceuticals from candidate systems, and the development of a metrology device for determination of intrauterine dimensions. The sophisticated metal metrology device has been converted into a feasible, inexpensive dye injected plastic prototype for extended clinical trials. This aspect of Battelle development must be continued and devices made available for all new clinical trials.

4. Relation to Other Research

In the field of contraceptive development, IUD research has been relatively neglected and is based at only a few sites.

Other research projects of any magnitude include: field studies of the CU-7 carried out by G. D. Searle and of the CU-T by the Population Council. These two organizations are also carrying out the in-depth studies of intrauterine copper's pharmacology, metabolism, carcinogenicity, and effects on the fetus, needed to obtain FDA approval to use copper bearing IUDs. Data developed by the Population Council will be available for all copper IUDs, so there is no need for AID to duplicate these studies. The Ford Foundation has studied a number of chemicals effective in controlling fertility when released from small sized IUDs.

AID has sponsored two major efforts to improve IUDs. The first of these is an ongoing clinical trials program to test clinical performance of IUDs in

developing countries. Initially carried out at the Pathfinder Foundation, this program is now a part of the International Fertility Research Program. The availability of this clinical testing network will be of great value to further the objectives of the currently proposed program. The second major IUD research program sponsored by AID has been the bioengineering research carried out by the Battelle Memorial Institute. A great deal of theoretical knowledge has been gained through this program; however, ties with clinical researchers were never intimate enough to allow rapid validation of new knowledge and designs through clinical trials. This expertise will be retained through participation of the project leader in the Battelle IUD program in the proposed new program.

5. Proposed Work Plan

This goal oriented research project will focus, through incremental design modifications and rapid clinical evaluation, to develop an IUD which has substantially reduced side effects, principally pain and bleeding, during the first three months of use.

(A) Proposed Activities

(1) Constant review and selection of inert and medicated devices.

(2) Modify best of current generation IUDs to overcome early side effects, while preserving already demonstrated desirable characteristics. Examples of this work would be:

(a) apply surface coatings and/or load the Lippes Loop and IUM

(b) structurally redesign the IUM to soften or round sharp edges.

(3) Modify IUDs which have demonstrated unique performance regarding other events such as expulsion and pregnancy. Examples of this work would be:

(a) structurally redesign the M-device

(b) surface coat and shape the spring coil.

(4) Rationally develop "new" IUDs, with a major emphasis on those suited to post-partum or post-abortal insertion. Examples of this work would be:

(a) develop "fundal arc" IUD

(b) develop "unbrella" type IUD

(5) Rapidly evaluate modified IUD designs in limited clinical trials in the United States. These trials will be conducted utilizing the Battelle developed plastic uterine metrology device. This aspect will thoroughly explore the prescription IUD concept.

(6) Introduce modified IUDs, shown promising in U. S. trials, into larger international trials through the International Fertility Research Program (IFRP) contributor network.

(7) Maintain a constant surveillance of all international experience with current, improved and new IUDs.

(8) Further modify improved IUDs and new designs, and expand international trials.

(B) Time Frame for Proposed Activities

July - Dec. 1975	Jan. - June 1976	July - Dec. 1976	Jan. 1977 - Sept. 1978
CONTINUED SURVEILLANCE OF IMPROVED AND NEW IUDS			
Modify Current IUDs	U.S. Clinical Trials	INTERNATIONAL TRIALS OF MOST PROMISING PRIMARY PROTOTYPES	
Coating or loading of existing IUDs. Examples: 1. Coating of Lippes Loop and Pleated Membrane with Hydron Progesterone Gelatin. 2. Redesign Pleated Membrane to "Wave" Device. 3. Redesign Pleated Membrane to soften all edges.			
	Modify or redesign M-Device Modify or redesign Spring Coil	U.S. Clinical Trials and Evaluation	INTERNATIONAL TRIALS
	Design New Fundal IUD to accomplish A-P Uterine Distention (Umbrella type) (with or without Membrane)	U.S. Clinical Trials and evaluation	INTERNATIONAL TRIALS
		CONTINUATION OF EVALUATION OF ALL PROMISING AND CONTINUED MODIFICATION TO FURTHER IMPROVE IUDS FOR PATIENTS ACCEPTANCE IN THE DEVELOPING WORLD	

(C) Expected End Results

At the end of the contract period, this research program should have produced several improvements in current IUDs and a few new IUDs of promise. The concept of prescription of IUDs for women with particular characteristics and size and shape of uterus should be advanced. A series of field trial result reports based on the IFRP data collection system should document these accomplishments. It is also expected that these reports will advance knowledge of the mechanism of action of IUDs in human populations.

6. Research Methodology

(A) Rationale for the Activities to be Undertaken in the Proposed Research Program

(1) Modification of the best of current generation IUDs -

The first direction is to take the best of the current generation of IUDs and apply a variety of coatings to them which could alter the events of the first three months of use. Potential coatings (gelatin, hydron progesterone, etc.) could be added, either singly or in combination, to the Lippes Loop and the IUM in their current states. Hydron coatings could be used to adhere progesterone to the IUD. A straight gelatin coating which would slowly melt at body temperature would allow for a period of adjustment of the IUD in the uterus. Gelatin could also be explored for a sustained release coating of a progestin which could be of great value in reducing untoward events and improving patient acceptance and continuation rates. Since the Lippes Loop can be considered the "benchmark" of IUD performance, it could be "loaded" as well as coated.

The IUM could also be improved by simply softening or rounding the edges and replacing the pleats with waves or undulations which would prevent the sharp impressions in the endometrium which could be the source of bleeding.

Within six months, limited trials should begin in order to immediately appraise the effects on intermenstrual bleeding and pain during the first three months of use of these modified devices. Those devices which are acceptable could be introduced into international trials through the IFRP within one year. The effort of improving current generation IUDs will take the highest priority as it is the least expensive to accomplish in the shortest period of time.

(2) Modification of IUDs having demonstrated unique performance regarding other events -

Simultaneously, those devices such as the M-Device and the Spring Coil which have demonstrated unique performance regarding other events such as expulsion and pregnancy should be pursued with simple modifications. These two devices are classic examples of the efficacy of thickness, a parameter which has been relatively neglected to date. The M-Device could be restudied to determine its mechanism of retention by hinging the legs. Coatings again could play an important role in early events and patient acceptance.

These devices could be produced within a matter of months so that by the end of the first year a number of modified devices could be put into limited clinical trials. Following these limited trials the devices could be discarded or pursued on an international basis.

(3) Development of "New" IUDs -

New IUDs should be developed rationally, based on knowledge of known good and bad design features. A major objective will be development of post-partum and post-abortal IUDs and getting them into early clinical trials.

In this regard, development of a relatively small surface device which would gently distend the uterine walls might accomplish the same effects as a large thick device but would minimize surface contact and perhaps reduce the bleeding. Candidate devices might include a "fundal arc" (abbreviated M-Device or a modified M with hinges) as well as an umbrella type design to test the hypothesis of A-P (anterior-posterior) distention of the uterine cavity (thickness concept).

(4) Clinical evaluation and further design modification -

IUD design modifications would first be rapidly evaluated in limited clinical trials. Those showing promising improvement would then be introduced into larger scale international trials through the IFRP. The second and third year of the project would be devoted to expansion of further new designs and further modifications of already improved IUDs and to implementation of international trials through the IFRP. During the third year international trials of new devices and continuation of all viable studies should be completed.

(5) As other organizations and individuals will be developing and evaluating new IUDs, it will be necessary through the life of the contract to obtain as much information as possible on these devices in order to detect a better device, whatever its origin.

(B) Administrative Design of the Proposed Research Program

(1) The administrative design of the project will be as follows:

(a) The Principal Investigator will direct all activities of the proposed research program. He will be advised by the Core Advisory Committee.

(b) Subcontracts for bioengineering modifications, for development of bioactive devices, and for provision of adequate numbers of devices for clinical trials will be made by the IFRP. Implementation of all subcontracts will be coordinated by the Administrative Assistant responsible to the Program Administrator of IFRP as liaison between AID, the Principal Investigator and his Program Assistant, engineering consultants, and the subcontractor.

(c) Subcontracts will be arranged for small U. S. clinical trials by IFRP.

(d) International clinical trials will be conducted through the IFRP Contributor network.

(e) Approval will be obtained from the IFRP Protection of Human Subjects Committee prior to initiation of clinical studies both in the U. S. and overseas.

(f) FDA approval for medical, modified and new devices will be obtained by IFRP.

All of these functions must be reviewed by the Core Advisory Committee and coordinated by the Administrative and Program Assistants.

(2) Core Advisory Committee

(a) Membership

The program will be medically oriented with interdisciplinary contributions from bioengineers and the pharmaceutical industry. The Core Advisory Committee has been so selected, and includes the following members:

Principal Investigator	Leonard Laufe, M.D.
Engineering Director	Robert Wheeler
Engineering Assistant	Thomas Lardner, Ph.D.
International Clinical Studies Director	Elton Kessel, M.D.
Clinical Assistant	Douglass Thompson, M.D.
Pharmaceutical and Clinical Consultant	Harry Rudel, M.D.
Clinical Consultants	Lonnie Burnett, M.D. Achilles Sobrero, M.D.
Fabrication/Manufacturing Consultants	By invitation, depending on expertise
Observers (AID Project Managers)	J. Joseph Speidel, M.D. Mary I. Perry

By keeping the Committee relatively limited and utilizing individuals from various disciplines, it is felt that a much more rapid and coordinated level of activity can be generated to accomplish the intended objective of this research program.

(b) Responsibilities

The responsibilities of the proposed research will stem from advice from the Core Advisory Committee which will lead to subcontracts for needed services to multiple disciplines and levels of expertise. This would allow for the opportunity to utilize multiple capabilities. Close relationship with the IFRP for international clinical trials will be mandatory. The Core Advisory Committee, under the leadership of Dr. Laufe, will convene at least quarterly and will advise concerning the following actions:

- selection of IUD modifications to be made
- identification of subcontractors to make the modifications and provide prototypes in adequate numbers for clinical testing
- identification of subcontractors or other sources to perform small scale U. S. clinical trials

- review clinical performance and selection of devices for introduction to international clinical trials through IFRP.

- reassessment of priorities and selection of devices for further modification

- identification of subcontractors to further modify devices and provide adequate numbers for larger scale international trials

- surveillance for new IUDs from all domestic and international sources for potential addition to the program

- liaison with and IND approvals from FDA for U. S. trials of medicated devices

The IFRP and the Principal Investigator will have overall responsibility for assuring that the work plan is carried out in the time frame for proposed activities

7. Researcher Competence

Leonard Laufe, M.D. (Principal Investigator) - Dr. Laufe is Chief, Division of Obstetrics and Gynecology at the Western Pennsylvania Hospital in Pittsburgh. He has had a long and varied interest in medical instrumentation including IUDs. He has improved and designed three obstetric forceps, predicated on function and bioengineering rather than empiricism. Since 1966 he has been involved with the Battelle Columbus Laboratories in various studies and designs of obstetric forceps regarding the forces they generate upon the newborn. In the late 1960s he was the recipient of a three year Hartford Foundation grant to measure and study the forces generated upon the newborn by crossed and divergent forceps. From these studies numerous publications have appeared and most important, an outlet forceps which reduces the compressive force to the newborn head by 33% has been developed and is now commonly employed.

Other areas of interest have included design efforts in uterine cannulae, cervical dilators, and tanaculums. This has been accomplished in conjunction with the Marco Instrument Company of New Jersey.

In 1969 Dr. Laufe subsidized a study at the Battelle Columbus Laboratories for an engineering approach to IUDs. This report produced 53 potential new designs and explored new candidate materials such as improved plastics and Nitinol, a new alloy with a thermosensitive memory. This material was presented and published by the Pathfinder Fund as part of its special meeting of the Medical Advisory Committee held on May 26, 1970.

Dr. Laufe has participated in collaborative studies of a variety of IUDs, including the Hall-Stone Ring, the LEM, and the IUM. He supervised the rapid implementation of the Pittsburgh CU 7 study which included the Western Pennsylvania Hospital, Magee-Women's Hospital, and the Planned Parenthood of Pittsburgh. He has served as a consultant to assist the establishment of IUD evaluation and data collection programs in developing countries.

Publications in this area include "An Evaluation of the Use Effectiveness of the Saf-T-Coil in Private Practice" and "Volume and Copper Concentration of Menstrual Discharge of Women Employing the Copper 7 and Other Types of Contraceptives." Presentation will be made at the next Association of Planned Parenthood Physicians meeting regarding the IUM and new approaches to IUD design.

Dr. Laufe has been a member of the Battelle Medical Advisory Committee for improved IUDs since its inception in 1970 and carried out the early clinical studies of the effect of new IUDs on the endometrium (extirpated uteri) and the evaluation of the Battelle Developed uterine metrology device. He also conducted the largest first series of clinical insertions of the IUM.

For the past two years, Dr. Laufe has been Clinical Director of the AID supported Advanced Technology Fertility Management (AFTM) Program at Western Pennsylvania Hospital, which provides practical training in latest fertility control methods to physicians from developing countries. As consultant to the IFRP for the past several years, he is knowledgeable in multiple areas of research design and data collection procedures for international clinical trials conducted through the IFRP. He has travelled extensively in the developing countries training and introducing modern fertility control technology. He is highly sensitive to the problems of the developing world, particularly Bangladesh, India and Latin America.

Four Patents have been issued to Dr. Laufe. They are:

1) A Divergent Obstetric Forcep.
2) Improved IUDs, using Nitinol.
3) Safety Obstetric Forceps.
4) A Disposable Pressure Transducer for Obstetric Forceps.

Robert Wheeler (Engineering Director) - Mr. Wheeler of the Battelle Northwest Laboratories has been project leader for the AID supported IUD development program since 1970. He is most knowledgeable regarding candidate materials, IUD performance, bioengineering analysis and the design implications of single parameter modifications. His participation in the proposed program is considered essential to assure maximum utilization of the significant bioengineering achievements made in the field of IUD development under the AID supported IUD program at Battelle.

As Project Leader for IUD development, early pregnancy termination and similar fertility research programs at Battelle, he has travelled widely in the developing countries and is knowledgeable regarding their particular needs regarding fertility control and IUD contraception in particular.

Thomas Lardner, Ph.D. - (Engineering Assistant) - Dr. Lardner is professor of Theoretical and Applied Mechanics of Bioengineering at the University of Illinois. His interest in biomechanics and reproductive biology is long standing and he has an extensive bibliography documenting this. His compilation of current IUDs in the early 1970s represents a respected encyclopedia of knowledge in this field. As a member of the Medical Advisory Committee to the AID supported IUD program at Battelle, he is intimately familiar with the accomplishments of that program and how they can be used to benefit the proposed program.

Elton Kessel, M.D. (International Clinical Studies Director) - Dr. Kessel is currently Prinicpal Investigator for the approximately $6.5 million International Fertility Research Program (IFRP) which includes a major network of overseas clinic sites for field evaluation of fertility control technologies. He will be a most significant participant, as all international trials of modified IUDs will be arranged and carried out through IFRP clinics. His long experience with the Pathfinder Fund and currently with IFRP will present the interdisciplinary expertise for the implementation of international trials with immediate feedback through the IFRP data collecting system which is absolutely essential to the success of the proposed program.

Douglass Thompson, M.D. (Clinical Assistant) - Dr. Thompson of the University of Pittsburgh, currently Director of Out-Patient Community Service at the Magee Women's Hospital, will implement and evaluate rapid clinical trials of modified IUDs in a local setting. He has been a consultant to multiple Family Planning Programs including the Westinghouse Lab Corporation and The American College Health Association. Dr. Thompson has worked with Dr. Laufe on the Copper 7 program and serves with him on the Medical Advisory Committee of Planned Parenthood of Pittsburgh.

Harry Rudel, M.D. (Pharmaceutical and Clinical Consultant) - Dr. Rudel of Biological Concepts, Inc., was vitally involved in the development of synthetic progestins at the Syntex Corporation and has worked for years with Dr. J. Zipper of Chile. He was involved in the development of the Copper 7 with Searle and will bring to the project pharmaceutical expertise in bioactive devices. As a member of the Medical Advisory Committee to the Battelle IUD program, he is cognizant of important accomplishments under that program which should be utilized or expanded in the proposed program.

Lonnie Burnett, M.D. (Clinical Consultant) - Dr. Burnett of the Department of Obstetrics and Gynecology at Johns Hopkins University has been most interested in fertility control activities and will assist in the implementation of the development and evaluation of post-abortal and post-partum devices. He participated in early clinical trials of the IUM. His involvement in training physicians from developing countries in modern fertility control methods through the Advanced Technology Fertility Management (ATFM) program at Johns Hopkins makes him sensitive to problems of fertility control in the developing world.

Achilles Sobrero, M.D. (Clinical Consultant) - Dr. Sobrero is currently in the Department of Obstetrics and Gynecology at Prentice Women's Hospital at Northwestern University. As former director of the Margaret Sanger Research Bureau, he directed numerous clinical trials of IUDs and has published widely in the area.

(Fabrication/Manufacturing Consultants) - These consultants will be selected as needed based on the program's needs for fabrication, design, manufacturing or pharmaceutical know how. An example of such an individual would be John Marco. Mr. Marco of the Marco Instrument Company of New Jersey is the developer of many innovative medical instruments and modifications including the Lem Device, a post-partum IUD. Although it is no longer manufactured by the Searle Company, his interest and experience in developing a post-partum fundal seeking IUD would be valuable to this program. His ability to rapidly fabricate prototype devices could shorten the development of definitive products and short circuit the need for major expensive purveyors.

(Administrative Support) - One full time Program Assistant will be located in Pittsburgh with the Principal Investigator to provide administrative coordinating effort required. This person will arrange for meetings of the Core Advisory Committee and provide a liaison between subcontractors, the Principal Investigator, the Core Advisory Committee and IFRP.

To assure proper administrative support for the contract, an Administrative Assistant responsible to the Program Administrator of IFRP will be located in Chapel Hill, North Carolina, and be assigned full time to the contract. This person will be responsible for issuing subcontracts based on the selection by the Principal Investigator and IFRP.

Both the Administrative Assistant and Program Assistant positions are to be paid out of overhead.

8. Contribution to Institution Building

The following factors make the International Fertility Research Programme an ideal contractor to carry out the proposed program of research:

(A) Close ties to a large and active clinical testing capability is critical to the success of this program. This is assured by contracting directly with IFRP, through which all international, and possibly some U. S., clinical trials will be organized and carried out, and data collected and analyzed.

(B) The IFRP possesses an administrative organization with the capacity to handle the fiscal administrative requirements of the proposed program. It is highly experienced in AID procedures for negotiating subcontracts, technical services agreements, etc., which will be the major mechanism by which services are procured to accomplish the objectives of the program.

(C) The overhead rate of 30% at IFRP is lower than that of many universities and considerably less than that of "not for profit" institutions which engage in such developmental work. This may result economically in a larger proportion of the total budget being available for actual performance of research.

Although the IFRP will manage the program fiscally and contracturally, the focus of domestic program activities will be based in Pittsburgh, through Principal Investigator, Dr. Laufe. This will be in close contact with the two primary teaching hospitals in Pittsburgh; i.e., Western Pennsylvania and Magee Women's, where most of the initial, rapid, U. S. clinical testing feedback on device modifications will take place.

Magee Women's Hospital is the University hospital for Obstetrics and Gynecology. The Western Pennsylvania Hospital is an affiliated University Hospital with an active student and resident program in Obstetrics and Gynecology. Together they service more than 50% of the obstetric patients in the entire county and both have extremely active Family Planning Programs. Magee Women's has approximately 5,000 active Family Planning Patients and Western Pennsylvania Hospital approaches 3,000. It is anticipated that an average of 40 new insertions per month could be achieved through these two hospitals. This patient load will rapidly bring to fruition the early clinical trials for rapid evaluation of side effects in the first three months of use of improved or new IUDs.

9. Utilization Plans

It is expected that research findings from the proposed program would find wide and rapid dissemination and utilization:

(A) The IFRP, through which international clinical trials of modified IUDs will be conducted, has about 100 active clinic sites in 40

countries. This provides a direct and immediate avenue for introduction of improved devices, on a large scale, to many developing countries around the globe.

(B) Principal Investigator, Dr. Laufe, publishes actively. In turn this information can rapidly be incorporated in the Population Report Series put out by the AID supported Population Information Program, which has a current worldwide distribution of 85,000 copies of each publication.

(C) Dr. Laufe is Director of the Advanced Technology Fertility Management (ATFM) Program at the Western Pennsylvania Hospital, which is one of the four locations of AID's major training programs for developing country physicians in the most modern methods of fertility control. Thus, any improved, modified devices can be introduced quickly to these four training program sites and to the participating physicians from developing countries.

(D) The capabilities of research and development institutions in less developed countries will be strengthed through consultation, field trial experience and a working arrangement with scientists on this research program. Evidence of this capability should be seen in their publications in local and international journals and conference papers.

10. Budget Analysis

The proposing office considers the budget to be in keeping with the scope of work proposed. The IFRP offers a low overhead rate (30%) compared to most other research settings. The proposed program focuses on only highest priority research actions and requires a rate of expenditure about half that of the previously supported IUD research program carried out by the Battelle Memorial Institute.

11. Internal and External Reviews

This project has been reviewed within the Office of Population and approved by the AID Research and Development Committee. External reviews are not yet available.

12. Proposing Office General Evaluation

For the past 4 1/2 years, AID has supported a program of IUD development at the Battelle Memorial Institute. While a number of significant bioengineering achievements have resulted, the gap between laboratory developments and clinical evaluation was never adequately bridged.

The newly proposed program is highly medically oriented and based on a somewhat different philosophy toward IUD development, one with which the

Proposing office agrees and considers the most sensible based on the current status of IUD research and programmatic experience. Thus, the focus will be on events occurring within the first three months of IUD use, with rapid clinical testing of stepwise modifications in IUD design. This philosophy is based both on a better understanding of the clinical factors relating to performance and acceptance of IUDs in developing country family planning programs, i.e., most untoward events occur in the first three months, and on a clearer understanding that this approach has been the most successful so far to designing and developing better IUDs.

Dr. Laufe, Principal Investigator under the proposed program, has been active and innovative in design and clinical evaluation of IUDs for a number of years. As a member of the Medical Advisory Committee to the Battelle IUD program, he is thoroughly knowledgeable in the accomplishments of that program. Mr. Wheeler, project leader for the Battelle IUD program since its inception in 1970, will contribute 50% of his time to the new program. This should further assure a smooth transition between the two programs and that significant developments from the Battelle program are appropriately utilized in the new program.

The proposing office considers timely and responsive clinical trials to be the single most critical factor in the successful completion of the proposed program. Rapid U. S. clinical feedback from incremental design modifications appears relatively certain from the commitment of two hospitals in Pittsburgh. The essential close tie with a large international clinical testing capability should be guaranteed by contracting with the International Fertility Research Programme.

The proposing office concurs with the plan that a select multidisciplinary Core Advisory Committee of clinicians, bioengineers, pharmacologists and development/fabrication experts advise on all research aspects of the program. The proposed committee members, all of whom have agreed to participate, are well known for their experience, expertise, and accomplishments in the field of IUD design, development, and testing. Their diversified backgrounds, coupled with their common intense interest in development of improved IUDs, should provide innovative and effective direction to the proposed program.

In conclusion, the proposing office has confidence that, building from experience gained in the Battelle IUD program, the newly proposed and more clinically oriented program has a high probability of achieving an effective IUD, with very early pain and bleeding side effects reduced to low enough levels that the IUD will find wider patient acceptance and improved use effectiveness in the developing world.

Mary I. Perry
Signature of Monitor - Mary I. Perry

PTR/cwf
Signature of R. T. Ravenholt
Director, Office of Population

J. J. Speidel
Signature of Monitor - J. J. Speidel

Harrietts S. Crowley
Signature of (Mrs.) Harrietts S. Crowley
Acting Assistant Administrator for PHA

DEVELOPMENT OF IMPROVED AND NEW IUDS

INTERNATIONAL FERTILITY RESEARCH PROGRAM

IV Budget

July 1, 1975 - June 30, 1978

	July 1, 1975- June 30, 1976	July 1, 1976 Sept.30, 1976 Interim Quarter	Oct. 1, 1976 Sept.30, 1977	Oct. 1, 1977 Sept.30, 1978	Total
Personnel:					
Direct Salaries	$ 12,600	$ 3,150	$ 12,600	$ 12,600	$ 40,950
Fringe Benefits (21%)	2,646	662	2,646	2,646	8,600
Total Personnel	15,246	3,812	15,246	15,246	49,550
Consultants	6,900	2,070	8,280	8,280	25,530
Equipment	3,000	250	1,000	1,000	5,250
Disposable Supplies and Misc.	2,500	700	2,500	3,000	8,700
Travel	10,000	4,000	12,000	12,000	38,000
Publication Costs	500	100	500	500	1,600
Subcontracts	94,385	33,964	136,127	172,677	437,153
Overhead (30% Direct Costs)	39,825	13,693	52,958	63,908	170,384
Salaries Support	36,644	9,411	40,389	40,389	127,833
Total Cost	$210,000	$ 68,000	$269,000	$317,000	$864,000

DEVELOPMENT OF IMPROVED AND NEW IUDs

INTERNATIONAL FERTILITY RESEARCH PROGRAM

PERSONNEL

	Percent Employed	Fiscal Year July 1, 1975- June 30, 1976	July 1, 1975- Sept. 30, 1975	Oct. 1, 1976- Sept. 30, 1977	Oct. 1, 1977 Sept. 30, 1978
Direct Salaries:					
L. Laufe - Principal Investigator	25%	$9,000	$2,250	$9,000	$9,000
T. Lardner - Engineering Assistant	10%	3,600	900	3,600	3,600
Total Direct Salaries		12,600	3,150	12,600	12,600
*Indirect Salaries:					
Administrative Assistant - Chapel Hill	100%	$15,000	$4,125	$16,500	$18,150
Program Assistant - Pittsburgh	100%	13,000	3,575	14,300	15,730
Secretary	50%	3,500	963	3,850	4,235
Total Indirect Salaries		$31,500	$8,663	$34,650	$38,115
**Salaries Support:					
R. Wheeler - Engineering Director	50%	$31,110	$7,778	$33,855	$33,855
Thompson - Clinical Assistant	10%	6,534	1,633	6,534	6,534
		$37,644	$9,411	$40,389	$40,389

* Paid from Overhead

**Includes Overhead rate at Battelle 83% and Magee Womens Hospital 81.5%

Consultants

Core Advisory Committee:

L. Burnett - Clinical Consultant 10 days/year @$138
A. Sobrero - Clinical Consultant 10 days/year @$138
H. Rudel - Pharmaceutical Consultant 10 days/year $138

Other Manufacturing and Engineering Consultants:

July 1, 1975 - June 30, 1976 - 10 days @ $138

July 1, 1976 - September 30, 1976 - 15 days @ $138

October 1, 1976 - September 30, 1978 - 20 days/year @ $138

Non-Expendable Equipment

July 1, 1975 - June 30, 1976

3 desks	@ $300	$900
3 chairs	@ $100	300
2 typewriters	@ $400	800
1 transcriber	@ $400	400
2 book cases	@ $100	200
1 printing calculator		400
		$3000

July 1, 1976 - September 30, 1976

2 hand calculators @ $125-$250

October 1, 1976 - September 30, 1977

Heatsealer, Dies, Molds $1,000

October 1, 1977 - September 30, 1978

Dies, Molds for IUD Fabrication $1,000

Expendable Supplies and Miscellaneous

July 1, 1975 - June 30, 1976

Expendable Office Supplies	@ $100/month	$1,200
Telephone	@ $50/month	600
Postage and Miscellaneous		700
		$2,500

July 1, 1976 - September 30, 1976

Expendable Office Supplies	@ $100/month	$300
Telephone	@ $50/month	150
Postage and Miscellaneous		250
		$700

(October 1, 1976 - September 30, 1977)

Expendable Office Supplies	@ $100/month	$1,200
Telephone	@ $50/month	600
Postage and Miscellaneous		700
		$2,500

October 1, 1977 - September 30, 1978

Expendable Office Supplies	@ 100/month	1,200
Telephone	@ $60/month	720
Postage and Miscellaneous		1,080
		$3,000

Travel

July 1, 1975 - June 30, 1976

Core Advisory Committee:

Quarterly Meetings 4 @ $1,500	$6,000
Site visits to Subcontractors 4 @$500	2,000
Travel between Seattle/Pittsburgh/Chapel Hill	2,000
	$10,000

July 1, 1976 - September 30, 1976

Core Advisory Committee 1 @ $1,500	$1,500
Site Visits to Subcontractors 3 @ $500	1,500
Travel between Seattle/Pittsburgh/Chapel Hill	1,000
	$4,000

October 1, 1976 - September 30, 1978 (each year)

Core Advisory Committee 4 @ 1,500	$ 6,000
Site Visits to Subcontractors 6 @$500	3,000
Travel between Seattle/Pittsburgh/Chapel Hill	3,000
	$12,000

Publication Costs:

Each Year

AID Reports	$200
Core Committee Reports	200
Other Publication Expense	100
	$500

July 1, 1976 - September 30, 1976

Core Committee Reports $100

Subcontracts

The amount listed in each of the years is for the purpose of procuring personal and manufacturing services of individuals and organizations to modify existing IUDs, and develop new prototypes. Upon satisfactory performance of an IUD in early trials, production will be initiated to supply adequate numbers for clinical field testing. All procured services or manufacturing capabilities will be charged to this line item.

Indirect Costs:

Indirect Costs consist of Overhead calculated at 30% of total direct cost as negotiated with the Agency for International Development in January, 1975. For purposes of this proposal, the line item "Salaries Support" is not included in the base for calculating the Overhead amount since these figures include the overhead rate at Battelle (83%) and Majee Hospital (81.5%).