

9320527/99

SN 29861
FY 77 PD-AAM-783

AID 1350-1X (7-71)	DEPARTMENT OF STATE AGENCY FOR INTERNATIONAL DEVELOPMENT	1. Cooperating Country Worldwide	Page 1 of 20 Pages
		2. PIO/T No. 932-17-570-527- 73-301000 3231006	3. <input checked="" type="checkbox"/> Original or Amendment No. <u>XXX</u>
PIO/T	PROJECT IMPLEMENTATION ORDER/TECHNICAL SERVICES	4. Project/Activity No. and Title Development of Improved Intrauterine Contraceptive Devices (IUD) Battelle Memorial Institute	

DISTRIBUTION	5. Appropriation Symbol 72-1131007	6.A. Allotment Symbol and Charge 307-32-099-00-23-31 (Res.)	6.B. Funds Allotted to: <input checked="" type="checkbox"/> A.I.D./W <input type="checkbox"/> Mission																																									
	7. Obligation Status <input checked="" type="checkbox"/> Administrative Reservation <input type="checkbox"/> Implementing Document		8. Funding Period (Mo., Day, Yr.) From 6/30/73 to 6/30/74																																									
9.A. Services to XXXXXXXXXXXX Continue as of XXXXXX 6/30/73 and _____		9.B. Completion date of Services (Mo., Day, Yr.) 6/30/74																																										
10.A. Type of Action <input checked="" type="checkbox"/> A.I.D. Contract <input type="checkbox"/> Cooperating Country Contract <input type="checkbox"/> Participating Agency Service Agreement <input type="checkbox"/> Other AID/csd-2819																																												
10.B. Authorized Agent AID/W																																												
<table border="1"> <thead> <tr> <th colspan="2">Estimated Financing</th> <th>(1)</th> <th>(2)</th> <th>(3)</th> <th>(4)</th> </tr> <tr> <th colspan="2"></th> <th>Previous Total</th> <th>Increase</th> <th>Decrease</th> <th>Total to Date</th> </tr> </thead> <tbody> <tr> <td>\$1.00=</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td rowspan="2">11. Maximum A.I.D. Financing</td> <td>A. Dollars</td> <td></td> <td>487,230</td> <td></td> <td>487,230</td> </tr> <tr> <td>B. U.S.-Owned Local Currency</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td rowspan="2">12. Cooperating Country Contributions</td> <td>A. Counterpart</td> <td></td> <td></td> <td></td> <td>FUNDS RESERVED BY <i>JCB</i></td> </tr> <tr> <td>B. Other</td> <td></td> <td></td> <td></td> <td>POSTED 5/10/73</td> </tr> </tbody> </table>					Estimated Financing		(1)	(2)	(3)	(4)			Previous Total	Increase	Decrease	Total to Date	\$1.00=						11. Maximum A.I.D. Financing	A. Dollars		487,230		487,230	B. U.S.-Owned Local Currency					12. Cooperating Country Contributions	A. Counterpart				FUNDS RESERVED BY <i>JCB</i>	B. Other				POSTED 5/10/73
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13. Mission References

14. Instructions to Authorized Agent: The Research Advisory Committee at its March 7-8, 1973 meeting approved an additional approximate \$874,000 for a two year extension of work to June 30, 1975. This PIO/T is for the purpose of adding the first year of the two year funding authorized, or approximately \$487,230. This \$487,230 figure represents the FY 74 budget figure of \$462,230 plus \$25,000 for an IUD workshop. The contractor reports that all funds under the current contract will be expended by June 30, 1973.

Contacts: Gordon W. Duncan, Principal Investigator
Robert G. Wheeler, Principal Investigator

15. Clearances - Show Office Symbol, Signature and Date for all Necessary Clearances.

A. The specifications in the scope of work are technically adequate PHA/POP/R, J.J. Speidel <i>J.J. Speidel</i>	B. Funds for the services requested are available
C. The scope of work lies within the purview of the initiating and approved Agency Programs PHA/POP, E.R. Backlund <i>E.R. Backlund</i> 4/11/73	D. TA/RUR, E.J. Long <i>E.J. Long</i> TA/RUR, M. Rechcigl <i>M. Rechcigl</i> 5/10/73
E. PHA/POP, R.T. Ravenholt <i>R.T. Ravenholt</i>	F.

16. For the cooperating country: The terms and conditions set forth herein are hereby agreed to	17. For the Agency for International Development	18. Date of Signature
Signature and date: _____ Title:	Signature: <i>Go Coleman</i> Title: PHA/PRS, Chief	<i>May 14, 1977</i>

AID 1350-1X (9-70)	Cooperating Country	PIO/T No.	3231006	Page 2 of 20 Pages
	Worldwide	932-17-570-527-73-311781		
PIO/T	Project/Activity No. and Title Development of Improved Intrauterine Contraceptive Devices (IUD) Battelle Memorial Institute			

SCOPE OF WORK

19. Scope of Technical Services

A. Objective for which the Technical Services are to be Used

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

B. Description

(see Continuation Page)

Summary of Work Plan

Current activities will be extended to:

- (a) Use recently acquired knowledge about inert IUDs to achieve improved performance and acceptance through new designs.
- (b) Add controlled release medication to otherwise good IUDs to improve their contraceptive efficacy and other clinical performance characteristics.
- (c) Add medication to be released from IUDs for a period up to 6 to 12 months to reduce the high incidence of expulsion and pain-and-bleeding removals shortly after insertion.

(see Continuation Page)

C. Technicians

(1) (a) <u>Number</u>	(b) <u>Specialized Field</u>	(c) <u>Grade and/or Salary</u>	(d) <u>Duration of Assignment (Man-Months)</u>
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See Budget

(2) Duty Post and Duration of Technicians' Services

U.S.

(3) Language requirements

NA

(4) Access to Classified Information

NA

(5) Dependents Will Will Not **Be Permitted to Accompany Technicians** NA

D. Financing of Technical Services

(1) By AID - \$ 487,230

(2) By Cooperating Country -

AID 1350-1X (9-70)	Cooperating Country Worldwide	PIO/T No. 934-17-570-527-73-3231026	Page 3 of 20 Pages
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20. Equipment and Supplies (Related to the services described in Block 19 and to be procured outside the Cooperating Country by the supplier of these services)

A. (1) Quantity (2) Description	(3) Estimated Cost	(4) Special Instructions
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See Budget

B. Financing of Equipment and Supplies
 (1) By AID - \$ _____ (2) By Cooperating Country - _____

21. Special Provisions

- A. This PIO/T is subject to AID (contracting) (PASA implementation) regulations.
- B. Except as specifically authorized by AID, or when local hire is authorized under the terms of a contract with a U.S. Supplier, services authorized under this PIO/T must be obtained from U.S. sources.
- C. Except as specifically authorized by AID/W, the purchase of commodities authorized under this PIO/T will be limited to the U.S. under Geographic Code 000.
- D. Other (specify):
 Except as may be modified by the special provisions below, all other terms and conditions of the contract shall remain in effect and be applicable, as appropriate, to this amendment.

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22. Reports by Contractor or Participating Agency (Indicate type, content and format of reports required, including language to be used if other than English, frequency or timing of reports, and any special requirements)

The reporting requirements as set forth in the original contract, as modified by amendment No. 2, shall be deleted and superceded by the following:

All requirements of General Provision 16(a)(b)(c) pertaining to reports (except as modified herein) are applicable to this contract. Semi-annual research reports shall be prepared in the format as specified in Attachment A, "Guidelines for Preparation of the Research Annual Report," dated January 20, 1972, and submitted to the Technical Officer, PHA/POP/R, AID, Washington, D. C. 20523, in 20 copies, on or about January 15 and July 15 of each year. A substantive final report, in 20 copies, shall be submitted within 45 days of completion of work under this contract, as required under General Provision 16(c).

23. Background Information (Additional information useful to Authorized Agent and Prospective Contractors or Participating Agency; if necessary cross reference Block 19.C(4) above.)

Project Summary revised February 5, 1973
 Proposal dated November 1972
 Letter Wheeler to Speidel dated March 5, 1973
 Memo Wheeler to Duncan dated April 4, 1973
 Assistant Administrator's approval to submit project to RAC
 Summary of RAC's recommendations on proposals reviewed on March 7-8, 1973

24. Relationship of Contractor or Participating Agency to Cooperating Country and to AID

A. Relationships and Responsibilities

NA

B. Cooperating Country Liaison Official

NA

C. AID Liaison Officials

PHA/POP/R, J. J. Speidel/M. I. Perry

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		3. Project/Activity No. and Title Development of Improved Intrauterine Contraceptive Devices (IUD) - Battelle Memorial Institute 937-17-570-527-73- 911741	

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Continued

Within the first year the following will be accomplished for the pleated membrane and other inert designs: (a) Initiation of clinical testing; (b) making a standard design with inserter; (c) development of a model for nulliparas if required; (d) production of adequate numbers of any promising designs for broad clinical testing, i.e. 1000-10,000 as required; and (e) development and supply of families of IUD sizes for prescription series. The second year will be devoted to design refinement on the basis of clinical feedback and computer predictive modeling.

2. Bioengineering Studies

Bioengineering studies, including materials development and testing of specific design parameter effects on IUD performance, will be carried out. These studies will include testing of specifically required design modifications and materials for IUDs including, but not limited to: (a) Studies of the performance effects of transverse bend resistance and the use of anterior posterior projection to decrease expulsions; (b) bioengineering studies of new polymers as an IUD material; and (c) development of barium ferrite as a substitute for barium sulfate.

3. Toxicology Studies

Toxicology studies, as may be required by drug and device regulatory agencies for clinical use of inert IUDs, will be conducted. The exact nature of these studies will be defined in collaboration with the FDA, and may include hemograms, blood chemistries, subacute toxicity studies at multiples of human dosages, chronic drug studies, teratology, reproduction, and pharmacokinetic studies.

Of the total program effort, approximately 27% will be devoted to development of inert IUDs as described in (1) above and approximately 12% will be devoted to the bioengineering and toxicology studies described in (2) and (3) above.

II. Prescription of IUDs

The objective of this part of the program is to enhance IUD performance by prescription of IUDs using improved diagnostics and equipment.

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		3. Project/Activity No. and Title Development of Improved Intrauterine Contraceptive Devices (IUD) - Battelle Memorial Institute 931-17-570-527-73-3117411	
Indicate block numbers.	Use this form to complete the information required in any block of a PIO or PA/PR form.		
19 B Continued	<p>The intrauterine metrology instrument, developed under the current contract, will be used in conjunction with data from hystero-grams and field trials of new IUDs to identify the value of metrology and prescription in minimizing undesirable side effects from IUDs.</p> <p>Although the current instrument is capable of completely measuring the shape and size of the uterine lumen, attempts will be made to reduce the number of requisite measurements leading to simplification of the procedure. An economical metrology instrument will be developed when the requisite number of measurements is identified.</p> <p>Work on prescription of IUDs will include:</p> <ol style="list-style-type: none"> 1. Description of the size and shape variations of uteri in two or more populations through statistical analysis of U.S. and LDC double contrast hystero-grams. 2. Correlation of size and shape factors with readily measured characteristics of the patient. 3. Development of economical, safe and effective instruments for intrauterine metrology as a clinical tool. 4. Establishment of procedures to assure proper selection or fitting of an IUD suited to the individual patient. 5. Identification of patients for whom IUD contraception is contraindicated. <p>Within the first year the contractor will: (a) Complete computer program for analyzing Burnhill X-Ray File and carry out analysis of patient characteristics vs intrauterine size; (b) publish a paper on Determinants of Uterine Size and Shape; (c) analyze or obtain analysis of IFRP data and/or other computer files; (d) test thermoplastic IUD designed to reveal uterine shape; (e) make decision on best method to obtain required size data; (f) test prescription models against existing performance data to evaluate potential gain in continuance and other performance parameters; and (g) make at least 10 copies of the Battelle developed research model of the intrauterine metrology instrument and provide specifications to commercial vendors.</p> <p>During the second year the contractor will: (a) Test intrauterine measuring system; (b) complete inert IUD prescription protocol; and (c) complete prescription protocol for either inert or bioactive IUD option.</p>		

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Approximately 11% of the total program effort will be devoted to work on prescription of IUDs described above.

III. Bioactive IUD Development

Three types of bioactive materials systems will be studied:

1. Metal ion-releasing systems for contraceptive efficacy improvements.
2. Materials incorporating potent steroids released at very low rates to enhance contraceptive efficacy.
3. Systems which release medicaments primarily selected to suppress expulsion and/or pain and bleeding.

The following scope of work will be carried out:

1. Obtain Advice and Consent from the Medical Advisory Committee on IUD Medicaments

The early selection of medicaments in the three principal categories will be made. Clinicians with some interest in prosecuting a physician-sponsored IND will have been tentatively identified for metal ion and steroid efficacy trials as well as autonomic drugs or hormonal substances for suppressing events of expulsion and pain and bleeding. Cu-releasing compounds and micro-dose progestogens (e.g., d-norgestrel) will be among the active agents selected as candidates for contraceptive efficacy enhancement.

2. Identify Physicians Desiring to Examine Specific Approved Medicaments in Clinical Trials

With the agreement of the Medical Advisory Committee for specific candidate medicaments, Battelle will begin collaboration with previously identified investigators on target dose rates.

3. Determine Which Carrier and Medicament Pairs are Best Candidates

The contractor will maintain device design options by parallel investigations using elastomers such as the medical grades of polydimethylsiloxane and polymers having varying mechanical properties. Listed in order of decreasing stiffness, polymers

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carried over from the present program will include: (a) Polypropylene, (b) Polypropylene-polyethylene copolymers, (c) Polyethylene and (d) Ethylene vinyl-acetate. Added to these will be at least two biodegradable polymers. Suitability of these materials as carriers for each candidate medicament will be based on prior experimental work, where possible, and on laboratory experiments where needed. In the latter case, in vitro measurements of the diffusion rate of the medicament through the carrier will be made in one or both of the following ways: (a) Measurement of diffusion of the medicament in solution through a membrane of the candidate carrier material; (b) measurement of the release rate of the medicament from composites made of the carrier and medicament, using controlled flow techniques established under the current contract. (See July 1972 progress report.)

Based on the results of the experimental screening of materials systems, pairs of carriers and medicaments will be selected for further development and refinement. At least one delivery scheme will be available at the outset for copper release. Release schemes developed by others (e.g., the Alza-owned progestin delivery system) will be considered to the extent that: (a) Cooperative arrangements for their use can be made, and (b) suitability for intended use can result in an economic or time benefit for early fielding of devices.

4. Fabricate Release Kinetics Specimens

The contractor will redesign materials systems, incorporating changes in dispersant geometry or volume percent loadings to adjust release rates to the extent possible. Where more sophisticated microstructural systems engineering is warranted, the contractor will apply microencapsulation techniques to retard release rates or use biodegradable polymers in the form of coatings or lamellae to expose new surfaces for diffusion or to release free or encapsulated microdoses of medicaments to the uterine lumen.

5. Model the Release Kinetics of the Systems

Most promising materials identified through in vitro testing will be modeled kinetically and considered as potentially useful IUD configurations.

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6. Fabricate Specimens for In Vivo Studies of Release Rates and Toxicity

Having identified systems with suitable in vitro release rates for use in IUD configuration as intrauterine delivery systems, the contractor will fabricate test specimens for in vivo release determinations, using animal models. These specimens will principally be in the form of rods, helices and rings.

7. Start Chronic In Vivo Release Rate Tests, Examine Toxicology and Biocompatibility

Animal tests will be used for validation of the more detailed in vitro release studies performed in earlier activities. Some in vitro work using the in vivo configurations will be done under this activity as controls.

8. Select Final Candidates and Fabricate in IUD Configurations for Field Trials

In addition to fabrication of selected IUD configurations, appropriate inserters will be made available.

9. Measure Mechanical Properties

Using specimens fabricated in the same dies used for the inert IUDs, mechanical testing will be performed to measure compliance and strength characteristics of the devices in selected loading directions, using techniques already applied to existing IUDs under this program. Measurements of stress corrosion cracking will be made using fatigue loadings in a simulated uterine fluid medium.

10. Establish Quality Assurance Procedures

Quality assurance procedures will be established by selecting appropriate sampling methods and by physical, mechanical and chemical tests for processed devices. Material characterization must be rigorous enough to meet FDA requirements.

11. Test Actual Devices In Vivo and In Vitro

The release rates of actual bioactive IUDs made by a commercially usable fabrication process will be examined using a primate

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16. Start Phase I Evaluations

In most cases, Phase I evaluations will be conducted by a clinician under a physician-sponsored IND. In those instances where a clinician is not available for sponsorship, the contractor will pursue Phase I Clinical Pharmacology under a Battelle-sponsored IND, using clinicians as investigators. The contractor will provide materials and designs for adequate numbers of devices and develop the experimental design in collaboration with clinicians. Specialized analytical or evaluative services in hematology, histology, cytology and data collection will be provided by the contractor as needed. IFRP compatible data collection forms will be used to the extent possible.

17. Determine Most Effective Dose Rates

This activity may be pursued in two different ways, and is expected to be an on-going process with various materials systems throughout most of the program. These two ways are: (a) Temporary and expedient methods to deliver medicaments at known dose rates and (b) prototypical bioactive IUDs, where possible. Effects of dose rates known to be within a safe range (from animal toxicology studies) will be examined by: (a) Conventional and scanning electron microscopy histology of biopsy specimens; (b) histopathology of excised uteri from elective hysterectomy patients; and (c) relief of symptoms (e.g., reduced pain and bleeding through replacement of an inert with a medicated device of identical configuration).

Hematologic and other conventional tests (e.g., Spinnbarkeit and ferning behavior of cervical mucus) will be used to determine systemic and localized effects of the medicament.

18. Obtain IUDs with Correct Dose Rates

Based on preliminary Phase I human subjects experimental results, the contractor will select the lowest efficacious dose rate and prepare IUDs in adequate numbers, including inserters, for Phase II trials in U.S. clinics and for LD: field trials through the IFRP.

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19. Start Phase II and III Testing Using U.S. Clinics and IFRP

In most cases, it is expected that these studies will be carried out by clinicians who have filed physician-sponsored INDs. The contractor will serve in a supportive capacity, collecting and reducing data statistically as well as providing bridging activities between the sponsors, investigators and AID.

It is expected that Phase II studies will be conducted in U.S. clinics, with close control of experimental conditions, use of prescriptive and retrospective metrology, and careful documentation of prior patient histories. Careful screening of participants and close scrutiny of data will replace large numbers of human subjects, maximizing the confidence in Phase II results.

Phase III studies, using requisite large numbers of human subjects, will be conducted in LDCs through the AID-funded IFRP.

Where necessary, the contractor will carry out these investigations under a Battelle-sponsored IND.

During the first year the contractor will: (a) select candidate IUD material for first order release; (b) evaluate release rates in vitro on normal and time accelerated model; (c) start chronic in vivo release rate tests and toxicology studies; (d) select final candidates and fabricate IUD configurations; (e) determine how to obtain desired release rate from fluid filled IUD; (f) identify physician sponsors of IND; (g) select candidate medications; (h) calculate potential IUD continuance and acceptance gains; (i) determine desired period of effective bioactivity for progestin release IUDs; and (j) for Cu IUDs, establish fabrication, packaging, and sterilization procedures, make IND applications, prepare protocol package and start clinical testing.

During the second year, continuing for Cu IUDs and beginning for other bioactive IUDs, the contractor will: (a) Establish fabrication, packaging, and sterilization procedures; (b) make IND applications; (c) start Phase I evaluations; (d) prepare protocol package; (e) complete animal toxicology; (f) start U.S. testing and (g) start IFRP testing.

Approximately 50% of the total program effort will be devoted to bioactive IUD development, including approximately 13% for

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copper ion release IUDs, 13% for progestin release IUDs, and 24% for release of other medications.

IV. Supporting Services

During the amended contract period it is anticipated that certain additional research opportunities may present themselves, as a result of research findings by the contractor and others: and in response to the IUD Workshop to be held as described below, which will have high value in expediting IUD development and use. Such activities will be within the general scope of work of this contract, although they cannot be specifically defined at this time. They will further the objectives of the contract by supplying key information, materials development, evaluation and analytical services to support both research by the contractor and that of others.

Written approval of the AID Project Monitor is required prior to the initiation of supporting services under this section.

For each of the study areas I through IV (Inert IUDs, Prescription of IUDs, Bioactive IUDs and Supporting Services) the contractor will:

1. Establish Fabrication, Packaging, and Sterilization Procedures for Investigational Devices

This will include the establishment of specifications for manufactured devices, inserters, packaging, and sterilization with sufficient detail that preparation of several hundred to several thousand devices may be carried out by the contractor or by a commercial fabricator identified by the contractor. The contractor will identify sources of supply, negotiate prices, etc. to assist AID in its procurement of such commodities. A design, quality assurance, and fabrication manual for these IUD systems will be published.

2. Collaborate with Other IUD Research Efforts and Maximize Data Acquisition

The contractor will update its computer prediction model to include the newest devices, active devices and known less effective devices. To keep up-to-date with IUD research in

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support of the laboratory and clinical efforts under this contract, an active program of data acquisition and utilization from ongoing clinical trials and research in the field will be pursued. Contacts will include, but not be limited to, the following organizations and individuals: IFRP, WHO, Margaret Sanger Research Bureau, The Population Council, University of Southern California, Johns Hopkins University, Exeter, Alza, Ortho, Searle, Dr. Jaime Zipper. The contractor will keep the AID Project Monitor apprised of findings.

3. Maintain Liaison with the FDA

Testing schemes for new designs will take into account current FDA requirements (in the case of active devices) and proposed FDA regulations (which may regulate all IUDs) so human clinical testing can proceed under the program to the point of having an IUD ready for broad scale clinical testing by IFRP and/or elsewhere.

IUD WORKSHOP

As an ancillary project under the amended program, the contractor will hold a workshop bringing together approximately 30 to 40 experts in the IUD field to assess the current state of IUD technology and to define research priorities with respect to development of improved inert and bioactive IUDs. This workshop will be held within the first 6 months of the amended contract period. The AID Project Monitor will be afforded the opportunity to assist with the planning and participate in the workshop. Written approval of the AID Project Monitor will be obtained for the final workshop arrangements including location and dates, program format, selection of participants, and plans for publishing the proceedings.

CONTINUATION
SHEET

FORM SYMBOL

DEPARTMENT OF STATE
AGENCY FOR
INTERNATIONAL DEVELOPMENT

TITLE OF FORM

 Worksheet .suance

PAGE 17 OF 20 PAGES

1. Cooperating County
Worldwide

2.a. Code No.

2.b. Effective Date

2.c. Amendment
 Original OR No. 33. Project/Activity No. and Title
Development of
Improved Intrauterine Contraceptive Devices
(IUD) - Battelle Memorial Institute
~~932-17-570-527-73-313741~~Indicate block
numbers.

21 D

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Use this form to complete the information required in any block of a PIO or PA/PR form.

1. The level of effort in the performance of the amended contract shall be 191.3 total man-months of direct labor. All personnel included in subcontracts and as consultants or medical advisors will be in addition to the level of effort established in this amendment.
2. The key personnel clause under Amendment No. 2 should be deleted, and the following substituted:
 - a. Battelle Staff -
 - G. W. Duncan, Program Coordinator
 - R. G. Wheeler, Project Leader
 - R. L. Bernstine - Medical Advisor
 - N. R. Gordon, Senior Research Engineer
 - B. R. Lower, Research Engineer
 - G. Janson, Jr., Engineering Associate
 - D. R. Kalkwarf, Research Associate
 - M. R. Sikov, Research Associate
 - J. F. Williford, Research Scientist
 - b. Medical Advisory Committee Members -
 - Roger Bernard, M.D.
 - Thomas Lardner, PhD
 - Mary Lane, M.D.
 - Leonard Laufe, M.D.
 - Earl Parr, PhD.
 - Ralph Robinson, M.D.
 - Harry Rudel, M.D.
3. The contractor will maintain a medical advisory committee to provide consultation and advice on the direction of the research program. This committee shall be composed of experts in design, use, and evaluation of IUD's and will include medical personnel who can give guidance and assistance to the prototype design and clinical trials phases of this contract.
4. The contractor will obtain, with the exception of professional personnel identified by name in this amendment, prior approval of the AID Project Monitor on the selection of all professional personnel, consultants and medical advisors to work on this project, with or without compensation.

CONTINUATION
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FORM SYMBOL

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1. Cooperating County

Worldwide

2.o. Code No.

2.b. Effective Date

2.c. Original OR Amendment
No. 33. Project/Activity No. and Title Development of
Improved Intrauterine Contraceptive Devices
(IUD) - Battelle Memorial Institute
93Z-17-570-527-73-~~341741~~Indicate block
numbers.21 D
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Use this form to complete the information required in any block of a PIO or PA/PR form.

5. The contractor will obtain the written approval of the Contracting Officer before entering into any subcontracts, service agreements or collaborative relationships with institutions or individuals, not on the staff of this project, for any work performed under this contract. The contractor will ascertain before hand that such institutions or individuals are not being compensated by A.I.D. for the same services through other contracts or grants.
6. Each subcontract will include a key personnel clause.
7. The contractor will obtain the written concurrence of the AID Project Monitor for all clinical testing arrangements, both in the United States and overseas.
8. The rights to all data and publications will be in accordance with the clauses in the general provision which govern these items in research contracts. The contractor will assure that appropriate provisions are included in subcontracts or other collaborative arrangements so that the data, rights, and results of any work performed under this contract are in the public domain, insofar as possible.
9. The contractor will afford the A.I.D. Project Monitor the opportunity to review and provide comments on any proposed publication, prior to its publication, which pertains to work developed in connection with this contract in accordance with the general provisions.
10. The contractor is required to disclose to the Contracting Officer in the approved format (Attachment B) any patentable inventions developed in the performance of this contract.
11. Written authorization from the Contracting Officer will be required prior to all foreign travel under this contract.
12. Within the total estimated cost, the contractor may adjust line item amounts in the budget as reasonably necessary for the performance of the contract.
13. The proposal titled "Development of Improved Inert and Bioactive IUDs." dated November 1972 is incorporated here by reference for details in research design and methodology to be used during the amended contract period. In event of conflict between the proposal and the scope of work described in Block 19B, the scope of work described in Block 19B shall be controlling.

CONTINUATION SHEET

FORM SYMBOL

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1. Cooperating County
Worldwide

2.a. Code No.

2.b. Effective Date

2.c. Original OR Amendment No: 3

3. Project/Activity No. and Title Development of Improved Intrauterine Contraceptive Devices (IUD) - Battelle Memorial Institute 931-17-570-527-73-3117/11

Indicate block numbers.

Use this form to complete the information required in any block of a PIO or PA/PR form.

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22. A.I.D. Policy for Protection of the Individual as a Research Subject

Safeguarding the rights and welfare of human subjects involved in research supported by A.I.D. is the responsibility of the institution to which support is awarded. It is the policy of A.I.D. that no work shall be initiated under a grant, award, or contract for the support of research involving human subjects unless the research is given initial and continuing review and approval by an appropriate committee of the applicant institution. This review will assure that (a) the rights and welfare of the individuals involved are adequately protected, (b) the methods used to obtain informed consent are adequate and appropriate and (c) the risks and potential medical benefits of the investigation are assessed.

The institution must provide written assurance to A.I.D. that it will abide by this policy for all research involving human subjects supported by the A.I.D. This assurance shall consist of a written statement of compliance with the requirements regarding initial and continuing review of research involving human subjects and a description of the institution's review committee structure, its review procedures and the facilities and personnel available to protect the health and safety of human subjects. In addition to providing the assurance, the institution must also certify to A.I.D. for each proposal involving human subjects that its committee has reviewed and approved the proposed research before any work may be initiated.

Since the welfare of the subject is a matter of concern to A.I.D. as well as to the institution, A.I.D. advisory groups, consultants, and staff may independently review all research involving human subjects, and prohibit research which presents unacceptable hazards. This provision, however, shall not derogate in any manner from the responsibility of the institution set forth herein.

All of the above provisions apply to any research involving human subjects conducted outside of the United States, and in addition such overseas research will conform to legal and other requirements governing human research in the country where it is conducted.

In addition to the procedures set forth above, studies with unmarketed drugs will be carried out in compliance with provisions applicable to such studies in the country where such studies are conducted. In the United States, the regulations of the Food and Drug Administration will be followed and the evidence of such compliance provided to A.I.D.

Guidance on procedures to safeguard human subjects involved in research is found in the document "The Institutional Guide to DHEW Policy on Protection of Human Subjects," dated December 1, 1971. Compliance with these procedures, except as modified above is required.

BUDGET

<u>Staff Labor</u>	FY 74		FY 75	
	<u>Man-Months</u>	<u>Amount</u>	<u>Man-Months</u>	<u>Amount</u>
Program Coordinator(G.W.Duncan)	1.2	\$ 4,040	1.2	\$ 4,200
Project Leader(R.G.Wheeler)	7.3	18,800	6.3	17,050
Medical Advisor(R.L.Bernstine)	6.0	17,600	6.0	17,600
Senior Research Engineer(N.R.Gordon)	7.5	12,480	5.8	10,200
Research Engineer(B.R.Lower)	5.9	8,400	5.9	8,800
Engineering Associate(G.Janson,Jr.)	1.9	4,490	1.9	4,490
Research Associate(D.R.Kalkwarf)	9.9	23,700	8.7	21,980
Research Associate(M.R.Sikov)	3.0	7,730	3.0	7,950
Research Scientist(J.F.Williford)	11.0	14,350	9.1	12,560
Research Engineers	1.5	2,810	1.1	2,220
Development Engineers	0.7	1,350	0.5	900
Research Associates	0.6	1,380	0.5	1,330
Research Scientists	5.7	10,470	4.2	8,340
Supervision	1.5	4,010	1.3	3,570
Technicians	27.5	29,370	25.5	27,970
Laboratory Assistants	2.2	2,040	1.9	1,820
Craftsmen and Draftsmen	4.0	5,130	4.2	5,600
Technical Services Personnel	3.2	3,760	1.8	2,040
Secretary	<u>1.0</u>	<u>660</u>	<u>0.8</u>	<u>590</u>
Subtotal - Staff Labor	101.6	172,570	89.7	159,210
Consultants		9,100		7,900
Non-Expendable Equipment		None		None
Expendable Equipment and Supplies		8,920		3,700
Travel		8,590		7,880
Publication Costs		250		250
Other Direct Costs (Usage of Special Purpose Experimental Facilities and Equipment)		77,810		71,610
Indirect Costs (75% of Salaries)		130,030		119,960
Subcontracts (Device Fabrication)		<u>28,800</u>		<u>17,800</u>
Total Estimated Cost		436,070		388,310
Fixed Fee		<u>26,160</u>		<u>23,300</u>
Total		\$462,230		\$411,610

Two Year Total - \$873,840

Note to AID Contract Negotiator: The budget needs to be revised to ^{include} ~~provide~~ approximately \$25,000 for an IUD workshop to be held in the first year of the amended period. ~~If sufficient unexpended funds are not available from prior years obligations, appropriate adjustments should be made in the above budget to provide the necessary funds for the workshop.~~ Battelle should be requested to submit a revised budget for AID's consideration. ~~If any out backs in the above budget are required, the Technical Officer suggests they be made in the budget.~~

Fixed fee provided as per 11/11/73
(\$26,160) for cover just workshop.

Revised 5/10/75
by M. J. Newlin, P116/PPS